Single Technology Appraisal

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments [ID6325]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Gilead Sciences Ltd
   a. Company submission
   b. Severity analyses
      NB: These were submitted by the company after the EAG report was complete

2. **Company summary of information for patients (SIP)** from Gilead Sciences Ltd

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Lymphoma Action

5. **Expert personal perspectives** from:
   - Dr Sunil Iyengar, Consultant Haematologist – clinical expert, nominated by Gilead Sciences Ltd

6. **External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science
   a. EAG report
   b. Addendum

7. **External Assessment Report – factual accuracy check**

8. **NHS England responses to EAG information requests**

9. **NHS England – SACT data review**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma [ID6325]

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6325_Brexu-cel_RR MCL_NICE CES Main Dossier [RED]	1.0	Yes	14/02/25

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Abbreviations

Abbreviation	Definition
AAT	alanine aminotransferase
AE	adverse event
AIC	Akaike information criterion
ALC	absolute lymphocyte count
AlloSCT	Allogeneic stem cell transplant
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under curve
auto-SCT	autologous stem cell transplant
axi-cel	axicabtagene ciloleucel
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	best objective response
brexu-cel	brexucabtagene autoleucel
BSA	body surface area
BSH	British Society for Haematology
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CAR	chimeric antigen receptor
CAR T	chimeric antigen receptor T-cell
CDF	cancer drug fund
CEA	cost-effectiveness analysis
CI	confidence interval
CNS	central nervous system
CR	complete response
CRP	C-reactive protein
CRS	clinical release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DADS	directly accessed diagnostic services
DAPS	directly accessed pathology services
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DVT	deep vein thrombosis

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EPAR	European public assessment report
EQ-5D-5L	EuroQol-5 Dimension-5 Level
FACT-G	Functional Assessment of Chronic Illness Therapy – General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FAS	full analysis set
FCR	fludarabine, cyclophosphamide, rituximab
FDA	US Food and Drug Administration
FL	follicular lymphoma
HIV	human immunodeficiency virus
HRG	health resource group
HRQoL	health-related quality of life
IAS	inferential analysis set
ICANS	immune effector cell-associated neurotoxicity syndrome
ICER	incremental cost-effectiveness ratio
IL	interleukin
IRRC	Independent Radiology Review Committee
IV	intravenous
IVIG	intravenous immunoglobulin
IWG	International Working Group
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LTS	long term survival
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MCM	mixture-cure-model
MedDRA	Medical Dictionary for Regulatory Activities
MIMS	Monthly Index of Medical Specialties
MIPI	MCL International Prognostic Index
mITT	modified intent-to-treat
MRD	Minimal residual disease

Abbreviation	Definition
MRI	magnetic resonance imaging
NA	not applicable
NCCP	National Car T Clinical Panel
NCI	National Cancer Institute
NE	not estimable
NHL	non-Hodgkin’s lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	objective response rate
OS	overall survival
PD	Progressive disease
PDS	personal demographics service
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PO	per oral
PR	partial response
PS	performance status
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
r/r	relapsed or refractory
R-BAC	rituximab, bendamustine and cytarabine
R-bendamustine	Rituximab plus bendamustine
RC	rituximab plus chemotherapy
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
RCT	randomised controlled trial
R-CVP	rituximab, cyclophosphamide, vincristine, prednisolone
RR	Response rate
RWE	real-world evidence
SACT	systemic anti-Cancer therapy
SAE	serious adverse event
SCT	stem cell transplant
SD	standard deviation
SE	standard error

Abbreviation	Definition
SLR	systematic literature review
s-MIPI	simplified-Mantle Cell Lymphoma International Prognostic Index
SmPC	summary of product characteristics
SMR	standardised mortality ratio
SoC	standard of care
SPD	sum of the products of diameter
TA	technology appraisal
TFL	tables, figures and listings
ULN	upper limit of normal
VAS	visual analogue scale
VR-CAP	Rituximab, cyclophosphamide, doxorubicin, bortezomib, prednisolone
WBC	white blood cell

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

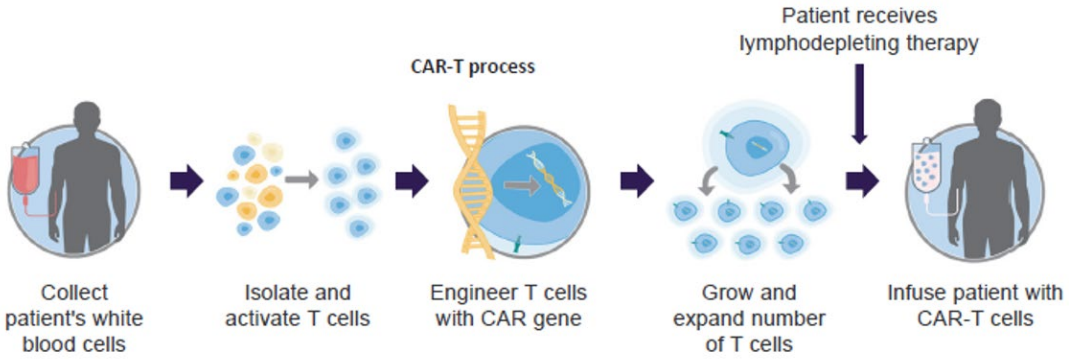
B.1.1. Decision problem

Brexucabtagene autoleucel (brexu-cel) has conditional marketing authorisation in the UK for treatment in adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) after two or more lines of therapy, including a Bruton's tyrosine kinase inhibitor (BTKi). This submission covers the marketing authorisation for the technology in this indication. The decision problem for this submission is summarised in Table 1, including justification for differences from the final scope.

B.1.2. Description of the technology being appraised

Brexu-cel is a chimeric antigen receptor (CAR) T-cell therapy directed against CD19 – a B-cell-specific cell surface antigen that is expressed in most B-cell malignancies, including MCL.[1] Brexu-cel is manufactured from patients' own T-cells, which are engineered *ex vivo* to express the CD19 antigen-specific CAR, enabling them to target and kill the CD19-expressing tumour cells when they are returned to the patient. Figure 1 depicts the steps involved in the manufacturing and administration of CAR T-cell therapy.

Figure 1: CAR T-cell therapy manufacturing and administration steps



Key: CAR, chimeric antigen receptor; CAR T, chimeric receptor antigen T-cell.

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	People with r/r MCL who have had at least 2 previous lines of therapy including a BTKi	Adult patients with r/r MCL who have previously received two or more lines of therapy including a BTKi	Minor word change to reflect adult population and the licensed indication
Intervention	Brexucabtagene autoleucel	Brexucabtagene autoleucel	Not applicable
Comparator(s)	Established clinical management including but not limited to: Chemotherapy with or without rituximab Zanubrutinib (subject to NICE evaluation) AlloSCT	Established clinical management including but not limited to: Chemotherapy with or without rituximab	AlloSCT is not a relevant comparator. AlloSCT may be used to consolidate a response to BTKi treatment in a minority of responding patients. In contrast, brexu-cel is positioned as a third-line treatment after BTKi failure. Zanubrutinib has not been appraised by NICE for the management of MCL and the main study supporting use of Zanubrutinib is in BTKi-naive MCL patients. In contrast, brexu-cel is positioned as a third-line treatment after BTKi failure.
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	Not applicable
Key: AlloSCT, allogeneic stem cell transplant; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor;			

The CAR construct used in brexu-cel is a single-chain antibody fragment directed against CD19 linked to CD3ζ and CD28 T-cell activating domains. Unique to the production of brexu-cel are the stages of enrichment and co-stimulation of the T-cells within step two of the manufacturing process depicted (Figure 1). This process is referenced to as the XLP process (hence the brexu-cel original product nomenclature). Table 2 summarises these stages of the manufacturing process. Regulatory authorities (the US Food and Drug Administration [FDA] and the European Medicines Agency [EMA]) provide clear guidance that these differences in manufacturing process yields a different product (Data on File).

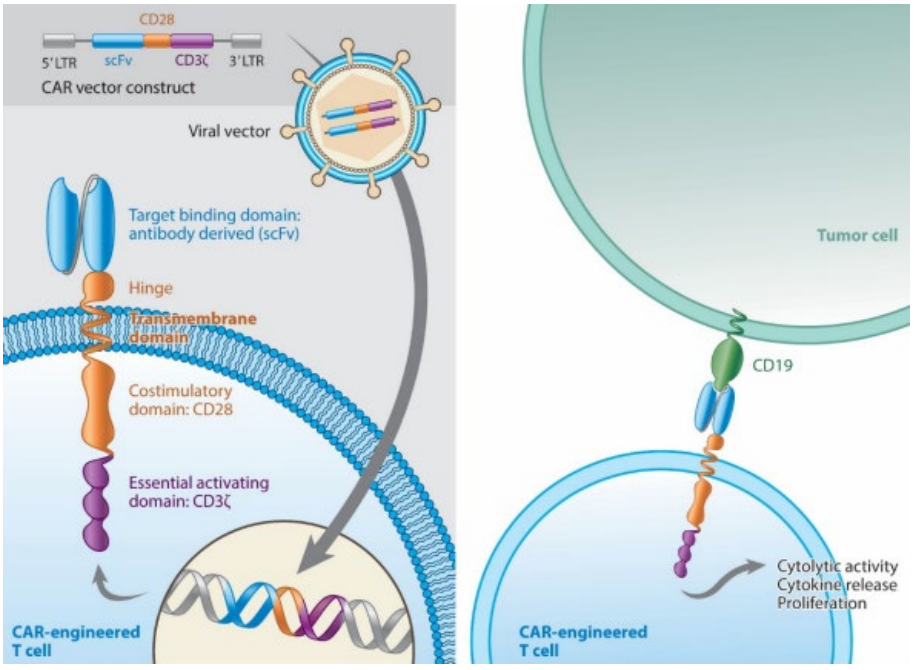
Table 2: Isolation and activation of T-cells manufacturing processes

	XLP process for brexu-cel
T-cell enrichment	Peripheral blood mononuclear cells fraction is enriched for T-cells by positive selection of CD4+ and CD8+ cells to remove blast and tumour cells.
T-cell stimulation	Co-stimulation is provided by exogenous anti-CD28 antibody

The XLP process was introduced to minimise hypothetical manufacturing and/or product quality issues related to premature activation and exhaustion of the CAR T-cells during the ex vivo expansion step of the manufacturing process if tumour cells are present in the leukapheresis harvest (step four of Figure 1).[2-4] This is important when producing a CAR T-cell therapy treatment for MCL, as tumour cells are more likely to be present in the blood than with other lymphomas. Such presence of circulating tumour cells has been reported in 26-34% of patients with MCL[5,6] which could be further increased in the relapsed or refractory (r/r) setting as a result of prior treatment with ibrutinib, leading to mobilisation of tumour cells into the blood.[7,8] Comparatively, the presence of circulating tumour cells in more common forms of non-Hodgkin's lymphoma (NHL) such as diffuse large B-cell lymphoma (DLBCL) is relatively rare.[9-11]

Table 3 provides summary information of the brexu-cel technology. The summary of product characteristics (SmPC) is provided in Appendix C.

Table 3: Technology being appraised

Approved name	Brexucabtagene autoleucel (brexu-cel)
Mechanism of action	Brexu-cel is a single-chain antibody fragment directed against CD19 linked to CD3ζ and CD28 T-cell activating domains; CD19 is a B-cell-specific cell surface antigen expressed in MCL. To prepare brexu-cel, a patients' own T-cells are engineered ex vivo to express the CD19 antigen-specific CAR, enabling them to target and kill CD19-expressing tumour cells when they are returned to the patient. Following CAR engagement with CD19-expresing 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 costimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including IL-2 production. Together, these signals stimulate proliferation of the CAR T-cells and direct killing of target cells. In addition, activated T-cells secrete cytokines, chemokines, and other molecules that can recruit and activate additional anti-tumour immune cells. This mechanism of action is depicted in the figure below. 
Marketing authorisation	The application for marketing authorisation with the EMA was submitted on 9 January 2020 with regulatory approval granted in December 2020.
Indication	Marketing authorisation: Adult patients with relapsed or refractory mantle cell lymphoma who have previously received two or more lines of systemic therapy including a BTK inhibitor
Method of administration and dosage	Brexu-cel is a single-infusion product, for autologous and intravenous use only. Each single-infusion bag contains a dispersion of anti-CD19 CAR T-cells in approximately 68 mL for a target dose of 2.0 x 10^6

	CAR T-cells/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg), with a maximum of 2 x 10^8 CAR T-cells. Prior to infusion, patients are treated with a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day intravenous for 3 days. Paracetamol 500 – 1,000mg oral and diphenhydramine 12.5 – 25mg intravenous or oral (or equivalent) is also recommended approximately 1 hour prior to infusion.
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 brexu-cel.
List price and average cost of a course of treatment	List price: £316,118
Patient access scheme	Available subject to a commercial agreement
Key: BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CAR T-cell, chimeric antigen receptor T-cell; EMA, European Medicines Agency; IL, interleukin; MCL, mantle cell lymphoma.	

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

B.1.3.1. Disease overview

NHL comprises a heterogeneous group of cancers of the lymphatic system. MCL is a rare form of NHL that develops from accumulation of abnormal (malignantly transformed) B-cells in the mantle zone of lymph nodes, often presenting at a late stage.[12,13] The initial mutation in almost all cases involves overexpression of cyclin D1, which in over 90% of tumours is as a result of the chromosome translocation, t(11:14) (q13;q32).[12,13] In the UK, approximately 590 people are diagnosed with MCL each year,[14] representing approximately 5% of all people diagnosed with NHL[15].

NHLs are categorised as low-grade or high-grade depending on how likely the lymphomas are expected to grow and spread (i.e., the aggressiveness of the cancer). While some patients may present with indolent disease and be managed with a 'watch and wait' approach until their disease is advanced to a stage warranting treatment,[16,17] MCL is typically considered a high-grade lymphoma in that it is fast growing; as a result, it is often already widespread at diagnosis.[18] Formal staging in lymphoma is conducted as per the Lugano classification, with Stage I

representing localised lymphoma and Stage IV representing lymphoma spread above and below the diaphragm, and to distant extranodal sites such as the lungs, liver, kidneys, brain or spinal cord.[19] the 2014 Lugano lymphoma response criteria are also used to characterise MCL treatment response. Unusually for lymphoma, MCL can also be found in the blood (see Section B.1.2).

Like most cancers, more advanced stage disease is associated with worse prognosis, but a more specific tool to assess risk, adopted to estimate prognosis and help guide treatment decisions in MCL, is the MCL International Prognostic Index (MIPI), based on a simplified score-based index (s-MIPI). Dependent on risk category (low, medium or high), 5-year survival estimates at diagnosis range from 15% to 60% (Table 4).

Table 4: Mantle Cell Lymphoma International Prognostic Simplified Index

	Simplified index scoring points			
Factors included	**0**	**1**	**2**	**3**
Age, years	< 50	50–59	60–69	≥ 70
ECOG PS	0–1	-	2–4	-
LDH, x ULN	< 0.67	0.67–0.99	1.0–1.49	> 1.5
WBC, x 10^9 L	< 6.7	6.7–9.9	10–14.9	≥ 15
Risk stratification				
	Simplified index scoring		**Estimated 5-year survival**	
Low	0–3 points		60%	
Intermediate	4–5 points		40%	
High	6–11 points		15%	

Key: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal; WBC, white blood cell.
Source: Hoster et al., 2008.[20]

Further prognostic factors in MCL include Ki-67 proliferation index ≥ 50%, blastoid morphology, *TP53* mutation and bulky disease (area of lymphoma over 5cm).[21,22] A modification of the MIPI that also considers Ki-67 proliferation index estimates 5-year survival at 85% for low-risk patients, 72% for low-intermediate risk patients, 43% for high-intermediate risk patients and 17% of high-risk patients.[22,23]

B.1.3.2. Outcomes for relapsed and refractory MCL patients

Unlike more common high-grade NHLs (e.g., DLBCL), MCL has generally been considered incurable.[18] Most patients receive chemo-immunotherapy as an early line treatment, while at first relapse BTKis have become the mainstay treatment. The prognosis of patients failing on BTKis has traditionally been dismal due to the lack of a promising further line of therapies; MCL patients inevitably relapse, and each subsequent treatment line is associated with worsening prognosis.[24]

CAR T therapy was introduced in the r/r MCL setting in 2021, and is now the standard of care for eligible r/r MCL patients post BTKi (see section B.1.3.4)[16] . The step change that the availability of CAR T has made to outcomes for patients with r/r MCL is clear, with UK real-world CAR T experience demonstrating substantial improvements in survival (12-month OS estimated at 74%)[25] compared to previous therapy options (median OS ranging between 10 to 14 months).[26,27]

The outcomes of patients prior to the UK availability of CAR T have been reported by the Haematological Malignancy Research Network. This report showed substantially reduced survival with each additional line of treatment in UK patients diagnosed with MCL between September 2004 and August 2017.[28] In this group, median survival decreased from 9.6 months with second-line treatment to 7.2 months with third-line treatment, 4.8 months with fourth-line treatment and 1.2 months with fifth-line treatment.[28] Although absolute survival estimates improved over time with the introduction of novel agents – most notably rituximab at first-line and ibrutinib at second-line – overall survival (OS) is still very limited.[29] Similar observations are seen in other real-world evidence sets across Europe and the US.[30,31]

Outcomes associated with post-BTKi chemo-immunotherapy in patients with r/r MCL have recently been explored in 2 real-world studies conducted in the UK and Europe.[26,32]. Prior to the introduction of CAR T, the studies underscored the urgent need for improved treatment, and demonstrated limited options post-BTKi, even in patients initiating post-BTKi therapies. In these studies, median OS ranged from 5.5 months (95% CI 3.9–8.2; given no additional treatment) to median OS 12.3 months (95% CI 7.4–17.6), with a trend towards better outcomes for patients receiving fewer lines of therapy prior to initiation of post-BTKi treatment[32], and marginally better outcomes for patients treated with rituximab, bendamustine and cytarabine (R-BAC; median

OS 14.0 months, 95% CI 8.1–19.8) versus alternative systemic treatments (median OS 11.6 months, 95% CI ,26–45, *P*=006)[26]. Other observational studies of mixed chemotherapy post-BTKi failure found similarly high unmet need in those patients managed with chemotherapy, reporting response rates ranging from 20%–48%, and median OS ranging from 6–10 months, emphasising the failure of treatments in the pre CAR-T era in achieving durable survival in post BTKi r/r MCL patients[33-37].

B.1.3.3. Burden of disease

By diagnosis, MCL is often widespread and a substantial burden of the disease is the impact on survival and the worsening prognosis with each relapse. Symptoms of MCL are similar to those of most other types of NHL and characteristically include painless swelling due to enlarged lymph nodes in the neck, armpit and groin, and B-symptoms (night sweats, high temperatures, weight loss and itching).[18,38] Depending on where the lymphoma spreads, other symptoms may include loss of appetite, diarrhoea, sickness, anaemia and fatigue,[39] while further additional symptoms relating to extranodal spread can also be observed, dependent on site[38].

Such physical burdens can impact patients' normal daily activities and functional well-being; as measured on the Functional Assessment of Chronic Illness Therapy – General (FACT-G) instrument, patients with r/r MCL have significantly reduced HRQoL compared with the general population.[40-42] A similar trend of reduced HRQoL has been reported comparing European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) scores in patients with r/r MCL versus general population norms: with respective scores for global quality of life, 61.8 versus 66.1; physical function, 78.4 versus 85.1; role function, 76.3 versus 84.3; social function, 76.3 versus 86.2.[43,44]

Evidence on patient HRQoL impacts associated with multiple relapses of MCL is scarce but given the worsening prognosis and based on evidence in other forms of NHL, the continued reduction in HRQoL can be expected. In follicular lymphoma (FL), a UK cross-sectional study showed patients with relapsed FL had lower physical, emotional, functional and social well-being scores as per the FACT-Lym compared with patients who were newly diagnosed, responding to treatment or disease-free.[45]

Before the availability of CAR T-cell therapy, patients with post BTKi r/r MCL had been subject to intense regimens of chemotherapy cycles in a hospital setting with little expectation of extended life. Moreover, when effective treatment options were exhausted, the mental strain on patients, their carers and family was excruciating, while not necessarily captured on HRQoL measures. With the availability of CAR T-cell therapy, the hope of potentially extended survival has provided substantial improvement on such less-measured psycho-social HRQoL constructs.[46,47]

Using simulation modelling, a recent study[48] supported by the European Union explored the overall temporal dynamics of how a disease and its treatment influence well-being and survival in patients receiving CAR T-cell therapy. The model showed that increases in tumour burden in patients while awaiting treatment and deterioration in physical well-being subsequently affects psychological well-being and overall HRQoL, and can further reduce later treatment efficacy, potentially leading to relapse. Whereas in patients who experience earlier and complete response, recovery of HRQoL at higher and durable levels was possible, and this in turn, ultimately resulting in significant improvements in survival.

B.1.3.4. Clinical care pathway

B.1.3.4.1. First-line treatment

MCL treatment options at first-line are well established.[26,49] When suitable, patients are treated with a high-dose cytarabine regimen followed by autologous stem cell transplant (auto-SCT) with or without rituximab maintenance.[16,50] Patients for whom an auto-SCT is unsuitable are generally treated with immunochemotherapy, most commonly comprising one of the following regimens with or without rituximab maintenance:[24]

- Rituximab plus bendamustine (R-bendamustine)
- Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP)
- Rituximab, bendamustine and cytarabine (R-BAC)
- Rituximab, cyclophosphamide, doxorubicin, bortezomib, prednisolone (VR-CAP)

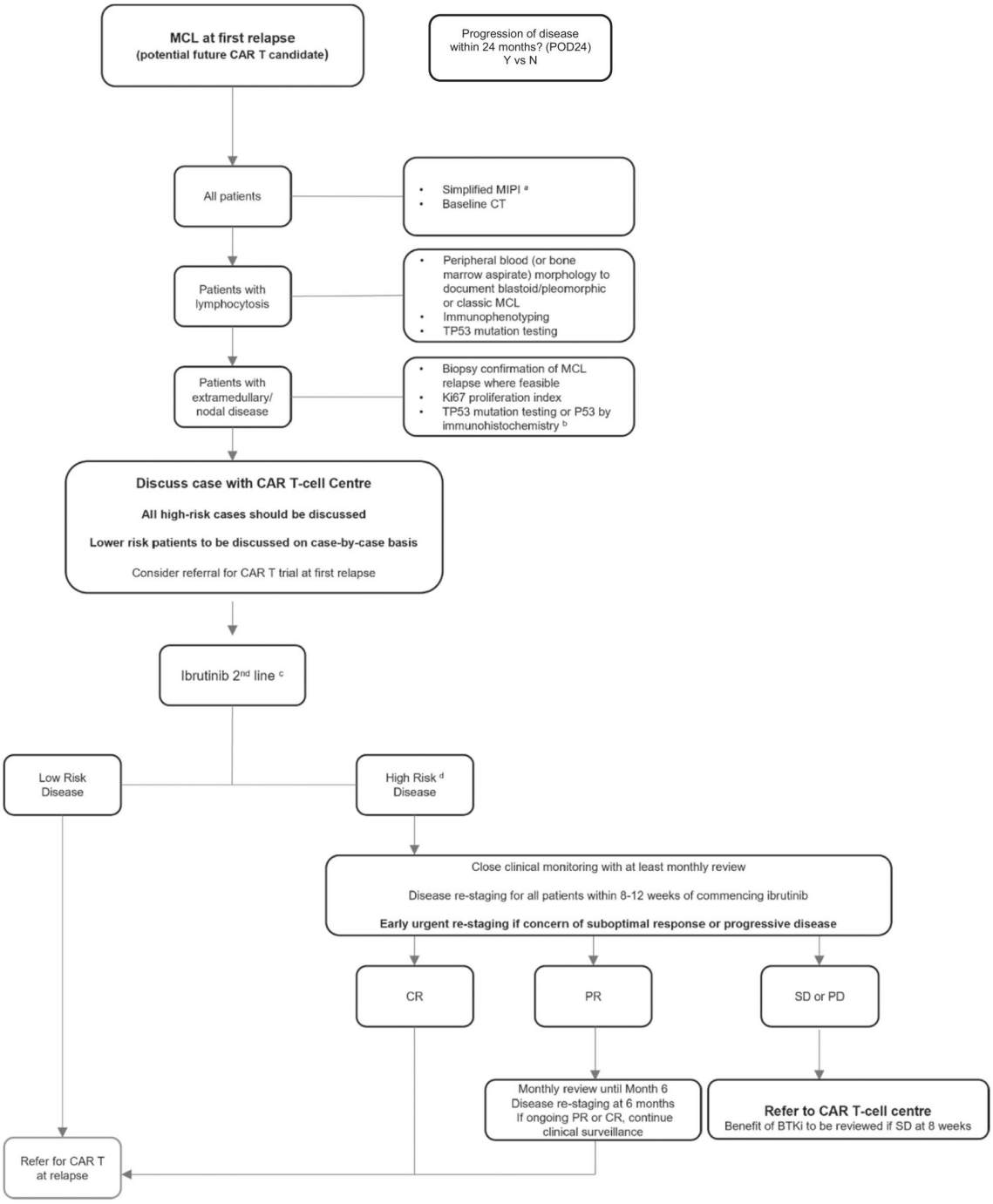
B.1.3.4.2. First relapse/second-line treatment

Figure 2 depicts the UK care pathway for MCL following first relapse, according to the British Society for Haematology (BSH) 2024 guidelines.[16]

At first relapse, Bruton's tyrosine kinase inhibitors (BTKis), which first provided a major advance in relapse treatment when licensed in 2013, are now considered standard of care in first r/r MCL.[16,51] Ibrutinib is routinely reimbursed by National Health Service (NHS) England,[50,52,53]. BSH guidelines recommend that high risk patients started on ibrutinib immediately undergo increased surveillance to monitor for relapse to ensure prompt referral to third-line therapy (Figure 2).[16,51]

For a small number of eligible patients, a consolidation to an ibrutinib response with allo-SCT can be considered but only while patients are still responding to ibrutinib (outcomes are considerably worse if performed later[16,24,54]).

Figure 2: MCL pathway after first relapse (for CAR T eligible patients)



Key: CAR, chimeric antigen receptor; CR, complete response; MCL, mantle cell lymphoma; PR, partial response; SCT, stem cell transplant
Source: BSH MCL guidelines, 2024[16]

B.1.3.4.3. Third- and later-line treatment

For eligible r/r MCL patients who relapse post BTKi, CAR-T is now considered the standard of care and is an established part of the treatment pathway (Figure 2).

Brexu-cel

The positive impact of the introduction of CAR T-cell therapy for patients with R/R MCL cannot be minimised. Since its first use in the UK, there have been two updates to BSH guidelines with incorporation of CAR T within the MCL treatment pathway; in 2022 CAR T-cell therapy was introduced into the guidelines, and in 2024 increased surveillance was recommended in BTKi patients assessed as eligible for CAR T to mitigate the risk of drop-out and improve access to CAR T treatment.

Brexu-cel was granted conditional marketing authorisation in 2019 by the EMA for r/r MCL for third- and later-line therapy following BTKi failure.[55] Since its inclusion in BSH guidelines, brexu-cel has been established as a third line therapy post-BTKi failure (Figure 2),[16] and now plays a firm and critical role in r/r MCL treatment within the UK[16] (Figure 2) and international MCL treatment practices[56,57].

The UK guidelines[16] particularly note favourable initial responses for brexu-cel (overall response rate [ORR] 91% and complete response [CR] 68%) with 37% of evaluable patients in ongoing response at a median follow-up of 35.6 months reported from the ZUMA-2 multicentre, phase 2 trial, of brexu-cel in patients with in post-BTKi r/r MCL.[4,58] In the 5Y data-cut, the median PFS and OS for the all-treated population were 25.8 months and 46.6 months, respectively.[49] This trial evidence[4,58] has been underscored by real-world data from both the UK[25,59] and international settings[60-62].

While early US and UK real-world evidence had supported trial-based efficacy and safety outcomes for those reaching infusion,[63] the significant drop-out rate between National CAR T Clinical Panel (NCCP) approval and T-cell harvest and/or infusion remained a cause for concern, [16,64,65] Hence, UK guidelines now recommend implementing surveillance strategies (Figure 2) for capturing early refractory or progressive disease in potential candidates to allow prompt CAR T initiation.[16,64]

Treatment options following brexu-cel

Treatment options beyond CAR T (or in those patients who are CAR T ineligible) are limited, with a continuing search for optimal combinations and sequencing of therapies. Current UK practice (aligned with guideline recommendations) considers immunochemotherapy (primarily rituximab or rituximab combination therapies) on this point of the MCL pathway.[16,64,65] Evidence from real-world practice established R-BAC as the default immunochemotherapy here; however, in the current BSH treatment guidelines R-BAC is referenced as the preferred regimen only in patients *ineligible* for CAR-T, other patients are directed toward trial-based therapies.[16,64,65] Other options at this stage in patient management also include palliative care.

B.1.3.5. Summary of unmet medical need

Prior to CAR T, treatment options were extremely limited, and survival outcomes were very poor in patients with r/r MCL post BTKi failure. Since 2021, CAR T has been transformative in providing a treatment option that offers the hope of long-term survivorship in one infusion. with no further developments relevant to this group since its introduction. The main unmet need now is in those patients who cannot make it to or are not eligible for CAR-T, however, removal of brexu-cel would result in a recreation of pre CAR-T levels of unmet need in this r/r MCL patient group.

B.1.3.6. Proposed positioning for Brexu-cel

Brexu-cel now has an established role in UK MCL treatment guidelines as the SoC for CAR T eligible patients who have received two or more lines of therapy including BTKi. Early identification, and close monitoring of BTKi patients with a view to an early referral to CAR T is crucial. Since the availability of brexu-cel on the Cancer drug fund (CDF), it has become an established therapy in a setting where patients would otherwise have very limited treatment options. Arguably, through continued availability of brexu-cel as a third line therapy and by following a protocol incorporating early and stringent risk-based surveillance, patients with r/r MCL post BTKi failure can continue to experience clinically significantly improved survival. This positioning of brexu-cel is in line with the current BSH guidelines in this setting.[16]

B.1.4. Equality considerations

No equality issues are foreseen.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

Clinical evidence relevant to brexu-cel in the treatment of r/r MCL after two or more lines of systemic therapy, including a BTKi, was identified through a systematic literature review (SLR). An updated SLR supplemented the SLRs conducted for the original submission (see TA677[66]). See Appendix B for full details of the process and methods used to identify and select the clinical evidence.

B.2.2. List of relevant clinical effectiveness evidence

Table 5 summarises the clinical effectiveness evidence supporting brexu-cel for the treatment of r/r MCL after two or more lines of therapy and BTKi failure. Relevant studies are here defined as studies that are within the scope of this evaluation.

Table 5: Clinical effectiveness evidence – brexu-cel (summary)

Study ID	Study design	Population (n)	Treatment (n)	OS	PFS	ORR
Wang 2020 [4]	ZUMA-2	r/r MCL with up to 5 prior therapies including BTKi (74)	brexu-cel (n=68)	✓	✓	✓
Wang 2022 [58]	ZUMA-2 plus high risk sub-groups	r/r MCL with up to 5 prior therapies including BTKi (74)	brexu-cel (n=68)	✓	✓	✓
Wang 2024 [67]	ZUMA-2 5-year data (including LTFU*)	r/r MCL with up to 5 prior therapies including BTKi (74)	brexu-cel (n=68)	✓	✓	✓

Key: brexu-cel: brexucabtagene autoleucel; LTFU: long-term follow-up; PFS: progression-free survival; OS: overall survival; ORR: overall response rate

*Per ZUMA-2 protocol, after 24mo follow-up all patients (if accepted) will be enrolled in LTFU.

An emerging base of RWE is now available for the use of brexu-cel in this indication.[25,61,68,69] These studies are not used to inform this submission or the economic model. A list of these studies is reported in Appendix B. In addition, the ZUMA-18 study [68], an expanded access study conducted in the US for a broader population than the one evaluated in this submission, is also listed there.

The primary source of clinical effectiveness evidence for brexu-cel is the ZUMA-2 clinical trial[4,58,63,67,70]. The Public Health England report on real-world data from the Systemic Anti-Cancer Therapy (SACT) database,[71] which was conducted as part of the managed access scheme following the initial appraisal of brexu-cel, is included under additional clinical evidence (see section B.2.12) but not used in the model.

Table 6: Clinical effectiveness evidence – ZUMA-2

<table>
<tr><td>Study (NCT)</td><td colspan="5">ZUMA-2 (NCT02601313)</td></tr>
<tr><td>Study design</td><td colspan="5">ZUMA-2 is an ongoing, Phase II, multicentre, open-label, single-arm study evaluating the efficacy and safety of brexu-cel in relapsed/refractory MCL</td></tr>
<tr><td>Population</td><td colspan="5">Adult patients with relapsed/refractory MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTKi (ibrutinib and/or acalabrutinib)</td></tr>
<tr><td>Intervention</td><td colspan="5">brexu-cel</td></tr>
<tr><td>Comparator</td><td colspan="5">None (ZUMA-2 is a single-arm trial)</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">ZUMA-2 presents the pivotal, regulatory, clinical evidence in support of brexu-cel in the r/r MCL indicated setting</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• OS
• PFS
• Response rates
• Adverse effects of treatment
• HRQOL</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Incidence of anti-CD19 CAR antibodies
• Levels of anti-CD19 CAR T-cells in blood
• Levels of cytokines in serum
• Minimal residual disease (post-hoc analysis)</td></tr>
<tr><td colspan="6">Key: BTKi, Bruton tyrosine kinase inhibitor; HRQoL, health-related quality of life; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival.
Notes: Outcomes in bold are those directly used in the economic modelling. Response rate is only implicitly captured in the cost-effectiveness analysis, through the related measures of overall survival and progression-free survival. HRQoL is sourced elsewhere see Section B.3.4)</td></tr>
</table>

In line with the decision problem (see section B.1.1), the comparator for this submission is defined as rituximab-containing therapy (specifically R-BAC) given as a third-line or above following BTKi. Similar to the previous submission, no

comparative evidence is available comparing brexu-cel against R-BAC in this setting. The evidence for R-BAC (McCulloch 2020) is summarised in section B.3.3.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence – ZUMA-2

B.2.3.1. Overview

Table 7 provides a summary of the trial methodology for ZUMA-2.

Figure 3 provides a summary of post BTKi patients enrolled and treated across different cohorts and highlights those of relevance to this appraisal; this is discussed in detail throughout this submission (aligning to ZUMA-2 data publications).

In Cohort 1, patients received either axicabtagene ciloleucel (axi-cel) or brexu-cel. The axi-cel arm was closed following the development of the XLP manufacturing process described in Section B.1.2 and all patients subsequently enrolled to ZUMA-2 received brexu-cel. Patients from Cohort 1 that received brexu-cel at a dose of 2.0 x 10^6 anti-CD19 CAR T-cells/kg body weight will be included in this submission

Cohort 2 comprised a second cohort for a reduced dose of brexu-cel (0.5 x 10^6 anti-CD19 CAR T-cells/kg body weight) which was opened following early observation of high expansion of CAR T-cells with the initial target dose of brexu-cel (see Section B.2.4). The risk/benefit ratio of the Cohort 1 dose was deemed the optimal dose before Cohort 2 reached full enrolment. Cohort 2 does not reflect the licensed dosing of brexu-cel in the UK and is not discussed any further in this submission.

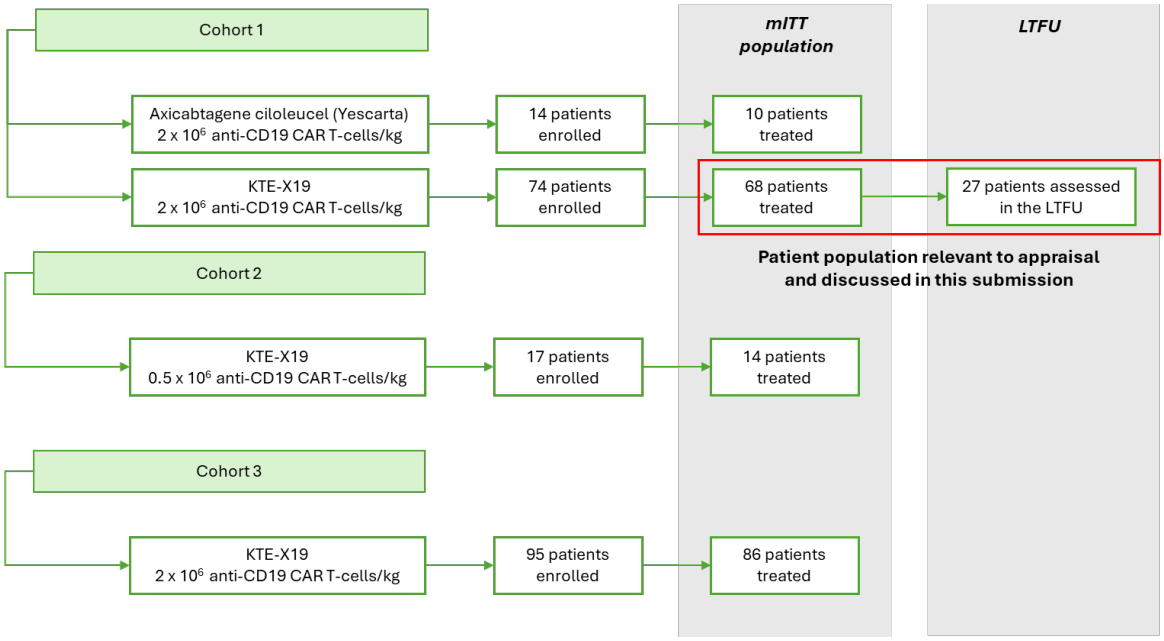
A third cohort of the ZUMA-2 trial, Cohort 3 (not reported here), enrolled patients who were BTK-naïve [72]. These patients do not reflect the licensed indication of brexu-cel in the UK; thus Cohort 3 is not discussed in this submission.

The data presented in this submission represent patients from Cohort 1 who received brexu-cel at the licensed dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight. This cohort comprises 74 enrolled patients (and for analyses purposes referred to as the Full Analysis Set [FAS]); of which 68 patients were treated (and for analyses purposes referred to as the modified intent-to-treat [mITT] analysis set for efficacy outcomes and the safety analysis set for safety outcomes). The first 60

patients treated with brexu-cel in Cohort 1 formed the base for statistical hypothesis testing of the primary endpoint and were referred to as the inferential analysis set (IAS). The IAS cohort was reported in full in the original submission. In line with the original submission, the mITT population informs the clinical effectiveness evidence and is used in the economic model. Apart from section B.2.4, where other cohorts are reported as the basis for hypothesis testing, the mITT is reported throughout.

After completion of at least 24 months of assessments, subjects who received an infusion of anti-CD19 CAR T-cells were given the opportunity to transition to a separate long-term follow-up study (ZUMA-2 LTFU), after providing signed informed consent. Outcomes for this cohort are reported as part of the mITT and included in the updated 60m reporting (section B.2.6).

Figure 3: Patient cohorts of ZUMA-2



Key: CAR T-cell, chimeric antigen receptor T-cell; LTFU: Long-term follow-up; mITT: Modified intention-to-treat
Source: Adapted from ZUMA-2 CSR[73]

Each patient proceeded through several study periods, including leukapheresis (where white blood cells for the manufacturing of CAR T-cell therapy are obtained), bridging therapy (if required for patients to remain eligible for CAR T-cell infusion, that is, to keep the patient's condition stable during the manufacturing period) and

conditioning chemotherapy (to induce lymphocyte depletion and create an optimal environment for expansion of anti-CD19 CAR T-cells in vivo) prior to CAR T-cell treatment. A single intravenous dose of CAR T-cell therapy was administered to all patients. Those who achieved at least a partial response (PR) had the option to receive a second course of conditioning chemotherapy and CAR T-cell therapy if their disease subsequently progressed >3 months after the initial infusion, providing the relapse was confirmed to be CD19-positive.

All patients were to be evaluated for disease response by an Independent Radiology Review Committee (IRRC) per the Internal Working Group (IWG) Lugano Classification[74] (primary endpoint). Response assessments were also to be determined by the site investigators (secondary endpoint). Other secondary endpoints included additional efficacy analyses (best objective response [BOR], duration of response [DOR], PFS and OS), safety analyses and HRQoL outcomes.

Table 7: Summary of trial methodology for ZUMA-2

Trial number (acronym)	NCT02601313 (ZUMA-2)
Location	33 site locations across North America (USA: 25) and Europe (France: 3; Germany: 2; Netherlands: 3)
Trial design	ZUMA-2 is an ongoing Phase II, multicentre, open-label, single-arm study evaluating the efficacy and safety of brexu-cel in relapsed/refractory MCL.
Eligibility criteria for participants	**Inclusion criteria:** • Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or presence of t(11;14) • Up to five prior regimens for MCL. Prior therapy must have included: – Anthracycline or bendamustine-containing chemotherapy and – Anti-CD20 monoclonal antibody therapy and – Ibrutinib or acalabrutinib • Relapsed or refractory disease, defined by one of the following: – Disease progression after last regimen – Failure to achieve a PR or CR to last regimen (refractory) • At least one measurable lesion (lesions previously irradiated considered measurable only if progressive disease was documented following completion of radiation therapy) – If the only measurable disease was lymph node disease, at least 1 lymph node was ≥ 2 cm • No evidence of CNS lymphoma (as determined by MRI)

	• At least the following must have elapsed prior to planned leukapheresis: – 2 weeks or 5 half-lives (whichever was shorter) since any prior systemic therapy or BTK inhibitors – 3 half-lives since any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy • Toxicities due to prior therapy must have been stable and recovered to ≤ Grade 1 (except for those clinically nonsignificant) • Age ≥ 18 years • ECOG performance status of 0 or 1 • ANC ≥ 1,000/μL; platelet count ≥ 75,000/μL; ALC ≥ 100/μL • Adequate renal, hepatic, pulmonary and cardiac function defined as the following: – Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 ml/min – Serum ALT/AST ≤ 2.5 ULN – Total bilirubin ≤ 1.5 mg/dL, except in patients with Gilbert's syndrome – Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram, and no clinically significant electrocardiogram findings – No clinically significant pleural effusion – Baseline oxygen saturation > 92% on room air • Negative pregnancy test for women of childbearing potential **Exclusion criteria:** • History of malignancy other than non-melanomatous skin cancer or carcinoma *in situ* unless disease free for ≥ 3 years • Auto-SCT within 6 weeks of planned brexu-cel infusion • History of alloSCT • Prior CD19-targeted therapy, with the exception of patients who received brexu-cel in this study and were eligible for retreatment • Prior CAR T-cell therapy or other genetically modified T-cell therapy • History of severe, immediate hypersensitivity reaction attributed to aminoglycosides or any of the agents used in this study • Presence of fungal, bacterial, viral, or other infection that was uncontrolled or required IV antimicrobials for management • History of HIV infection or chronic active hepatitis B or C infection • Presence of any in-dwelling line or drain (Ommaya reservoirs and dedicated central venous access catheters were permitted) • History or presence of fluid malignant cells or brain metastases; history of CNS lymphoma

	• History or presence of CNS disorder such as seizure disorder, cerebrovascular ischaemia/haemorrhage, dementia, cerebellar disease, cerebral oedema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement • History of myocardial infarction cardiac angioplasty or stenting, unstable angina, active arrhythmias, or other clinically significant cardiac disease within 12 months of enrolment • Cardiac atrial or cardiac ventricular lymphoma involvement • History of symptomatic DVT or pulmonary embolism within 6 months of enrolment • Possible requirement for urgent therapy due to ongoing or impending oncologic emergency • Primary immunodeficiency • Any medical condition likely to interfere with assessment of safety or efficacy of study treatment • Live vaccine ≤ 6 weeks prior to the planned start of conditioning • Women of childbearing potential who were pregnant or breastfeeding • Patients of both sexes who were not willing to practise birth control from the time of consent through 6 months after brexu-cel infusion • Patient unlikely to complete all protocol-required study visits or procedures (including follow-up) or comply with the study requirements for participation, as judged by the investigator • History of autoimmune disease that resulted in end organ injury or required systemic immunosuppression or systemic disease-modifying agents within 2 years of enrolment
Study periods and trial drugs	• Screening • Enrolment/leukapheresis: patients were considered enrolled in the study when they commenced leukapheresis. – At least 12–15 L were to be processed to obtain approximately 5-10 x 10^9 mononuclear cells – In addition to meeting inclusion criteria, patients were required to have no evidence or suspicion of an infection prior to leukapheresis and to have CRP levels < 100 mg/L • Bridging therapy: patients could receive bridging therapy after leukapheresis and up to 5 days prior to the initiation of conditioning chemotherapy – Considered for any patient but particularly for those with high disease burden at screening (> 25% marrow involvement and/or ≥ 1,000 leukaemic phase mantle cells/mm^3 in peripheral circulation) at the discretion of the investigator and after discussion with the medical monitor – Bridging therapy regimens permitted included (i) dexamethasone 20–40 mg or equivalent PO or IV daily for 1–4 days or dose adjusted for age/comorbidities as per local or institutional guidelines (ii) ibrutinib 560 mg PO daily or most recent dose if there had previously been a dose adjustment (iii) acalabrutinib 100 mg PO every 12 hours or most recent dose if there had previously been a dose adjustment

	– After bridging a repeat baseline PET-CT was performed • Conditioning chemotherapy: all patients were to receive a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day for 3 days – Prior to the initiation of conditioning chemotherapy, the patient must have shown no evidence or suspicion of an infection • Investigational product treatment: all patients were to receive a single IV infusion of brexu-cel after a 2-day rest period post-completion of conditioning chemotherapy – assigned as Day 0 – If the infusion was delayed by > 2 weeks, conditioning chemotherapy was to be repeated – The following medications were to be administered 1 hour prior to infusion (i) paracetamol 500–1,000 mg PO (ii) diphenhydramine 12.5–25 mg IV or 25 mg PO – Cohort 1 patients were to receive a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg, with a maximum dose of 2 x 10^8 anti-CD19 CAR T-cells/kg for patients ≥ 100kg
Settings and locations where the data were collected	• Patients were to be hospitalised for treatment with brexu-cel and were to remain in hospital for a minimum of 7 days after treatment (unless otherwise required by a country's regulatory agency) • Patients were to remain hospitalised until all brexu-cel-related non-haematological toxicities had returned to Grade ≤ 1 or baseline. Patients were also to remain hospitalised for ongoing brexu-cel-related fever, hypotension, hypoxia, or an ongoing central neurological toxicity if the event severity was Grade > 1 or if deemed necessary by the treating investigator • Patients may have been discharged with non-critical and clinically stable or slowly improving toxicities if the event was Grade > 1, if deemed appropriate by the investigator • Routine laboratory assessments were to be performed by the local institutional laboratory
Prior and concomitant medication	• Corticosteroid therapy at a pharmacological dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs were to be avoided for 7 days prior to leukapheresis and 5 days prior to brexu-cel infusion used for bridging therapy • Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after brexu-cel infusion unless used to manage brexu-cel-related toxicities. Other medications that may interfere with evaluation of brexu-cel such as non-steroidal anti-inflammatory agents were also to be avoided for the same time period unless medically necessary • Treatment for lymphoma other than what was defined/allowed in the protocol were prohibited except as needed for treatment progression after brexu-cel infusion • Investigators were allowed to prescribe medications or treatments deemed necessary to provide adequate supportive care, including growth factor support and routine anti-emetic prophylaxis and treatment except for the excluded medications as per eligibility

Primary endpoint	• ORR, defined as the incidence of CR or PR as per the Lugano classification, as determined by the IRRC • Response assessment (via PET-CT scan) began 4 weeks (± 3 days) after the brexu-cel infusion and are to be conducted every 3 months up until Month 72 and annually thereafter • Patients with symptoms suggestive of disease progression were to be evaluated at the time that the symptoms occurred
Secondary endpoints	• BOR, defined as CR, PR, stable disease, progressive disease and not evaluable as per the Lugano Classification, as determined by the IRRC • ORR and BOR, as previously defined as per the IWG 2007 criteria and Lugano Classification, as determined by the investigator • DOR, defined as the time from first objective response to disease progression or death • PFS, defined as the time from brexu-cel infusion date to the date of disease progression or death from any cause. Progression was determined using both IRRC and investigator assessment – Defined as the time from the date of enrolment to the date of disease progression or death from any cause for the FAS • OS, defined as the time from brexu-cel infusion date to the date of death from any cause. Patients will be followed for survival every 3 months up until Month 72 and annually thereafter • Safety assessments including the monitoring of AEs and clinically significant changes in laboratory values occurred throughout the conduct of the study. AEs were coded with the MedDRA version 22.0 and severity was graded using the NCI CTCAE version 4.03 • HRQoL, assessed using the EQ-5D questionnaire at screening (for baseline scores), Week 4 (± 3 days), Month 3 (± 1 week) and Month 6 (during the long-term follow-up period) before any other assessments or procedures
Pre-planned sub-groups	• Selected efficacy and safety endpoints were performed in subgroups defined by baseline covariates, use of concomitant tocilizumab and corticosteroids, and use of bridging therapy. Baseline covariates included: – ECOG performance status – Demographic characteristics (age, sex, race) – Relapsed/refractory group (relapsed after auto-SCT, relapsed after last MCL chemotherapy, refractory to last MCL chemotherapy) – Morphologic characteristics (classical, blastoid) – Ki-67 index – CD19 positivity – t(11;14) presence – Cyclin D1 overexpression – Disease stage (I, II, III, IV) – Extent of disease (B-symptoms, splenic involvement, extranodal disease, bulky disease, bone marrow involvement) – s-MIPI

	– Number and type of prior regimens – Prior BTK inhibitors – Tumour burden (SPD of selected nodes of target lesions)
Key: AE, adverse event; ALC, absolute lymphocyte count; alloSCT, allogeneic stem cell transplant; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; auto-SCT, autologous stem cell transplant; BOR, best objective response; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CRP, C-reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IRRC, independent radiology review committee; IV, intravenous; IWG, International Working Group; MCL, mantle cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PO, per oral; PR, partial response; s-MIPI, simplified-Mantle Cell Lymphoma International Prognostic Index; SPD, sum of the products of diameter; ULN, upper limit of normal. **Source:** ZUMA-2 CSR[73]	

B.2.3.2. Baseline characteristics

Table 8 provides a summary of baseline characteristics, including demographic and clinical characteristics, and bridging therapy needs in Cohort 1. In line with agreement in the previous submission, only the mITT population is reported.

> **The Modified Intent-to-treat (mITT) group:** The 68 patients in Cohort 1 who received brexu-cel at a dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight. This analysis set best represents the decision problem population and was used in subsequent economic analysis; this resubmission follows the same approach.

Across all treated patients, high-risk features were common at baseline and most patients had received at least three prior lines of therapy (81%). All patients had relapsed or demonstrated refractoriness to BTKi therapy as per protocol and the most common BTKi previously received was ibrutinib (85%). A high proportion of patients had disease that did not respond to BTKi treatment (refractory disease) or had relapsed during BTKi (88%).

Bridging therapy with BTKi and/or steroid treatment was considered for rapidly progressing disease to keep MCL stable during manufacturing of brexu-cel, but was not intended to result in tumour regression. Twenty-five patients in the mITT group (37%) received bridging therapy; of these, 23 had post-bridging PET-CT scans and

the majority had an increase in the sum of product diameter (SPD) mm^2 from screening, indicating tumour progression despite bridging.[70]

Table 8: Baseline characteristics of patients in ZUMA-2 (Cohort 1)

	mITT (n = 68)
Median age, years (range) Age ≥ 65 years, n (%), mean age	65 (38-79) 39 (57) 63.2
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
ECOG 0/1, n (%)	68 (100)
Intermediate/high-risk s-MIPI, n (%)	38 (56)
Ki-67 proliferation index at diagnosis, n/N (%) ≥ 30% ≥ 50%	 40/49 (82) 34/49 (69)
TP53 mutation, n/N (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease[a], n (%)	38 (56)
MCL morphology[b], n (%) Classical Blastoid Blastoid or Pleomorphic Other	 40 (59) 17 (25) 21 (31) 1 (1)
Median no. of prior therapies (range)[c] ≥ 3 prior therapies, n (%)	3 (1-5) 55 (81)
Prior anthracycline or bendamustine, n (%)	67 (99)
Prior anti-CD20 mAb, n (%)	68 (100)
Prior auto-SCT, n (%)	29 (43)
Prior BTKi, n (%) Ibrutinib Acalabrutinib Both	68 (100) 58 (85) 16 (24) 6 (9)
Relapsed or refractory disease, n (%) Relapse after auto-SCT Refractory to most recent prior therapy Relapse after most recent prior therapy	68 (100) 29 (43) 27 (40) 12 (18)
BTKi relapsed or refractory disease, n (%) Refractory to BTKi Relapse during BTKi	68 (100) 42 (62) 18 (26)

Relapse after BTKi	5 (7)
BTKi intolerant[d]	3 (4)
Received bridging therapy, n (%)	25 (37)
Ibrutinib	14 (21)
Acalabrutinib	5 (7)
Dexamethasone	12 (18)
Methylprednisolone	2 (3)
Ibrutinib plus steroid	4 (6)
Acalabrutinib plus steroid	2 (3)

Key: auto-SCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; mAb, monoclonal antibody; MCL, mantle cell lymphoma; mITT, modified intent-to-treat; PD, progressive disease; s-MIPI, simplified-Mantle Cell Lymphoma International Prognostic Index.
Notes: [a], excludes bone marrow and splenic involvement; [b], morphology was unknown for 10 patients; [c], induction plus consolidation/maintenance and/or all treatments occurring between sequential complete responses were counted as 1 regimen; [d], patients had a relapse after or had disease that was refractory to subsequent therapies before trial entry.
Source: ZUMA-2 CSR[73]; Wang et al. 2020.[4]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence – ZUMA-2

B.2.4.1. Summary

Table 9 provides a summary of the statistical analysis and definitions of analysis sets in ZUMA-2 that are relevant to the indication of brexu-cel in BTKi-exposed patients. In contrast to other sections of this submission, the mITT and the IAS are described for Cohort 1, in order to provide a complete understanding of the study hypothesis and set up of the ZUMA-2 trial. An overview of Cohort 2 is similarly provided.

The study was to evaluate two doses of brexu-cel. Cohort 1 was to include at least 60 and up to approximately 80 patients treated with brexu-cel; Cohort 2 was to include up to approximately 40 patients. Five interim analyses were performed (four for Cohort 1 and one for Cohort 2) before the primary analysis.

Patients in Cohort 1 were to receive a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight, with a maximum dose of 2 x 10^8 anti-CD19 CAR T-cells for subjects ≥ 100 kg. Patients in Cohort 2 were to receive a target dose of 0.5 x 10^6 anti-CD19 CAR T-cells/kg body weight, with a maximum dose of 0.5 x 10^8 anti-CD19 CAR T-cells for subjects ≥ 100 kg.

The dose for Cohort 2 was based on results from an interim analysis of 28 patients in Cohort 1 who had the opportunity to be followed for 3 months after the anti-CD19 CAR T-cell infusion. This analysis demonstrated that patients in Cohort 1 had approximately 3- to 5-fold higher peak expansion and cumulative exposure (area under the curve [AUC]0-28) values of anti-CD19 CAR T-cells relative to the peak and AUC0-28 observed in patients treated with axicabtagene ciloleucel in ZUMA-1. Because anti-CD19 CAR T-cell peak and AUC0-28 were associated with Grade 3 or higher neurologic events in ZUMA-1[75], Cohort 2 was added to ZUMA-2 to evaluate the safety and efficacy of a 4-fold lower dose of brexu-cel. However, preliminary analysis of patients in Cohort 2 revealed that anti-CD19 CAR T-cell expansion in these patients was less robust than anticipated, which could negatively impact clinical efficacy. Further, an ad-hoc analysis performed at the same time of 28 patients treated with brexu-cel in Cohort 1 who had the opportunity to be followed for 12 months after the anti-CD19 CAR T-cell infusion demonstrated durable responses and a manageable safety profile, suggesting that the dose of 2 x 10^6 anti-CD19 CAR T-cells/kg was associated with a positive risk: benefit profile. Thus, the brexu-cel dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight used in Cohort 1 was deemed the optimal dose for treatment of MCL. Cohort 1 was re-opened, and all additional subjects were enrolled and treated at the dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight.

The primary analysis was to be conducted after 60 patients in Cohort 1 were treated with brexu-cel and had the opportunity to be assessed for response 6 months after the Week 4 disease assessment. Analysis sets relevant to brexu-cel cohorts are detailed in Table 9; the analysis set used for hypothesis testing was the IAS that included the first 60 patients in Cohort 1 who were treated with brexu-cel. Data from Cohort 2 were to be descriptive only.

A historical control response rate of 25% was used to test the hypothesis objective, detailed in Table 9. This was determined before the study began and was based on two retrospective studies that were published at the time of ZUMA-2 protocol development.[36,76] In these studies, outcomes after mixed salvage therapy were evaluated in patients with r/r MCL whose disease had progressed during or following treatment with a BTKi (a required prior therapy for ZUMA-2 eligibility). Patients who

had ≥ 3 prior lines before receiving the BTKi had objective response rates (ORRs) to mixed salvage therapy of approximately 25%. This has subsequently been validated through meta-analysis of more recently published studies investigating mixed salvage therapy after discontinuing treatment with a BTKi. This analysis reported a clinically consistent pooled ORR of 28%, despite most reporting investigator determined responses (that are often higher than those determined by central assessment[77]).

Table 9: Summary of statistical analyses for ZUMA-2

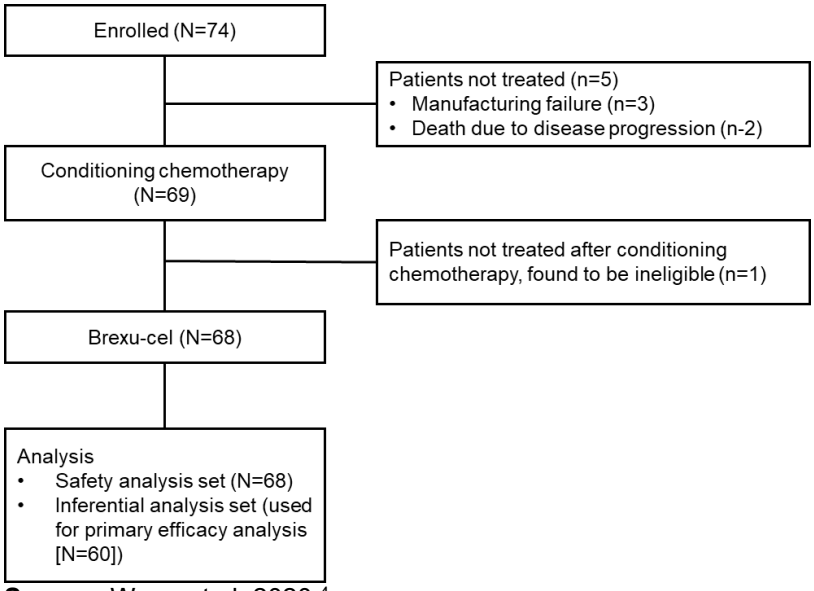
Hypothesis objective	The ORR to brexu-cel using central assessment would be significantly higher than the prespecified historical control rate of 25%. This hypothesis was to be tested in the inferential analysis set of Cohort 1. Data from Cohort 2 were to be descriptive only.
Statistical analysis	ORR was calculated as the number of responders per analysis set. CIs for the ORR were calculated using the Clopper–Pearson method. Wilson's method, the Agresti–Coull method and the modified Jeffrey's method were used in sensitivity analyses. Time-to-event estimates were calculated using the Kaplan–Meier approach and KM plots, estimates and 2-sided 95% CIs generated. Proportion of patients alive and proportion of patients alive and progression-free at 3-month intervals were also estimated for OS and PFS analyses, respectively.
Analysis sets	**IAS:** the first 60 patients in Cohort 1 who were treated with KTE-X19 2 x 10^6 anti-CD19 CAR T-cells/kg body weight. This analysis set was used for efficacy analyses in Cohort 1 and the hypothesis testing of the primary endpoint at the time of the primary analysis **Cohort 1:** FAS: all patients enrolled with the intention to treat with brexu-cel at a dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight (n=74). mITT / safety analysis set: all patients treated with brexu-cel 2 x 10^6 anti-CD19 CAR T-cells/kg body weight (n=68). **Cohort 2:** FAS: all patients enrolled with the intention to treat with brexu-cel at a dose of 0.5 x 10^6 anti-CD19 CAR T-cells/kg body weight (n=17). mITT / safety analysis set: all patients treated with brexu-cel 0.5 x 10^6 anti-CD19 CAR T-cells/kg body weight (n=14).
Sample size, power calculation	A sample size of 60 patients in Cohort 1 had at least 96% power to distinguish between an active therapy with a true response rate of ≥ 50% from a therapy with an ORR of 25% or less, with a one-sided alpha level of 0.025.

Data management, patient withdrawals	Patients without any disease response assessment were considered 'not done'. All patients in the inferential analysis set had a post-baseline assessment. PFS and OS for patients who had not met criteria for progression and/or were alive at the data cut-off date were censored at the last evaluable disease assessment date. DOR and PFS for patients who had a new anticancer therapy (including SCT) while in response were censored at the last evaluable disease assessment date prior to the initiation of the new therapy.
Key: CI, confidence interval; DOR, duration of response; FAS, full analysis set; IAS, inferential analysis set; KM, Kaplan-Meier; mITT, modified intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant. **Source:** ZUMA-2 CSR.[73]	

B.2.4.2. Patient disposition data

Figure 4 provides a summary of patient disposition data for Cohort 1 (the treated sub-set of which represents our mITT population). Brexu-cel was successfully manufactured for 71 patients leukapheresed (96%) and administered to 68 patients (92%). Of the three patients for whom brexu-cel manufacturing failed, none proceeded to additional leukapheresis (due to deep vein thrombosis, death from progressive disease and withdrawal of consent).[4] The median time from leukapheresis to delivery of brexu-cel to the study site was 16 days (range: 11–128 days); the median time from leukapheresis to administration of brexu-cel to the patient was 27 days (range: 19–134 days).[4,73] Two patients who had successful manufacturing of brexu-cel died from progressive disease before receipt of conditioning chemotherapy (Figure 4). After the receipt of conditioning chemotherapy, one patient with atrial fibrillation was deemed ineligible for infusion.[4]

Figure 4: Patient disposition data for Cohort 1 of ZUMA-2 (brexu-cel)



Source: Wang et al. 2020.[4]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of ZUMA-2 was conducted using the Downs and Black checklist[78]. Full details of the critical appraisal are provided in Appendix B. This appraisal was conducted for the initial submission, we note that the adapted CASP checklist is now preferred, this checklist is used for the assessment of the SLR studies.

Within the context of a single-arm study design, the overall risk of bias in ZUMA-2 is thought to be low. The primary endpoint (ORR) was determined by an IRRC (central assessment) per the IWG Lugano classification and provides an objective estimate of treatment effect of relevance to clinical practice (where response to treatment is the primary measure of effect). In terms of intervention, patients treated with brexu-cel in Cohort 1 reflect the administration and dosing practice of brexu-cel expected in clinical practice, in line with the dosing stipulated in the marketing authorisation.

Other aspects that could influence the relevance of ZUMA-2 to the decision problem include the generalisability of enrolled patients to those presenting in clinical practice. Overall, the risk of bias resulting from any generalisability concerns is thought to be against brexu-cel, with key differences observed in treatment history (more extensive in ZUMA-2 than optimum third-line positioning in clinical practice)

and BTKi refractory status (higher in ZUMA-2 than observed in clinical practice).See section B.2.14.3 for further discussion on the UK-generalisability of ZUMA-2.

B.2.6. Clinical effectiveness results of the relevant studies - ZUMA-2

Brexu-cel cohorts and analysis sets for which data are presented are summarised in Table 10. Five year outcomes are now available for the ZUMA-2 cohorts (Data on File) however some parameters are not reported for this latest 60-month data, in these cases a clear annotation is made and the latest published data are used.

Table 10: Summary of data available across brexu-cel cohorts and analysis sets

Cohort	Analysis set	n	Data available	Submission location
Cohort 1	mITT	68	Efficacy	Section B.2.6
Cohort 1	LTFU	27	Efficacy (sub-set of mITT)	Section B.2.6
Cohort 1	mITT	68	HRQoL	Section B.2.6
Key: HRQoL, health-related quality of life; LTFU, long-term follow-up; mITT, modified intent-to-treat. **Notes:** mITT includes all patients treated with brexu-cel at a target dose of 2 x 10^6 CAR T-cells/kg body weight as per the marketing authorisation				

The population for which data are presented throughout the rest of this section is consistent with the reporting in section B.2.3 and is limited to the mITT population:

The Modified Intent-to-treat (mITT) group: The 68 patients in Cohort 1 who received brexu-cel at a dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight. This analysis set best represents the decision problem population; is used in subsequent economic analysis and was the focus for the initial submission (TA 677).

Primary analyses are based on a cut-off date of 04 April 2024 (Data on File). At this time, the median follow-up among mITT patients was 67.8 months (range: 58.2-88.6 months). The median follow-up in LTFU patients was 70.2 months (range: 58.2-88.6). Note that the latest evidence is reported in tables, figures and listings (TFL)

format and a full clinical study report is not yet available for the latest cut of the ZUMA-2 dataset.

B.2.6.1. Response and duration of response

Table 11 summarises response data for the mITT group. Response data are reported for the 3-year data cut reported in Wang et al [58] The data available in the latest data cut (04 April 2024 (Data on File[79])) aligns with the data presented in this section.

Table 11: Summary of response using central assessment (IRRC) per IWG Lugano classification for all enrolled (leukapheresed) patients

	brexu-cel
	mITT (n = 68)
Objective response rate (CR + PR), n (%) [95% CI]	62 (91) [50.1, 73.2]
Complete response rate, n (%) [95% CI]	46 (68) [55.2, 78.5]
Partial response, n (%) [95% CI]	16 (24) [14.1, 35.4]
Stable disease, n (%) [95% CI]	3 (4) [0.9,12.4]
Progressive disease, n (%) [95% CI]	3 (4) [0.9,12.4]
Median time to response, months (range) Initial response Complete response	 2.3 -
Key: CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; IWG, International Working Group; mITT, modified intent-to-treat; PR, partial response. **Notes:** CIs are reported as per the Clopper–Pearson method used for primary analyses. **Source:** Wang 2023 [58]	

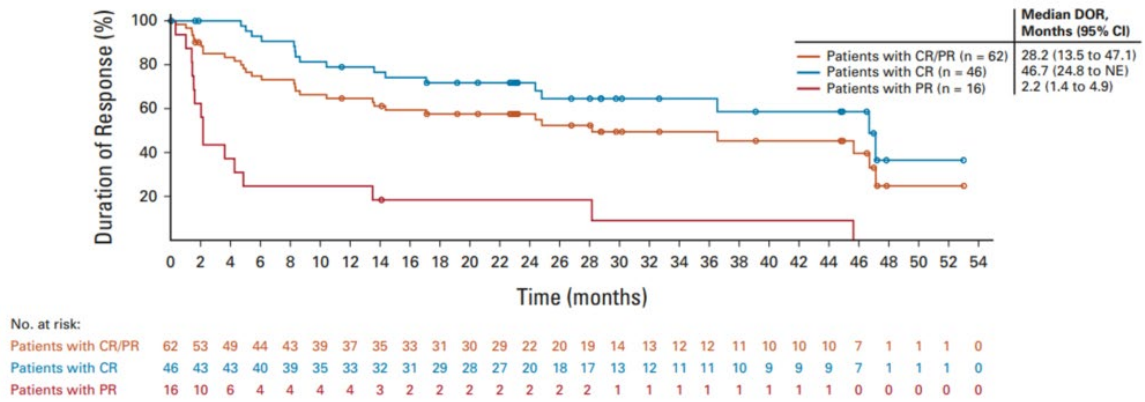
The ORR using central assessment (IRRC) per Lugano classification (primary endpoint) was 84%, with a complete response (CR) rate of 62%. [58]

Note that in the data reported in the original submission, the ORR was significantly higher than the prespecified historical control rate (25%) at a 1-sided alpha level of 0.025 ($p < 0.0001$) and thus the primary endpoint of ZUMA-2 was met.[73]

Initial response was typically observed at the first disease assessment post treatment (Week 4), with a CR observed by Month 3. Among 42 patients who initially had a PR or stable disease, 25 (60%) subsequently had a CR. [58]

The median duration of response was reported by type of response in the 3-year data reported in Wang et al.[58]. Figure 5 illustrates that the median duration of response (DOR) was 28.2 months among the 62 responders. Specifically, the median DOR was 46.7 months for patients with a complete response (CR, n=46) and 2.2 months for patients with a partial response (PR, n=16). Among the first 28 patients treated, who had a median follow-up of 51.1 months, the median DOR was 36.5 months for the 26 responders, with 29% maintaining an ongoing response.

Figure 5: Duration of response of patients in all-treated population stratified by response



Key: CI, confidence interval; CR: Complete response; DOR: Duration of response; PR: Partial response.
Source: Wang et al. 2023 [58]

B.2.6.2. Progression-free survival

PFS is reported for the 5-year mITT data cut reported in Wang et al [67] based on the 60-month tables figures and listings (TFL) from ZUMA-2 (Data on File).

Figure 6 shows that the median PFS was 25.3 months (12.7-46.6). At the time of analysis, median follow-up was 67.8 months (58.2-88.6) 44 patients (65%) had progressed or died.

Figure 6: Progression-free survival (mITT analysis; Cohort 1)

Key: CI, confidence interval; CSR, Clinical Study Report; IRRC, Independent Radiology Review Committee; NE, not estimable.
Note: Kaplan-Meier Plot of Progression-Free Survival Using Investigator Read per Cheson 2007 from Parent Study and LTFU Primary Malignant Disease Status (Cohort 1: KTE-X19)
Source: ZUMA-2 TFLs.[80]

B.2.6.3. Overall survival

OS is reported for the 5-year mITT data cut reported in Wang et al [67] based on the 60-month tables figures and listings (TFL) from ZUMA-2 (Data on File[79]).

Figure 7 shows that the median OS was 46.5 months (95% CI: 24.9–60.2). At the time of analysis (01 April 2024), 44 patients (65%) had died[4,73]

Figure 7: Overall survival (mITT analysis; Cohort 1)

Key: CI, confidence interval; OS, overall survival.
Source: ZUMA-2 TFLs (Data on File)

B.2.6.4. Health-related quality of life

Table 12 summarises EQ-5D scores, which decreased from baseline to Week 4 (reflecting the period when patients are most likely to experience acute treatment-related toxicity); however, scores in mobility, self-care, usual activities and overall health (according to the EQ-5D visual analogue scale [VAS]) improved by Month 3, with overall health returning to baseline status or better in most patients by Month 6.[4]

Table 12: EQ-5D summary by visit (Cohort 1; modified intent-to-treat)

EQ-5D-5L Dimension	Screen	Week 4	Month 3	Month 6
Mobility				
N	62	51	54	40
Patients reporting no problems, n (%)	53 (85)	25 (49)	37 (69)	30 (75)
Patients with deterioration from screening[a], n (%)	-	21 (41)	13 (24)	8 (20)
Self-care				
N	62	52	54	40
Patients reporting no problems, n (%)	59 (95)	35 (67)	45 (83)	37 (93)
	-	16 (31)	9 (17)	3 (8)

EQ-5D-5L Dimension	Screen	Week 4	Month 3	Month 6
Patients with deterioration from screening[a], n (%)				
Usual activity				
N	65	51	55	41
Patients reporting no problems, n (%)	53 (82)	22 (43)	38 (69)	30 (73)
Patients with deterioration from screening[a], n (%)	-	25 (49)	13 (24)	8 (20)
Pain / Discomfort				
N	65	54	55	42
Patients reporting no problems, n (%)	43 (66)	34 (63)	33 (60)	28 (67)
Patients with deterioration from screening[a], n (%)	-	9 (17)	13 (24)	5 (12)
Anxiety / Depression				
N	65	54	55	42
Patients reporting no problems, n (%)	49 (75)	36 (67)	38 (69)	26 (62)
Patients with deterioration from screening[a], n (%)	-	11 (20)	12 (22)	10 (24)
EQ-5D Visual Analogue Scale				
N	65	52	55	42
Mean (SD)	82.0 (15.4)	74.5 (15.6)	80.1 (15.6)	84.8 (17.5)
Median (range)	85 (75–95)	78 (60–89)	83 (70–92)	90 (80–95)
Patients with deterioration from screening[b], n (%)	-	26 (50)	16 (29)	5 (12)

Key: EQ-5D-5L, EuroQol-5 Dimension-5 Level; SD, standard deviation; VAS, visual analogue scale.
Notes: [a], deterioration defined as worsening by at least 1 level on the 5-level scale; [b], deterioration defined as VAS reduction of ≥10 on the 0-100 scale where higher scores indicate better health.
Source: Wang et al. 2020 (supplementary appendix).[4]

B.2.6.5. Minimal residual disease

Minimal residual disease (MRD) was analysed in 29 patients. Twenty-four of these patients (83%), 19 of whom had a CR and 5 of whom had a PR, had no detectable residual disease (defined as <1 in 100,000 cells) at Week 4, and 15 of 19 patients with available data (79%) had no detectable residual disease at Month 6.[4]

B.2.7. Subsequent treatments used in the relevant studies

Wang 2020 (supplementary material)[4] reported that two patients in the mITT group had an allo-SCT while in a brexu-cel-induced remission; a further [redacted] patients started a new anti-cancer therapy (non-SCT) prior to progressive disease post-brexu-cel.[73] [redacted] received subsequent anti-cancer therapy post-progression, most commonly venetoclax (10%) or ibrutinib (9%) (Table 13).

Table 13: Subsequent anti-cancer therapies (Cohort 1; modified intent-to-treat)

	brexu-cel (n = 68)
Subsequent anti-cancer therapy, n (%)	[redacted]
Venetoclax	[redacted]
Ibrutinib	[redacted]
Dexamethasone	[redacted]
Lenalidomide	[redacted]
Radiotherapy	[redacted]
Acalabrutinib	[redacted]
Bortezomib	[redacted]
Cytarabine	[redacted]
Rituximab	[redacted]
Cyclophosphamide	[redacted]
Fludarabine	[redacted]
Obinutuzumab	[redacted]
Abemaciclib	[redacted]
Antithymocyte immunoglobulin (rabbit)	[redacted]
Copanlisib	[redacted]
Decitabine	[redacted]
Fludarabine phosphate	[redacted]
Melphalan	[redacted]
Melphalan hydrochloride	[redacted]
Methotrexate	[redacted]
Key: CSR, clinical study report. **Source:** ZUMA-2 CSR.[73]	

B.2.8. Subgroup analysis

The ORR was consistent across pre-planned subgroups of Cohort 1, including those defined by baseline demographics, clinical characteristics and treatment history. No pre-planned subgroup had an ORR < 75%, and several demonstrated 100% response. All pre-planned subgroup analyses are provided in Appendix E.

B.2.9. Meta-analysis

Meta-analysis is not required for brexu-cel as ZUMA-2 singularly provides data for this intervention. ZUMA-2 is a single-arm study, and comparator data are sourced

from the literature. In the previous submission, the committee concluded that data from McCulloch et al (2020) should be used to inform the clinical effectiveness evidence for the comparator [66]. The evidence base has not changed since the previous appraisal (see Appendix B for a summary of comparator evidence retrieved in the updated systematic literature review and full description of McCulloch 2020).

B.2.10. Indirect and Mixed Treatment Comparisons

Indirect and mixed treatment comparisons were not conducted (please see above).

B.2.11. Adverse reactions

The section is based upon the ZUMA-2 trial data cut from October 2023 (Data on File[79]). The latest data cut from this trial (01 April 2024) does not report the data to the same level of granularity.

The population for which data are presented throughout this section is:

The safety analysis set: The 68 patients in Cohort 1 that received brexu-cel at a dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight. This analysis set is equivalent to the mITT group that is reported for efficacy outcomes.

B.2.11.1. Safety summary

All patients treated experienced at least one adverse event (AE). Table 14 presents an overview of AEs for the safety analysis set of Cohort 1 based on evidence from the 36-month data; tabulations were not updated in the 48- or 60-month data. Approximately two thirds of patients experienced a serious adverse event (SAE), and just over half of patients experienced an SAE deemed related to brexu-cel. SAEs that occurred in at least three patients are provided in Appendix F.

There were two deaths observed due to AEs in the first year of follow-up: one patient experienced pneumonia on Day 37 that was considered related to conditioning chemotherapy, and one patient experienced staphylococcal bacteraemia on Day 134 that was considered related to conditioning chemotherapy and brexu-cel.[4] Three new fatal AEs were observed at 36 month follow-up but none were related to brexu-cel[58]; no fatal AEs were observed in the later follow-up data (48 and 60-month).

Table 14: Safety summary (Cohort 1; safety analysis set)

	brexu-cel (n = 68)
Any adverse event, n (%) Worst Grade 3 Worst Grade 4 Worst Grade 5	[redacted]
Any serious adverse event, n (%) Worst Grade 3 Worst Grade 4 Worst Grade 5	[redacted]
Any brexu-cel-related adverse event, n (%) Worst Grade 3 Worst Grade 4 Worst Grade 5	[redacted]
Any brexu-cel-related serious adverse event, n (%) Worst Grade 3 Worst Grade 4 Worst Grade 5	[redacted]
Source: Table 14.3.1.1.1a; data cutoff 05Oct2023	

B.2.11.2. Common adverse events

Table 15 summarises treatment-emergent AEs that occurred in ≥ 30% of patients treated at target dose based on evidence from the 48-month TFLs (as above). These included pyrexia [redacted] neutropenia [redacted], thrombocytopenia [redacted], anaemia [redacted] and hypotension [redacted].[4] Data are reported from the 48-month data-cut (October 2023) where available, otherwise reported from the pivotal publication.

Table 15: Common adverse events (AEs that occurred in ≥ 30% of patients) (Cohort 1; safety analysis set)

n (%)	brexu-cel (n=68)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any adverse event	68 (100)	0	1 (1)	11 (16)	46 (68)	2 (3)
Pyrexia*	[redacted]					
Neutropenia*	[redacted]					
Thrombocytopenia*	[redacted]					
Anaemia*	[redacted]					

n (%)	brexu-cel (n=68)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypotension	35 (51)	4 (6)	16 (24)	13 (19)	2 (3)	0
Chills	28 (41)	17 (25)	11 (16)	0	0	0
Hypoxia	26 (38)	2 (3)	10 (15)	8 (12)	6 (9)	0
Cough	25 (37)	14 (21)	11 (16)	0	0	0
Hypophosphatemia	25 (37)	2 (3)	8 (12)	15 (22)	0	0
Fatigue	24 (35)	10 (15)	13 (19)	1 (1)	0	0
Headache	24 (35)	15 (22)	8 (12)	1 (1)	0	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Hypoalbuminaemia	23 (34)	5 (7)	17 (25)	1 (1)	0	0
Hyponatraemia	22 (32)	15 (22)	0	7 (10)	0	0
Nausea	22 (32)	11 (16)	10 (15)	1 (1)	0	0
AAT increase	21 (31)	13 (19)	2 (3)	5 (7)	1 (1)	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Hypokalaemia	21 (31)	12 (18)	4 (6)	3 (4)	2 (3)	0
Tachycardia	21 (31)	14 (21)	7 (10)	0	0	0

Key: AAT, alanine aminotransferase; AE, adverse event.
Source: Wang et al. 2020[4] *Table 14.3.1.1.1a; data cutoff 05Oct2023

Common adverse events observed are reflective of cytokine release syndrome (CRS), neurological events and B-cell aplasia. These are described in detail below.

B.2.11.2.1. Cytokine release syndrome

CRS is triggered by the activation of T-cells on engagement of their T-cell receptors or CARs with cognate antigens expressed by tumour cells.[81] The activated T-cells release cytokines and chemokines, as do bystander immune cells. CRS typically manifests as constitutional symptoms such as fever, nausea, malaise, fatigue, myalgia, hypotension and hypoxia, but can result in significant haemodynamic instability and/or in more severe cases other organ toxicity. Mild to moderate CRS is usually self-limiting and can be managed with close observation and supportive care. Severe CRS necessitates medical management with tocilizumab alone or with steroids. However, CAR T delivery centres are increasingly well experienced in managing these toxicities in a way that, generally, keeps them from becoming severe. Patients at high risk of severe CRS include those with high disease burden,

those with comorbidities, and those who develop early onset CRS within 3 days of cell infusion.

Table 16 summarises CRS events. Of the mITT population, 91% experienced a CRS event. Most of these events were Grade 1–2; 15% experienced a CRS event of Grade ≥ 3. Median time to onset of CRS was 2 days and all CRS events resolved after a median duration of 11 days. CRS events by Grade are detailed in Appendix F. No Grade 5 (fatal) CRS events occurred.

Table 16: Summary of CRS events (Cohort 1; safety analysis set)

	brexu-cel (n = 68)
Any CRS event, n (%) Grade ≥ 3	62 (91) 10 (15)
Symptom of CRS, n (%) Pyrexia Hypotension Hypoxia Chills Tachycardia Headache Alanine aminotransferase increased Aspartate aminotransferase increased Fatigue Nausea	 62 (91) 35 (51) 23 (34) 21 (31) 16 (24) 15 (22) 10 (15) 9 (13) 9 (13) 9 (13)
CRS management, n (%) Tocilizumab Corticosteroids Vasopressors	 40 (59) 15 (22) 11 (16)
Median time to onset of CRS, days (range)	2 (1–13)
Median time to onset of Grade 3 or higher CRS, days (range)	4 (1–9)
Median duration of CRS events, days	11
Patients with resolved CRS events, n/N (%)	62/62 (100)
Key: CRS, cytokine release syndrome. **Source:** Wang et al., 2020.[4]	

B.2.11.2.2. Neurological events

The mechanism underlying CAR T-cell associated neurotoxicity is currently unknown.[81] Symptoms can be hard to predict, and neurological evaluation is

recommended at least every 8 hours post-CAR T-cell infusion. Mild neurological events can be managed with close observation and supportive care, but moderate to severe events require medical management with steroids alone or in conjunction with tocilizumab. Patients at high risk of neurological events include those with high disease burden, those with prior history of neurological comorbidities, and those who develop CRS.[82]

Since development of the ZUMA-2 protocol, these symptoms are referred to under the umbrella term of immune effector cell-associated neurotoxicity syndrome (ICANS). This term was not in circulation prior to 2019 and neurological events for ZUMA-2 mITT are summarised according to their original protocol definitions.

Of patients treated in Cohort 1 of ZUMA-2, 63% experienced a neurological event, approximately half of which were Grade ≥ 3, as summarised in Table 17. Nearly all neurological events resolved after a median duration of 12 days (Table 17). Neurological events by Grade are detailed in Appendix F.

No Grade 5 (fatal) neurological events occurred. One patient had Grade 4 cerebral oedema but fully recovered with aggressive multimodality therapy. The neurotoxicities fully resolved, with the patient remaining in CR 24 months later.

Table 17: Summary of neurological events (Cohort 1; safety analysis set)

	brexu-cel (n = 68)
Any neurological event, n (%) Grade ≥ 3	43 (63) 21 (31)
Symptom of neurological event, n (%) Tremor Encephalopathy Confusional state Aphasia	 24 (35) 21 (31) 14 (21) 10 (15)
Neurological event management, n (%) Tocilizumab Corticosteroids	 18 (26) 26 (38)
Median time to onset of neurological event, days (range)	7 (1–32)
Median time to onset of Grade 3 or higher neurological event, days (range)	8 (5–24)
Median duration of neurological events, days	12

	brexu-cel (n = 68)
Patients with resolved neurological events, n/N (%)	37/43 (86)
Source: Wang et al., 2020.[4]	

B.2.11.2.3. B-cell aplasia

B-cell aplasia describes low numbers of, or absent B-cells, reflected in low blood cell counts (cytopenia) that can reduce a patients' ability to fight infection. B-cell aplasia is often present in MCL patients because of their disease and exacerbated in r/r MCL patients as a result of treatments that destruct healthy B-cells alongside cancerous B-cells. Conditioning chemotherapy and CAR T-cell therapy can also result in such destruction, although the exact mechanisms are unclear.

Grade 3 or higher cytopenias included neutropenia ([redacted]), thrombocytopenia ([redacted]) and anaemia ([redacted]) according to the 48-month datacut.[4] A total of [redacted] of treated patients had cytopenias of Grade 3 or higher more than 90 days after the infusion of brexu-cel, including neutropenia ([redacted]), thrombocytopenia ([redacted]) and anaemia ([redacted]). Infection of Grade 3 or higher occurred in [redacted] of patients, with serious infection of Grade 3 or higher occurring in [redacted] of patients. Infection events by Grade are detailed in Appendix F.

No cases of replication-competent retrovirus, Epstein–Barr virus–associated lymphoproliferation, haemophagocytic lymphohistiocytosis, or brexu-cel–related secondary cancers were reported in any of the data cuts (up to 60 months)

B.2.11.3. Safety overview

The safety profile observed in ZUMA-2 is typified by CRS, neurological events and B-cell aplasia. CRS and neurological events typically resolve, while infections are more persistent. However, start of B-cell recovery was observed in the majority of patients who had an ongoing response at 6 months (21 of 34 patients [62%]).[4]

Since the availability of CAR T therapies, clinical practice has significantly evolved and clinicians are increasingly comfortable in managing toxicity related to the therapy; subsequently the safety profile is improved in the real-world compared to the ZUMA-2 study.[83] Emerging real world evidence from the UK indicates that rates of Grade ≥ 3 CRS and neurological events in r/r MCL patients receiving brexu-cel

are lower than those reported in ZUMA-2 (12% versus 15% and 22% versus 31%, respectively)[25]. This is in line with other indications, where real-world data of high-grade lymphoma patients treated with CD19 CAR T-cell therapy in NHS England has shown lower rates of Grade ≥ 3 CRS and Grade ≥ 3 neurological events than reported across the pivotal clinical trials[84]. Longitudinal studies support improvements in AE - In a paper published in Oct-23, outcomes for 726 DLBCL patients were compared, with patients divided into those approved for treatment between Dec-18 to Dec-19 (DLBCL-ERA-1) and those approved for treatment between Jan-20 to June-22 (DLBCL-ERA-2). Despite objectively poorer baseline characteristics in DLBCL-ERA-2 versus DLBCL-ERA-1, both efficacy and safety outcomes significantly improved in ERA-2[85]. It is reasonable to conclude that the safety profile of brexu-cel will continue to improve with additional clinic experience.

B.2.12. Ongoing studies

ZUMA-2 is the main clinical trial for this evaluation. Several other studies exist for brexu-cel within MCL, however, none of these are applicable to the decision problem being evaluated here, due to their differing scope. Other ongoing and completed studies (including those conducted in real world settings) are summarised in Appendix B, section 1.4

B.2.13. Additional clinical evidence

The SACT database analysis

B.2.13.1. Overview

Since the introduction of brexu-cel through the Cancer drug fund (CDF), real-world data has routinely been collected as part of the Systemic Anti-Cancer Therapy (SACT) dataset, provided by the National Disease Registration Service, NHS England[86]. The SACT database collects systemic anti-cancer therapy treatment patterns and outcomes on a national scale from all NHS England providers. SACT collected data on brexu-cel as part of the managed access agreement following entry of brexu-cel to the CDF in 2021. SACT evidence is presented as a scenario analysis in the cost-effectiveness analysis (but note limitations described below).

B.2.13.2. Methods

The NHS England Blueteq® system provide a reference list of all patients with an application for treatment with brexu-cel for r/r MCL. The Blueteq applications were linked to Patient NHS numbers within the NDRS routinely collected data to provide SACT treatment history. Inclusion criteria comprised adult patients with relapsed/refractory MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTKi (ibrutinib and/or acalabrutinib) and who were approved for CAR T therapy. All patients were traced to obtain their vital status using the personal demographics service (PDS); NHS numbers linked SACT records to CDF applications for brexu-cel in the Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application, including information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT. Patients were traced for their vital status on 12 January 2024. This date was used as the follow-up date (censored date) if a patient was still alive. The median follow-up was the patients' median observed time from the start of their treatment to death or censored date. The only endpoint evaluated was OS, calculated from the CDF brexu-cel treatment start date (i.e., survival from the treatment start date was calculated using the patient's earliest treatment date in the SACT dataset for the treatment of interest).

B.2.13.3. Patients and treatment

Between 19 January 2021 and 30 September 2023, 97 applications for brexu-cel were identified in the Blueteq system. Following appropriate exclusions, 92 unique patients who received treatment were included for analyses. The median age of the analytic population was 67.5 years (69 and 67 years for males and females, respectively). Of all patients, 20% were under 60 years; 42% were aged 60-69 years and 38% were aged 70 years or over. Performance status was missing for 46% of patients; 38% had an ECOG score of 0 or 1; mIPI classification was not reported.

B.2.13.4. Brexu-cel clinical effectiveness

Of the 92 patients who received brexu-cel, [redacted] patients survived to the end of the follow-up period (25 September 2024). The minimum follow-up was 11.9 months (362 days) from the last CDF application. The median follow-up time was 17.2

months (522 days). The maximum follow-up for survival was 44.2 months (1,345 days) Figure 8 shows the Kaplan-Meier curve for OS, censored at 25 September 2024; median survival was [redacted]. OS at 6 months was [redacted], at 12 months [redacted], at 18 months [redacted], at 24 months [redacted], and at 36 months [redacted]. Sensitivity analysis using a cohort of patients with a minimum follow-up of six months provided results consistent with analysis of the full analytic population. Response and duration of response were not reported in the SACT database for brexu-cel.

Figure 8: SACT Kaplan-Meier survival plot (n=92)

B.2.13.5. Further evidence needs

The SACT data provided relate to 92 pts receiving brexu-cel between 19 January 2021 and 30 September 2023 and followed up to 12 January 2024.

There would be high research value in including a larger sample of patients followed up across a longer period (for example to the maximum time allowed within the managed access contract). This was requested by the Company but not granted.

Patient enrolment spanned the two changes to the BSH guidelines described in section B.1.3.4.3. Sub-set analysis was requested by the company to differentiate cohorts pre and post the 2022 practice updates. This request was not granted.

The availability of data best representing current CAR T clinical practice is important as there have been rapid evolutions in CAR T delivery and management since 2021; if these changes are not accounted for, the benefits of CAR T are underestimated.

B.2.13.6. Further comments

As explained in our Decision Problem Form, Scope Consultation Response and correspondence with NICE/NHSE, in August 2022 UK clinical practice in the use of brexucabtagene autoleucel in R/R MCL changed. During the first year of brexucabtagene autoleucel use in the UK, drop-out between approval and treatment administration was high, with [redacted] of patients experiencing “manufacturing failure”, compared to [redacted] in ZUMA-2. Early diagnosis and referral were identified as important steps to improve success. In August 2022 an addendum to BSH guidelines was issued, specifically to minimise delays initiating brexucabtagene autoleucel and improve outcomes. Subsequent to this change, the manufacturing failure rate has fallen [redacted]. It would be reasonable to expect this change to translate into improvements in outcomes.

The current SACT report provided to Gilead and NICE has a treatment cut-off date of 30 September 2023 and is unrepresentative in that it only reflects around a year of current treatment practice. In order to evaluate the full benefits of brexucabtagene autoleucel as currently used in the UK, we requested an extension to the SACT data collection to a treatment cut-off date of 31 December 2024 and a separate analysis of cohorts treated before and after August 2022. It is acknowledged that the Data Collection Agreement anticipated the end of the data collection period to be December 2023, however this was agreed in December 2020 when neither Gilead nor NHS England had knowledge of the subsequent addendum to the BSH Guidelines which substantially altered the treatment pathway. We believe that the subgroup analysis described above and the extension to the patient tracking timeline will likely capture potential overall survival gains resulting from this change in practice and provide stronger evidence allowing for a higher quality NICE submission with reduced uncertainty.

Proceeding with this appraisal on the basis of the unrepresentative SACT data and misleading analysis provided to date, would create a risk of an unfair procedure and potential unreasonable appraisal outcome with significant patient impact. For this reason the economic analysis provided in this submission is considered a more reliable estimate of the expected effects of using brexu-cel in clinical practice than the SACT data and the clinical evidence from SACT is not used.

B.2.14. Interpretation of clinical effectiveness and safety evidence

B.2.14.1. Principal findings from the clinical evidence

The ZUMA-2 trial demonstrates that brexu-cel provides an effective treatment option for patients with r/r MCL who have previously received a BTKi. Brexu-cel critically serves a patient group who had significant unmet medical need and a very poor prognosis prior to CAR T availability; patients were unlikely to achieve sustainable response with further treatment and were not expected to survive beyond a year (see B.1.3); brexu-cel provides an unmatched treatment option in this setting.

In ZUMA-2 over 90% of patients treated with brexu-cel achieved an objective response, with two thirds of patients achieving a CR. At the time of 5-year data analysis (01 April 2024), 17 patients (37%) remained in ongoing response (all in CR) and median OS was estimated at 46.5 months, far exceeding the typical life expectancy of patients with r/r MCL who have previously received a BTKi (see section B.2.6.1). Such high responses are unprecedented in the post-BTKi setting

At a median follow-up of 67.8 months (range: 58.2-88.6), median PFS was 25.3 months (95% CI 12.7-46.6) and median OS was 46.5 months (95% CI 24.9-60.2). Over 80% of patients treated with brexu-cel survived for at least 12 months, with the probability of survival to 60 months estimated at 38.5% (95%CI 26.7-50.1).

While key AEs associated with brexu-cel comprise CRS, neurological events and infections, in real-world UK practice the rates of Grade ≥ 3 CRS and neurological events have been lower than those reported in ZUMA-2 (12% versus 15% and 22% versus 31%, respectively)[25]. These disparate rates of AEs between trial and UK real-world settings suggest that CAR T centres are increasingly adept at preventing serious AEs. Moreover, no new safety signals were detected in the 5-year outcomes

data follow-up and no secondary malignancies were reported in LTFU[67]. Based on other CAR-T indications and real-world evidence from YESCARTA[85] it is reasonable to expect a further improvement in the safety profile of brexu-cel with time.

The reported survival rates are unprecedented in the post-BTKi non-CAR T setting, with observational studies reporting post-BTKi treatment outcomes estimating median OS at between 5.5 months (for patients who are not able to access subsequent treatment) to 14.0 months (for patients on optimal management) [32,51,87-90].

B.2.14.2. Strengths and limitations of the evidence base

ZUMA-2 was the first prospective clinical trial in the r/r MCL post-BTKi setting and provides high-quality evidence of ground-breaking treatment effect for a patient group that previously had no established treatment options. The ZUMA-2 evidence represents the longest term follow-up for CAR T treatments in r/r MCL: at a median of 67.8 months (range: 58.2-88.6) at the latest data lock (01 April 2024); the trial remains ongoing with 27 patients enrolled in LTFU to date.

The duration of response in ZUMA-2 supports an expectation of continued long-term treatment benefit from brexu-cel (17 patients remain in ongoing response as of April 2024). As MRD-negative status has previously been shown to correlate to longer PFS and OS in the MCL setting,[91,92] the high level of MRD-negativity observed in patients treated with brexu-cel (83% at 4 weeks) further underscores the potential for long-term survivorship associated with the treatment. These results are consistent with emerging real-world outcomes for brexu-cel in the third-line setting [25,32,63,69].

In absence of a true ‘standard of care’ in the third-line setting, an appropriate control arm for brexu-cel could not be pre-defined. Moreover, a placebo control arm for ZUMA 2 was deemed unethical given that patients had already failed multiple prior therapies. It remains challenging to identify an alternative treatment for the patients included in this submission as brexu-cel has now become an established option in patients who are eligible for CAR T treatment. The comparator data for this submission were, therefore, necessarily drawn from a historical post BTKi cohort.

B.2.14.3. Applicability of clinical evidence to practice

The generalisability of ZUMA-2 to a UK clinical setting, already established in the initial brexu-cel submission, continues to be supported by emerging RWE. ZUMA-2 represents heavily pre-treated patients who had failed all standard treatment options, with 56% classified as moderate to high risk per sMIPI, and 68% refractory to ibrutinib. RWE suggests that patients receiving brexu-cel in the UK are slightly less pre-treated, with lower numbers refractory to ibrutinib (30%) but with a higher proportion classified as moderate to high risk according to sMIPI (78%)[25].

Demographically, patients enrolled in ZUMA-2 (median age of 65 years in ZUMA-2)[83] have been found to be comparable to UK patients with r/r MCL in the real-world (median age of 68 years [range 41-78]) and representative of patients expected to receive brexu-cel in UK clinical practice. However, it remains expected that over time, it would be patients slightly younger than the 'average' patient who would be considered for brexu-cel treatment, specifically those free of significant co-morbidities and end-organ dysfunction in line with the ZUMA-2 eligibility criteria.

B.2.14.3.1. Prior and subsequent therapy

The previous therapies received by participants in ZUMA-2 are considered generally reflective of UK clinical practice, except for those in the trial who received prior acalabrutinib, which does not have marketing authorisation in the EU/UK, where standard second-line treatment is ibrutinib. There are no known differences between these two BTKi agents, and sub-group analyses (Appendix E) show no clear differences in response to brexu-cel based on type of prior BTKi.

Therapies received after brexu-cel by the trial population of ZUMA-2 are also reflective of UK clinical practice, and varied substantially given the lack of 'standard of care' in the later-line r/r MCL setting (unchanged since 2021 [see B.1.3.4]). While venetoclax has previously been made available for off-label compassionate use in UK patients and the most common post- brexu-cel treatment in ZUMA-2, it is not indicated for MCL nor widely adopted due to a lack of durable response[93] However, as emphasised in the initial submission, the potential impact of the use of these non-standard treatments post- brexu-cel is expected to be limited.

B.2.14.3.2. Summary

ZUMA-2 comprises 67.8 months (range: 58.2-88.6) of patient follow-up, the longest for CAR T in the post-BTKi r/r MCL setting. The persistent duration of brexu-cel response supports strong optimism for long-term survivorship in r/r MCL patients.

Reported survival rates (median PFS 25.3 months; median OS 46.5 months) are unprecedented in the post-BTKi setting prior to the availability of CAR T. Outcomes post BTKi pre-brexu-cel were extremely limited with studies reporting median OS at between 5.5 months (for patients who are not able to access subsequent treatment) to 14.0 months (for patients on optimal chemo-immunotherapy, i.e. R-BAC) [32,51,87-90]

From the UK health-care-delivery perspective, AEs relating to CRS and neurological events are increasingly well managed in UK CAR T centres, and the infrastructure required to deliver CAR T therapies in UK clinical practice is now firmly established. Brexu-cel serves a patient group with significant unmet medical need prior to CAR T introduction. If post BTKi r/r MCL patients did not have access to brexu-cel there would be no effective management option for these patients in current UK practice.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic literature review was conducted to identify relevant cost-effectiveness studies. The search strategy from the original submission was re-run on 11 November 2024. Full details of these searches and the findings are reported in Appendix G.

The search identified 5 cost-effectiveness studies for brexu-cel for patients with r/r MCL published since completion of the original submission— Marchetti 2023[94], Ball 2022[95], Loupas 2022[96], Petersohn 2022[97] and Simons 2021[97]. All studies developed partitioned survival models to estimate lifetime events and costs, incorporating long term survival (LTS) assumptions at 5-years. In each case, brexu-cel clinical effectiveness evidence was taken from ZUMA-2 findings. Four of the studies compared brexu-cel against a mixed basket of chemotherapies, with one study including BTKis in this basket[97] . Only one study compared brexu-cel against R-BAC (Marchetti 2023)[94]. This study was conducted in an Italian setting resulting in an estimated incremental cost-effectiveness ratio (ICER) of €64,798 per QALY gained. Only one study, Petersohn 2022[98], was evaluated in the English setting. This study utilised mixture-cure-methods and, based on 25.5 month ZUMA-2 data, estimated an ICER of £67,713 per QALY gained when comparing brexu-cel against a mixed standard of care. All studies used the local list price of brexu-cel in their analysis.

No studies were identified assessing the decision problem: i.e. evaluating the cost-effectiveness of brexu-cel in the management of r/r MCL in patients who have previously received two or more lines of therapy including a BTKi, in the UK setting and using the most up to date evidence from the ZUMA-2 study. We therefore conducted a de novo cost-effectiveness analysis to support this submission.

B.3.2. Economic analysis

B.3.2.1. Patient population

The patient population considered in this analysis aligns with the population assessed in the original submission and comprises adults with r/r MCL who have previously received two or more lines of therapy including a BTKi, in accordance with the EMA licence for brexu-cel and reflective of the pivotal ZUMA-2 trial population.

As described in Section B.2.3, ZUMA-2 investigated the safety and efficacy of brexu-cel in patients with r/r MCL. Specifically, in patients where disease had progressed on (i) anthracycline- or bendamustine-containing chemotherapy, (ii) an anti-CD20 antibody, and (iii) a BTKi (ibrutinib and/or acalabrutinib). The mean age of the ZUMA-2 population was 63.2 years.

Two practising NHS England Consultants were interviewed in January 2025, to ensure our economic approach for this resubmission was consistent with expert clinical expectations, as described in Section B.3.14. Consultants surmised that based on current practice, the ZUMA-2 mITT group was representative of patients likely to receive brexu-cel in an NHS England clinical setting (ie r/r MCL after progression or failure on BTKi and in line with current BSH guidelines [16]).

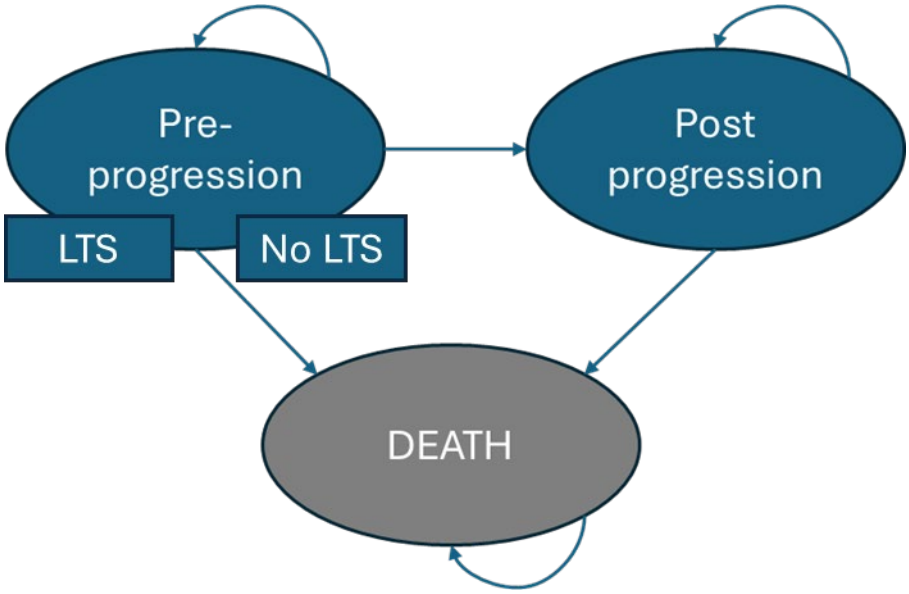
B.3.2.2. Model structure

A de novo cost-effectiveness model was developed in Microsoft Excel® for the original submission (TA 677)[66]; model inputs were updated for this resubmission, but the underlying framework is consistent with the original submission model.

Note that the original submission fitted a mixture-cure-model (MCM) to the ZUMA-2 24-month data; the committee preferred an alternate approach based on differentiation of a cure timepoint for patients who did not progress (herein referred to as the long term survivorship, LTS, timepoint) An MCM was not explored for this re-submission and ZUMA-2 data were used to support a more simple LTS approach.

A partitioned survival approach with three health states (pre-progression, post-progression and death) was specified. Figure 9 presents the model's structure.

Figure 9: Model structure schematic



Key: LTS: Long-term survivorship

The partitioned survival model has three mutually exclusive health states:

- Pre-progression
- Post-progression
- Death

All patients begin the model in the pre-progression health state. This health state is further categorised to distinguish patients who remain in pre-progression for prolonged periods. This was done to explicitly capture the proportion of brexu-cel patients who remain in pre-progression as 'long-term survivors' (LTS).

This approach was consistent with both previous published analyses[94-98] and previous NICE technology appraisals (Table) where the step-change in outcomes with CAR-T therapies is incorporated.

From the pre-progression health state, patients may transition to the other health states or remain in this health state at each model cycle. Following progression, patients are unable to transition back to the pre-progression health state and can only transition to the 'death' state; an absorbing health state. At any time point in the

model, a patient can be alive with non-progressed disease (pre-progression, further categorised by LTS), alive with progressed disease (post-progression) or dead.

In a partitioned survival model, OS and PFS are modelled independently and the proportions of patients in each health state over time are derived directly from the OS and PFS projections. The proportion of patients who are dead in each model cycle is estimated by one minus estimated survival, the proportion of those in the post-progression state is estimated by gap between OS and PFS projections, and the proportion in the pre-progression state is the gap between the PFS projection and the x axis. The approach is representative of the clinical pathway for r/r MCL in that a patient's treatment course and outcomes will depend largely on whether their disease has progressed or remained progression free (see section B.3.3 through B.3.5).

B.3.2.2.1. General model settings

The analysis perspective is that of the NHS and Personal Social Services (PSS) in England for costs and direct health effects on individual patients for outcomes, in line with the NICE reference case.[99]

The model uses a 1-month cycle length (30.44 days). Brexu-cel acquisition and administration costs are not half-cycle corrected; they are assumed to be administered at the start of the model. This is consistent with the dosing of brexu-cel, which is given as a one-off infusion. For simplicity, the quality of life and cost implications of AEs, except for ongoing intravenous immunoglobulin (IVIG) therapy, are assumed to occur at the start of the model (see Sections B.3.4.3 and B.3.5.4); as such, these are neither half-cycle corrected or subject to time-preference discounting. Again for simplicity, to avoid complexities arising from tracking time-dependencies in a cohort-level model, subsequent alloSCTs are assumed to occur at the start of the model.

All other costs and outcomes – i.e. those captured after the initial model cycle – are half-cycle corrected; assumed to fall half-way through a cycle; to better account for the fact that some (costs) can occur at any point during the cycle, while others (health outcomes) are spread across time.

A discount rate of 3.5% per annum is applied to costs and QALYs, as specified by the NICE reference case.[99] The cost-effectiveness analysis assumes a lifetime time horizon. The analysis time horizon is limited to 50 years, which is sufficient to capture the plausible maximum life expectancy for the ZUMA-2 mITT patient group (mean age 63 years). This approach is considered to be appropriate, given the data-driven expectation that brexu-cel will offer long-term survivorship for some patients.

B.3.2.2.2. Comparison to previous NICE technology appraisals

In the previous submission, the only published NICE single technology appraisal of treatment for relapsed or refractory MCL was TA502; *Ibrutinib for treating relapsed or refractory mantle cell lymphoma*; this guidance was published on 31 January 2018.[52]

For this resubmission, a search was conducted on the NICE website on 28 Oct 2024, with search term “mantle cell lymphoma”. The search did not find any additional relevant NICE technology appraisals for R/R MCL published between 2021 and 2024 (apart from the original submission for brexu-cel in this indication). We broadened the search to include other brexu-cel TAs in order to explore whether methodologies or inputs might be relevant to our model and included TA 893.[100]

Table 18 compares the features of the current economic appraisal to these TAs.

Table 18: Features of the current economic analysis versus previous appraisals

Factor	Previous appraisals			Current appraisal	
Title	**TA677: Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma**	**TA893: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over** [100]	**TA502: Ibrutinib for treating relapsed or refractory mantle cell lymphoma** [101]	**Chosen values**	**Justification**
Model structure	Partitioned survival Markov model	Partitioned survival Markov model	Partitioned survival Markov model	Partitioned survival Markov model	In line with previous technical appraisal (TA677), a partitioned survival model is appropriate
Health states considered	Pre-progression, post-progression and death (pre-progression differentiates pre and post LTS states)	Event-free survival, progressed disease, death (event free survival differentiates between pre and post cure)	Pre-progression, post-progression and death	Pre-progression, post-progression and death (pre-progression differentiates pre and post LTS states)	In line with previous technical appraisal (TA677), these health states reflect disease pathway.
Time horizon	50 years (lifetime)	57 years (lifetime)	15 years (lifetime)	50 years (lifetime)	A lifetime horizon is appropriate; long enough to reflect all important differences in costs or outcomes between the technologies being compared, in line with the reference case.[99]
Patient population	R/R MCL patients who have failed two or more lines of therapy including a BTKi	R/R B-precursor acute lymphoblastic leukaemia patients	R/R MCL patients	R/R MCL patients who have failed two or more lines of therapy including a BTKi	In line with decision problem and marketing authorisation
Intervention	Autologous anti-CD19-transduced CD3+ cells (brexu-cel)	Autologous anti-CD19-transduced CD3+ cells (brexu-cel)	Ibrutinib	Brexucabtagene autoleucel	In line with decision problem
Comparators	R-BAC	Philadelphia-chromosome-negative (FLAG-based combination chemotherapy; inotuzumab ozogamicin) Philadelphia-chromosome-positive (Inotuzumab ozogamicin; FLAG-IDA)	R-CHOP, R-CVP, FCR, RC	R-BAC	CAR-T is now the recommended post BTKi management for MCL patients; R-BAC would be an alternative option for r/r MCL patients who have previously received 2 or more lines of therapy including BTKi inhibitor, if CAR-T were not available; R-BAC was the committee's preferred comparator in 2021 [16])

Excess mortality assumption (LTS)	Applied: The committee considered higher mortality risks than the general population but did not specify a single value applied to background mortality for LTS	Applied; Patients assumed to be cured incur excess mortality compared to general population; SMR of 1.09 applied to the background mortality Source: Maurer et al 2014	Not applied	Applied; SMR of 1.09 applied to the background mortality for LTS Source: Maurer et al 2014	In line with prior technical appraisals, an SMR of 1.09 was deemed appropriate from LTS and validated by NHS consultants; Substantial additional data is now available showing long term survival after treatment with brexu-cel
Long term survivorship timepoint assumption	Long term survivorship timepoint base case: 5 years	Long term survivorship timepoint base case: 3 years Rationale: For patients who receive alloSCT, there is generally a higher death rate during the first 2 years post-SCT which rapidly reduces thereafter.	Not applied	Long term survivorship timepoint base case: 4 years Rationale: Wang 2024 report very few disease related deaths or progressions >48 months after treatment initiation in ZUMA-2	In line with ZUMA-2 data [67] and emerging RWE[25] , a 48-month LTS timepoint is not contradicted.
Source of utilities	Pre-progression utility: ZUMA-2 patient-reported EQ-5D-5L data Post-progression utility: Drived from previously published estimates in TA502	Utility for pre-infusion, event-free survival and progressed disease states: ZUMA-3 HRQoL data Utility for cured patients: General population utility AE utility: Literature-based utilities	Pre-progression: 0.78; Post-progression: 0.68; R-chemo disutility: 0.20; EQ-5D-3L data from pooled Phase III RCT (RAY/MCL3001) and Phase II study (SPARK/MCL2001) data Impact of R-chemo toxicity on HRQoL taken from expert clinical advice and compared with available published literature.	Pre-progression: 0.824 (ZUMA-2 EQ-5D-3L data); Pre-progression, LTS: 0.821 (general population utility); Post-progression: 0.724 (estimated based on TA 502 reported increment)	In line with the reference case[99]; patient -based utilities are preferred; LTS utility is based on general population utility in line with other appraisals, post-progression utility is estimated in line with previous submission
Source of costs	Standard UK sources including eMIT and MIMS for drug costs, and NHS reference costs for resource use costs.	Generic drug costs were sourced from eMIT. Terminal care costs from Geoghiou and Bardsley 2014 All other cost inputs were sourced from NHS reference costs, PSSRU unit costs, or previous NICE technical appraisal.	Standard UK sources including eMIT and MIMS for drug costs, and NHS reference costs for resource use costs.	Standard UK sources including eMIT and MIMS for drug costs, and NHS reference costs for resource use costs.	UK sources considered most reflective of costs incurred by NHS England.

Key: AE, adverse event; alloSCT, allogeneic stem cell transplant BTKi, Bruton tyrosine kinase inhibitor; eMIT, electronic Market Information Tool; FCR, fludarabine, cyclophosphamide, rituximab; HRQoL, health-related quality of life; LTS, long term survival; MCL, mantle cell lymphoma; MIMS, Monthly Index of Medical Specialties; NHS, National Health Services; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; R/R, relapsed or refractory; R-BAC, rituximab, bendamustine and cytarabine; RC, rituximab plus chemotherapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RCT, randomised controlled trial; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; RWE, real-world evidence; SMR, standardised mortality ratio

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention

The intervention, brexu-cel, is implemented in the model as per the marketing authorisation and is reflective of the decision problem described in Section B.1.1.

Brexu-cel is an autologous CAR T-cell product in which a patient's T-cells are engineered to express receptors that result in elimination of CD19-expressing cells. Following CAR engagement with CD19+ target cells, a downstream signalling cascade is activated to stimulate proliferation of the CAR T-cells and direct killing of target cells. The process of generating and administering the engineered T-cells is described in Section B.1.2.

Brexu-cel is a single-infusion product, for autologous and intravenous use only. Each single-infusion bag contains a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg. Prior to infusion, patients are treated with a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day for 3 days, and some patients are treated with bridging chemotherapy.

B.3.2.3.2. Comparator

The comparator considered in the economic model defaults to standard of care in the absence of CAR-T, R-BAC. Specifically, the comparator arm is consistent with the preferred regimen for patients who do not receive CAR-T and reflects the comparator specified in the scope (Rituximab or rituximab containing regimens).

As detailed in Section B.1.3.4, treatment options at first line and at first relapse (second line) are well established. Following second-line BTKi (ibrutinib) failure, the standard of care is CAR-T therapy in those patients who are eligible and a clear alternate at this line of therapy is not defined; however, consultants interviewed for this re-submission agreed that if there were a case where CAR-T was unavailable, R-BAC would be the default management option in these patients.[102]

Additional comparators were specified in the final NICE scope, alloSCT and zanubrutinib, and were deemed inappropriate. As stated in the original submission, alloSCT is not considered a relevant comparator and would not be used as an alternative treatment to brexu-cel for patients who have relapsed/demonstrated

refractoriness after receiving a BTKi. Rather, it might be used to consolidate a response to BTKi treatment, but, importantly, it would be performed while patients are still responding to BTKi therapy and only considered for a minority of patients (those considered young and fit enough for transplant and with a suitably matched cell donor).[50,103] This position has not changed since TA677 and consultants interviewed for this resubmission agreed that alloSCT would not be considered a comparator for CAR-T.

Zanubrutinib is not a comparator for CAR-T and pivotal trials place it firmly as a comparator to currently available BTKi (ibrutinib ie at an earlier line). The consultants for this resubmission agreed that Zanubrutinib would not be considered as a third line treatment option.

B.3.3. Clinical parameters and variables

The clinical parameters used to inform the brexu-cel and comparator arms in the economic model, and their respective sources, are summarised in Table 19 and discussed in more detail throughout this section and, in the case of AE rates, Section B.3.4

Table 19: Data sources of clinical parameters used in the model

Component	Application with the model	Source(s) for brexu-cel	Source(s) for SoC
PFS (Section B.3.3.2)	Used to fit parametric survival curves to capture lifetime PFS estimates	• ZUMA-2 Cohort 1, mITT population • UK lifetables for background mortality[104] • Literature (Maurer et al., 2014) for LTS[105]	• McCulloch 2020 • UK lifetables for background mortality[104]
OS (Section B.3.3.3)	Used to fit parametric survival curves to capture lifetime OS estimates		
AE incidence (Section B.3.4.4)	Informed the proportion of patients who incur the disutility associated with each AE	• ZUMA-2 Cohort 1, mITT population	• N/A
Utility values (Section B.3.4.1-.5)	Used to inform utility of pre-progression and post-progression	• ZUMA-2 Cohort 1, mITT population (pre-progression) • TA502 for post-progression • Ara and Brazier 2010[106] for LTS • Wider literature (AE utility effects)	• ZUMA-2 Cohort 1, mITT population (pre-progression) • TA502 for post-progression

Key: AE, adverse event; mITT, modified intent to treat; N/A, not applicable; OS, overall survival; PFS, progression-free survival; TA, technology appraisal.

B.3.3.1. Clinical effectiveness data overview

B.3.3.1.1. Brexu-cel

Brexu-cel OS and PFS evidence is taken from ZUMA-2 patient data. Survival analyses for brexu-cel were conducted using the mITT analysis set as described in Sections B.3.3.2.1 and B.3.3.3.1 (all patients treated with any dose of brexu-cel; N = 68).

Latest available brexu-cel PFS and OS Kaplan–Meier data (04 April 2024 database lock) are presented in Figure 10 and Figure 11, respectively. The approach used to capture lifetime outcomes, and its alignment to guidance in NICE Decision Support Unit (DSU) Technical Support Document (TSD)[107], is described across Section B.3.3.2.1 and B.3.3.3.1.[107]

Available follow-up of the ZUMA-2 study reports very few events after month 48, many patients censored for OS (ie still living) between months 48-72 and a plateau thereafter. This is captured in the model through the LTS model component with thresholds defined according to best interpretation of currently available data.

Figure 10: Progression-free survival in ZUMA-2 mITT population

Key: mITT, modified intent to treat.

Figure 11: Overall survival in ZUMA-2 mITT population

Key: mITT, modified intent to treat.

In order to inform the timepoint for LTS we reviewed the ZUMA-2 survival curves. A 48-month assumption is applied based on the available data. These data support an argument that by 48-months the probability of brexu-cel patients dying from progressive disease is substantially reduced. In addition, subsequent data is based on increasingly small numbers at risk. NHS consultants agreed that the data do not contradict this LTS assumption, the assumption is also consistent with mounting RWE[25]. Note that the LTS assumption applies only to brexu-cel patients.

B.3.3.1.2. Standard of care

SOC is defined as the expected management if CAR-T therapies were not available, R-BAC (as CAR-T-eligible patients are routinely managed according to BSH guidelines). As ZUMA-2 is a single-arm trial, efficacy estimates for SoC were sourced from the published literature. The available evidence base has not changed since the original submission and we take the same approach in this re-submission.

The study used to estimate the efficacy of SOC is McCulloch 2020[27]. This study was focussed on use of R-BAC in r/r MCL patients who had progressed or failed on two or more lines of therapy including a BTKi (i.e. a patient group in line with the decision problem and reflecting the licensed indication for brexu-cel).The PFS and OS Kaplan–Meier data available for SoC are shown in Figure 12 and Figure 13, respectively. This is consistent with the approach taken in the initial submission.

Figure 12: Standard of care progression-free survival Kaplan–Meier plot: McCulloch 2020

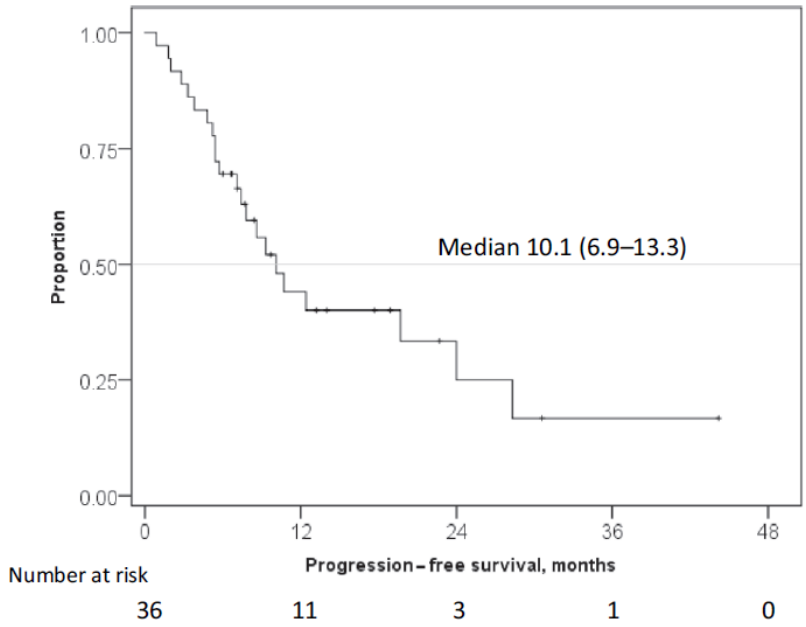
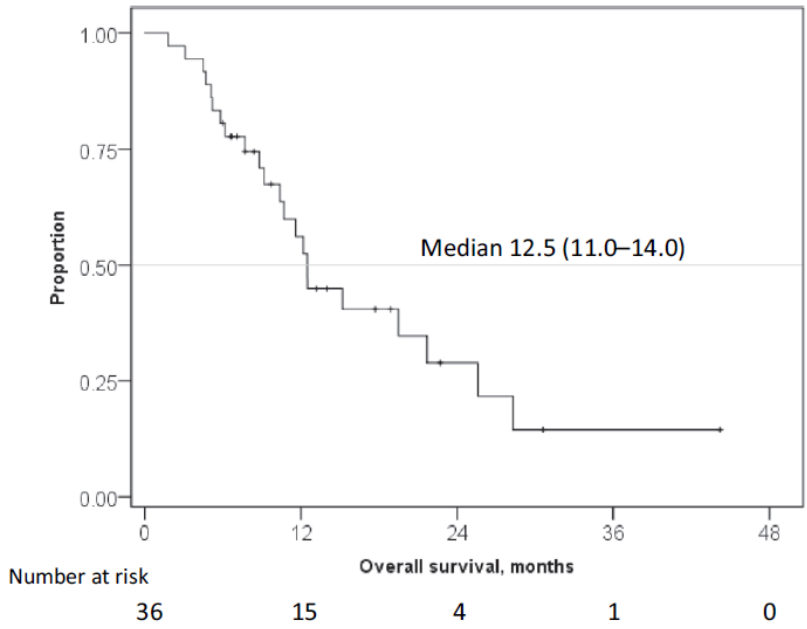


Figure 13: Standard of care overall survival Kaplan–Meier plot: McCulloch 2020



B.3.3.2. Progression-free survival analysis

B.3.3.2.1. Brexu-cel

Standard parametric curves

A range of standard parametric survival models were fitted to brexu-cel PFS data under a relative survival framework, under which the total hazard equals the hazard derived from background mortality plus the MCL-related hazard. As specified in NICE TSD 14, the following parametric models were explored:

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

These models are graphically represented alongside ZUMA-2 PFS Kaplan–Meier data in Figure 14. AIC and Bayesian information criterion (BIC) statistics and landmark estimates are presented in Table 20.

Figure 14: Brexu-cel progression-free survival: standard parametric curves

Key: KM, Kaplan–Meier.
Note: LTS assumption is not reflected in the figure

Table 20: brexu-cel: progression-free survival: standard parametric curve AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Median PFS	PFS estimates (%) at each landmark value				
				2 y	5 y	10 y	20 y	30 y

Exponential	[redacted]							
Generalised gamma	[redacted]							
Gompertz	[redacted]							
Log-logistic	[redacted]							
Log-normal	[redacted]							
Weibull	[redacted]							

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival
Notes: Median values are provided in units of years. Best fitting model in bold. Projected PFS values here are not accounting for the LTS assumption.

Based on the goodness-of-fit statistics, the lognormal distribution provides the best fit to the Kaplan–Meier data. The lognormal distribution also seems to be a good visual fit to the data based on the estimated survival curve in Figure 14.

B.3.3.2.2. Standard of care

Comparator PFS consists of the data from McCulloch 2020.[93,108] Various parametric survival distributions were fitted to digitised data under a relative survival framework, and the most appropriate distribution chosen based on AIC and visual inspection.

The standard six parametric models (as described in B.3.3.2.1) were fitted to the digitised PFS data from McCulloch (using digitiser software: DigitizeIt[109]).[27] These models are presented graphically in Figure 15. Goodness-of-fit statistics, in the form of AIC, are reported in Table 21.

Figure 15: McCulloch et al. progression-free survival: standard parametric curves

Key: KM, Kaplan–Meier; PFS, progression-free survival; SoC, standard of care

Table 21: McCulloch et al. progression-free survival: standard parametric curve AIC statistics

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

By assessing the visual fit of the models fitted to PFS from McCulloch et al.[27], visually all six models are similar to the observed data. The AIC indicated that the log-normal model provides the best statistical fit to observed data.

B.3.3.3. Overall survival analysis

B.3.3.3.1. Brexu-cel

Standard parametric curves

Adopting the procedure used to model PFS, a variety of standard parametric curves were used to model brexu-cel OS under a relative survival framework. These models are graphically represented alongside ZUMA-2 OS Kaplan–Meier data in Figure 17. AIC and BIC statistics and landmark estimates are presented in Table 22.

Figure 16: brexu-cel overall survival: standard parametric curves

Table 22: brexu-cel: overall survival standard parametric curve AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Median OS	OS estimates (%) at each landmark value				
				2 y	5 y	10 y	20 y	30 y

Exponential	[redacted]							
Generalised gamma	[redacted]							
Gompertz	[redacted]							
Log-logistic	[redacted]							
Log-normal	[redacted]							
Weibull	[redacted]							

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.
Notes: Median values are provided in units of years. Best fitting model in bold. Projected OS values here are not accounting for the LTS assumption

Based on the goodness-of-fit statistics, the lognormal model has the lowest AIC, and the exponential model has the lowest BIC, though the AIC or BIC difference between models was within 2, suggesting comparable goodness-of-fit of the 2 models.

Long-term survival assumption

The lognormal model (under a relative survival framework) was selected to model the overall survival hazard before the LTS timepoint. The hazard after the LTS timepoint was assumed to be based on the background mortality among the age- and gender- matched population, with an SMR of 1.09 applied to adjust for excess mortality. The estimated OS was assumed to be equal to the estimated PFS whenever PFS becomes larger than OS in terms of absolute survival.

General population mortality rates may be inappropriate given the impact of prior treatments on survival in r/r MCL patients; an estimate of disease-adjusted mortality from DLBCL is available and considered appropriate for long term r/r MCL survivors. An SMR of 1.09, derived from Maurer et al (2014)[105] is used in the model base case to adjust for excess mortality in long-term survivors. The study assessed the mortality of DLBCL patients who were event-free at 2 years (defined in the context of DLBCL as long term survivors). The input was discussed with NHS consultants interviewed for this re-submission. Despite being taken from a non-MCL cohort, the input was considered relevant as the requirement is to define an applicable SMR for

LTS (i.e., at a point where expected mortality is no longer considered driven by disease progression); while data are available for MCL cohorts, they do not meet the requirement of defining an SMR that would be relevant to an LTS population.

To explore the impact of the SMR on the model outcomes, a scenario assuming unadjusted general population mortality for long-term survivorship was modelled (B.3.11.3). Additionally, due to the uncertainty around this parameter, the SMR parameter is also varied within one-way sensitivity analyses (Section B.3.11.2).

B.3.3.3.2. Standard of care

Comparator OS consists of the data from McCulloch 2020.[27]

The standard six parametric models were fitted to the digitised OS data from McCulloch. [27], see Figure 18. Statistical goodness of fit measures, in the form of AIC, are reported in Table 23.

Figure 17: McCulloch et al. overall survival, standard parametric curves

Key: KM, Kaplan–Meier.

Table 23: McCulloch et al. overall survival, standard parametric curve AIC statistics

Model	AIC: McCulloch et al.
Exponential	[redacted]
Generalised gamma	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Weibull	[redacted]

Key: AIC, Akaike information criterion
Notes: Best fitting model in bold.

Based on the AIC values, lognormal distribution was selected as the best model for the OS distribution of the SoC arm. An LTS assumption is not relevant to SoC.

B.3.3.3.3. Comparison of base case survival for brexu-cel and standard of care

Figure 20 summarises lifetime base case projections of OS and PFS, across model arms, using the selected data and assumptions described throughout Section B.3.3. These figures illustrate the data-driven expectations of patient benefit offered by brexu-cel versus alternative NHS care for post-ibrutinib MCL patients (R-BAC).

Figure 18: Base case lifetime OS and PFS projections across model arms, alongside ZUMA-2 brexu-cel KM data

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

B.3.3.4. Time on treatment

Brexu-cel is a single-infusion product (i.e. it is given as a one-off infusion). For SoC, 4 cycles of treatment have been assumed based on calculations of data reported by McCulloch et al. [27] This is detailed in full in the SoC costs and resource use section (Section B.3.5.2.2).

B.3.4. Measurement and valuation of health effects

The symptoms associated with MCL are known to have a marked effect on patients' quality of life. As much is clear from patient accounts and submissions during the NICE TA502 ibrutinib appraisal. Patients cited fatigue as a particularly difficult and characteristic symptom[110], but active disease, in the absence of effective treatment, affects multiple domains of their quality of life – from mobility through to anxiety and depression.[111] The availability of CAR-T has transformed the QoL picture in MCL and patients now have a realistic prospect of >25 months of disease free survival.

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

The approach to estimation of patient -specific HRQOL is in line with the previous submission. EQ-5D-5L data were collected in ZUMA-2 within 28 days of enrolment, 4 weeks (+/- 3 days) after brexu-cel infusion, 3 months (+/- 1 week) after brexu-cel infusion and 6 months (+/- 1 week) after brexu-cel infusion. A total of 214 EQ-5D-5L observations were collected across 65 patients within the mITT group.

As recommended by NICE in their updated position statement in October 2019,[112] the crosswalk algorithm developed by van Hout et al. (2012)[113] was used to convert EQ-5D-5L scores into EQ-5D-3L utility. Table 24 shows summary EQ-5D-3L utility data over scheduled collections.

Table 24: ZUMA-2 EQ-5D-3L-equivalent utility data summary over scheduled data collection points

	Screening	Week 4	Month 3	Month 6
N observations	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
1st – 3rd quartile	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]

Key: EQ-5D-3L, EuroQol 5 Dimension 3 Level; SD, standard deviation
Notes: Estimates to 3 decimal places. n = 6 further observations from n = 2 patients who were retreated with brexu-cel also collected.

Only three EQ-5D observations were collected from patients who had progressed. As such, the ZUMA-2 data are considered informative for the pre-progression utility assumptions, but not directly informative for post progression utility assumptions.

Since EQ-5D-5L information were collected repeatedly over time, observations tend to be correlated across time points, resulting in non-independence of utility

estimates. To account for this regression analysis of the PFS EQ-5D-3L-equivalent utility data, an intercept-only linear mixed-effects model was used; this approach adjusts for the correlation between repeated measurements within the same patient.

The model treated EQ-5D-3L-equivalent utility score (U_{it}) as a dependent variable. To determine the relevant covariates, four different regression models were implemented by including an additional independent variable at time. Each included demographic characteristics, age (age_i) and sex (sex_i). The first accounted for no further covariates. The second, third and fourth accounted for timing of assessment in the following ways, respectively:

- As a variable counting the days from treatment (day_t), e.g. screening → - 28 (days), Month 3 → + 60 (days)
- As variable accounting for the number of visits that each patient had ($visit_t$)

As dummy variables; one for each visit (visit_1$_i$, visit_2$_i$, visit_3$_i$, visit_4$_i$,)

The best-fitting model by AIC was the fourth tested, including covariates for age, sex and a dummy variable for each visit. From the results of this model, mean PFS (pre-progression) utility was estimated to be [redacted], with standard error (SE) [redacted]. These inputs are used in the economic modelling in order to align with NICE preference for patient-based utilities estimated based on standard algorithms and UK mapping[114].

B.3.4.2. Mapping

As described in Section B.3.4.1, the EQ-5D-5L questionnaire was administered to patients in the ZUMA-2 trial. As also described in Section B.3.4.1 and consistent with the latest (October 2019) NICE guidance[115], the van Hout et al. algorithm was used to estimate EQ-5D-3L equivalent utility values from the EQ-5D-5L questionnaire data.[113]

B.3.4.3. Health-related quality of life studies

A systematic search for HRQL evidence from relapsed or refractory MCL patients was performed alongside the search for economic studies reported in Section B.3.1. It comprised an original search in March 2019, updated on 11 November 2024, and is reported in full in Appendix F. Across the included studies identified in the SLR update, only Petersohn 2022 reported UK utilities but no primary data were reported.

The study assumed pre-progression and post-progression health state utility from TA502. Pre-progression (long term-survival) utility was calculated from Ara and Brazier 2010 taking into account age and gender. Our current model combines an estimate of ZUMA-2 HRQOL for pre-progression patients with adjusted estimates for LTS and post progression health states (in line with published CEAs). This approach is in line with the estimation of utility in the original submission.

B.3.4.4. Adverse events

As discussed in Section B.2.11.3, since the approved access of brexu-cel and other CAR-Ts in NHS England, clinicians have become increasingly comfortable with toxicity management for CAR T-cell therapy. [83] Emerging real world evidence from the UK indicates that rates of Grade ≥ 3 CRS and neurological events in R/R MCL patients receiving brexu-cel are lower than those reported in ZUMA-2 (CRS: 12% versus 15% and neurological events: 22% versus 31%, respectively)[25]. However, it is acknowledged that there are short-term impactful AEs for many, therefore, a comprehensive approach has been taken to capturing these in the model for the brexu-cel arm based on ZUMA-2.

For the comparator arm, a more simplistic approach based on precedent has been taken and a conservative assumption of no comparator-based AEs is applied.

B.3.4.4.1. Adverse event rates

The analysis captures brexu-cel AE consequences based on the rates reported in the ZUMA-2 mITT analysis set. The cost-effectiveness model includes all Grade 3 and 4 brexu-cel-related AEs occurring in ≥ 5% of the ZUMA-2 cohort; consistent with the limits of the CSR reporting. For AE of particular clinical importance for CAR T-cell therapies (CRS requiring tocilizumab treatment), AEs of all grades were included in the model, in line with previous CAR T-cell therapy NICE appraisals.[116-118] The incidence of AEs included in the model are shown in Table 25.

Table 25: Incidence of patients with brexu-cel-related adverse events included in the model

Adverse event	Incidence*
Cytokine release syndrome (CRS)	■

White blood cell count decreased	[redacted]
Anaemia	[redacted]
Neutrophil count decreased	[redacted]
Hypotension	[redacted]
Hypoxia	[redacted]
Hypophosphataemia	[redacted]
Encephalopathy	[redacted]
Platelet Count decreased	[redacted]
Neutropenia	[redacted]
Pyrexia	[redacted]
Confusional state	[redacted]
Aspartate aminotransferase increased	[redacted]
Alanine aminotransferase increased	[redacted]
Hypertension	[redacted]
Pneumonia	[redacted]
Hyponatraemia	[redacted]
Thrombocytopenia	[redacted]
Leukopenia	[redacted]
Febrile Neutropenia	[redacted]
Acute Kidney Injury	[redacted]
Lymphocyte count decreased	[redacted]

Sepsis	[redacted]
Lymphopenia	[redacted]
Hypocalcaemia	[redacted]
Hypogammaglobulinaemia	[redacted]
Hypokalaemia	[redacted]
Respiratory Failure	[redacted]
Note: * Brexu-cel-related AEs with Grade 3 and above occurring in ≥5% of the ZUMA-2 cohort, except for CRS, which includes all patients treated with tocilizumab	

B.3.4.4.2. Adverse event utility decrements

The disutility and duration assumed for modelled AEs are presented in Table 26. In line with the methods used in the original submission (TA677), a disutility for hypogammaglobulinaemia was not applied as it is not thought to result in a reduction of health-related quality of life.[119]. For AEs whose disutility could not be identified, a disutility equal to the maximum of the identified non-CRS AE disutilities was assumed for a duration of 7 days. AE utility decrements were applied in the first model cycle for the expected AE duration. Note that for SoC, no AE disutility was applied. This was a conservative approach consistent with the original submission.

Table 26: Disutility and duration of adverse event

Adverse event	Disutility	Duration (days)	Reference
Cytokine release syndrome (CRS)	0.76	11	TA872[120]
Pyrexia	0.11	2	TA872[120]
Anaemia	0.12	14	TA872[120]
Platelet Count decreased	0.11	50	TA872[120]
Hypotension	0.15	5	TA872[120]
Neutrophil count decreased	0.15	17	TA872[120]
White blood cell count decreased	0.15	40	TA872[120]
Hypoxia	0.11	2	Assumed equal to Pyrexia

Hypophosphataemia	0.15	16	TA872[120]
Neutropenia	0.09	47	TA872[120]
Hyponatraemia	0.15	7	Assumption
Alanine aminotransferase increased	0.15	7	Assumption
Encephalopathy	0.15	12	TA872[120]
Hypokalaemia	0.15	7	Assumption
Hypocalcaemia	0.15	7	Assumption
Thrombocytopenia	0.11	63	TA872[120]
Aspartate aminotransferase increased	0.15	7	Assumption
Confusional state	0.15	7	Assumption
Hypertension	0.15	5	Assumed equal to Hypotension
Acute Kidney Injury	0.15	7	Assumption
Leukopenia	0.15	21	TA872[120]
Lymphocyte count decreased	0.15	64	TA872[120]
Pneumonia	0.15	7	Assumption
Respiratory Failure	0.15	7	Assumed equal to Pneumonia
Sepsis	0.15	7	Assumed equal to Pneumonia
Febrile Neutropenia	0.09	47	Assumed equal to Neutropenia
Lymphopenia	0.15	21	Assumed equal to Leukopenia
Hypogammaglobulinaemia	0	11	Hettle et al.[119]

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

Table 27 summarises the utility values used in the base case cost effectiveness analysis, signposting the reader to further description and justification of each estimate. The approach differs slightly to that reported in the previous submission.

Table 27: Summary of utility values for cost-effectiveness analysis

Health state	Utility value	Uncertainty	Reference in submission
Pre-progression	[redacted]	Section B.3.7	Section B.3.4.1
Pre-progression, LTS (Mean baseline age + 4y)	[redacted]		Section B.3.4.5
Post-progression	0.724		Section B.3.4.5

The pre-progression utility estimate, [redacted], is estimated from ZUMA-2 patient-reported EQ-5D-5L data, using regression analysis after applying the van Hout algorithm crosswalk to EQ-5D-3L-equivalent utility estimates, as described in Section B.3.4.1. In the absence of sufficient post-progression ZUMA-2 EQ-5D-5L patient data, the post-progression utility estimate, [redacted], was derived based on the difference between pre- and post-progression utilities reported in TA502.

In line with survival assumptions for long-term survivors, described in Section B.3.3, general population-equivalent utility is assumed for those in the progression-free health state following CAR T-cell therapy, i.e. from 48 months from baseline onwards. To do this, supplementary materials from Ara and Brazier's analysis of Health Survey for England data were used.[106] Specifically, linear regression results capturing general population EQ-5D utility as a function of age and gender were obtained. Baseline mean age in ZUMA-2 was 63.2 years; 83.8% of the group were male. The [redacted] utility estimate in Table 27 corresponds to a 67.2-year old 83.8% male individual; the assumed makeup of the alive cohort after 4 years.

Ara and Brazier data are also used to capture ageing trends in utility, for those health states with otherwise time-insensitive utility estimates.[106]

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

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

An update to the systematic search for published cost and healthcare resource identification, measurement and valuation data in r/r MCL was run alongside the searches for economic evaluation and HRQL data noted in Sections B.3.1 and B.3.4.3. Again, and as reported in Appendix I, an original March 2019 search was updated on 11 November 2024. Across the studies identified, none were considered relevant to this appraisal as all retrieved studies were conducted in the United States. The details of the included studies were reported in Appendix I.

As for HRQL assumptions, owing to the innovative nature of CAR T-cell therapy in this disease area, the r/r MCL cost and resource use literature cannot inform appropriate NHS cost resource use assumptions for unprecedented relapse-free long-term survivorship in MCL. Assumptions are in line with the original submission.

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

B.3.5.2.1. Brexu-cel costs and resource use

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

Drug acquisition costs:

- Bridging therapy costs
- Conditioning chemotherapy costs
- brexu-cel

CAR-T Tariff, including:

- Leukapheresis costs
- brexu-cel infusion and monitoring costs (including hospitalisation)
- Emergent AEs
- All other costs occurring within the first 100 days post infusion

For simplicity, all costs associated with brexu-cel treatment are assumed to be incurred at the start of the first model cycle as treatment is given as a single infusion.

Bridging therapy costs

In ZUMA-2, 36.8% of patients who were due to receive brexu-cel were given bridging chemotherapy with R-BAC (Rituximab 375 mg/m^2 day 1; Bendamustine 70 mg/m^2 days 2, 3; Cytarabine 500 mg/m^2 days 2-4) before infusion with brexu-cel (n= 25). The acquisition cost per patient was £1,362.17 (Table 32). It was assumed that if a patient requires more than one IV chemotherapy per day, only a single administration cost applies. The daily cost for IV administration was £394.17 (Table 34).

Conditioning chemotherapy costs

All patients in the mITT (n=68) underwent conditioning chemotherapy. Conditioning chemotherapy in ZUMA-2 consisted of intravenous infusions of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day administered for 3 days. This regimen is also aligned with the licence for brexu-cel. Unit costs for cyclophosphamide and fludarabine were taken from eMIT and are presented in Table 28 below .[121]

Table 28: Unit costs of conditioning chemotherapy

Conditioning chemotherapy	Formulation	Measure (mg)	Unit cost	Pack size	Source
Fludarabine	Solution for injection vials	50	£105.93	1	eMIT national database, 23 October 2024 [121]
Cyclophosphamide	Powder for solution for injection vials	1000	£13.11	1	eMIT national database, 23 October 2024[121]
	Powder for solution for injection vials	2000	£27.50	1	
	Powder for solution for injection vials	500	£11.18	1	

Key: eMIT, electronic Market Information Tool
Notes: *Although 2000mg vials of cyclophosphamide also available; it is assumed that 1000mg vials would be used preferentially as they cost less per mg.

For the dosing of fludarabine and cyclophosphamide, it was assumed that patients received only whole vials and that there was no vial sharing. Using the mean and standard deviation of body surface area (BSA) from ZUMA-2, the average number of vials that would be required to satisfy one administration of each of the intravenous administered drugs was calculated. Specifically, the BSA is assumed to follow a normal distribution and this distribution was used to calculate the proportion of patients requiring each number of vials to produce an accurate estimate of the mean number of vials required per patient per dose when wastage is taken into account.

Table 29 shows the combination of vials on average required per patient per dose.

Table 29: Average number of vials required per administration of conditioning chemotherapies

Conditioning chemotherapy	Dose needed	Vial size (mg)	Mean number of vials per patient per day
Fludarabine	30 mg/m^2/day	50 mg	1.91
Cyclophosphamide	500 mg/m^2/day	500 mg	0.47
		1,000 mg	1.00

Including wastage, the total cost per day of conditioning chemotherapy was £221. Conditioning chemotherapy is given over the course of 3 days; therefore, the total assumed cost of conditioning chemotherapy was £663.

The administration cost of conditioning chemotherapy per day was £488.57, based on the weighted average of day-case HRGs for malignant lymphoma, including Hodgkin's and Non-Hodgkin's, SA31A to SA31F, taken from NHS National Schedule of Reference Costs 2023-24. Therefore, the total assumed cost of administering conditioning chemotherapy was £1465.71.

Brexu-cel acquisition costs

As detailed in Section B.3.2.3.1, brexu-cel is administered as a one-off infusion. The acquisition cost of brexu-cel is assumed to be a one-off cost of [redacted] including shipping, engineering and generation of the CAR T-cells. This reflects the price at which brexu-cel is currently available to NHS England, as a flat rate discount of [redacted] from the list price of £316,118.

CAR-T tariff cost

A lump-sum cost of £41,101 for CAR-T drug administration covers the first 100 days of treatment. This tariff covers brexu-cel infusion and monitoring hospitalisation costs, leukapheresis costs and resource and costs related to emergent AEs that occur within the first 100 days post infusion (excluding AEs requiring LT infusion if IVIg). This methodology follows TA872[120].

While we have incorporated the tariff of £41,101, we do not agree with its application in the context of a NICE health technology appraisal submission. To truly estimate the incremental cost of delivering CART treatment to patients, a transparent bottom-up approach should be used to estimate costs and to arrive at an evidenced figure for inclusion.

In the interests of patient access to CART the figure of £41,101 was agreed for use in TA872, however there was not a formal agreement on how the figure was derived. In the Final Appraisal Document (FAD) of TA872 the NICE committee noted "while the current tariff represents the high hospital costs of establishing the infrastructure of a CAR T-cell therapy service…economics of scale may be expected over time". Efficiencies within the NHS have reduced the management costs of CAR T[85], and to believe efficiencies within the NHS have not been achieved is inconsistent with a core priority of the NHS Long Term plan[122].

Further to this, in line with the Methods Guide, the recommendations that NICE make must apply a clear and methodological approach that is evidence based and transparent, and we believe these guiding principles have not been met.

B.3.5.2.2. SoC costs and resource use

All patients from the SoC arm are assumed to receive R-BAC. This is in line with the preferred treatment assumption in the previous appraisal and McCulloch 2020[27].

Drug acquisition

Table 30 summarises the dose per vial, units per package, cost per package, and cost per mg for R-BAC based on expected resource outlined in McCulloch 2020. For sourcing these costs, the drugs and pharmaceutical electronic market information

tool (eMIT) and British National Formulary (BNF) were used. Where multiple options were presented for each dose, it was assumed that the pack providing the cheapest cost per mg is used. Furthermore, it is assumed that the cheapest combination of vials would be selected when preparing each individual dose.

Table 30: SoC individual drugs, cost per mg

SOC drug	Dose per vial (mg)	Units per package	Cost per package	Cost per mg
Rituximab[1]	100	2	£314.33	£1.57
	500	1	£785.84	£1.57
Bendamustine[2]	25	5	£40.86	£0.33
	100	1	£91.99	£0.92
	100	5	£127.14	£0.25
Cytarabine[2]	500	5	£30.79	£0.01
	1000	1	£7.76	£0.01
	2000	1	£14.81	£0.01
	100	5	£13.85	£0.03
Sources: [1] eMIT: Drugs and pharmaceutical electronic market information tool (eMIT). Department of Health and Social Care (2024). [2] BNF: British National Formulary (BNF). Joint Formulary Committee (2024). Accessed November 1st 2024 at https://bnf.nice.org.uk/				

Consistent with the approach used for costing the conditioning chemotherapies in the brexu-cel arm, the average number of vials that would be required for one administration of each of the intravenous administered drugs was calculated using the mean and standard deviation of BSA from ZUMA-2.

Table 31 shows the average combination of vials required per patient per dose.

Table 31: Average number of vials required per administration of SoC therapies

SOC drug	Dose needed (mg/m^2)	Vial size (mg)	Mean number of vials per patient per day per administration
Rituximab	375	100	2.75
		500	1.04
Bendamustine	70	25	2.00
		100	1.01
Cytarabine	500	500	0.47
		1000	1.00
		2000	5.8E-06
Source: McCulloch 2020[27]			

Once the cost per dose was established for each individual drug, the cost per regimen per cycle was calculated, as presented in Table 32. In addition, Table 32 shows the cycle frequency. This was assumed to equal the average number of cycles among patients who did not terminate treatment due to progressive disease in McCulloch 2020[27], since the model accounted for treatment discontinuation due to disease progression as a separate component. Here, the calculation assumed 3.5 cycles for those receiving 3 to 4 cycles, 5.5 cycles for those receiving 5 to 6 cycles, and 1 cycle for those who discontinued treatment due to toxicity (n=2) or unknown reason (n=1). The average number of cycles was therefore 4 cycles.

Table 32: SoC regimen drug acquisition costs per treatment cycle

Individual drugs schedule	Day of chemotherapy cycle			Total drug acquisition cost per treatment cycle	Cycle frequency
	Day 1	Day 2	Day 3		
Rituximab, Day 1	£1,246.14	£0.00	£0.00	£1,362.17	Every 4 weeks (4 treatment cycles assumed)
Bendamustine, Days 1-2	£42.06	£42.06	£0.00		
Cytarabine, Days 1-3	£10.64	£10.64	£10.64		

The number of administrations was calculated per monthly model cycle (30.44 days). This is presented in Table 33.

Table 33: Number of regimen administrations and calculated total SoC drug cost per model cycle

Regimen	Model cycle 1	Model cycle 2	Model cycle 3
R-BAC	1	1	2
Total SoC drug cost per cycle (Undiscounted)	£1,362.17	£1,362.17	£2,724.35

Drug administration

It is assumed that if a patient requires more than one IV chemotherapy per day, only a single administration cost applies. The costs used for IV administration are presented in Table 34.

Table 34: IV chemotherapy administration costs

Description / code / setting	Cost	Reference
Deliver Simple Parenteral Chemotherapy at First Attendance / SB12Z / Total	£394.17	NHS reference costs (2023-2024)[123]
Key: IV, intravenous.		

As for the SoC drug acquisition costing, once the cost per administration was established for each individual drug, the total administration cost for each treatment cycle was calculated. Table 35 presents the administration cost per regimen per treatment cycle and Table 36 presents the calculated total cost of SoC administration per model cycle. The total SoC cost per model cycle, considering both drug acquisition and administration, is shown in Table 37.

Table 35: SoC regimen administration costing per treatment cycle

Regimen	Individual drugs schedule	Day of chemotherapy cycle			Total drug administration cost per treatment cycle
		Day 1	Day 2	Day 3	
R-BAC	Rituximab, Day 1	£394.17	£0.00	£0.00	£1,182.50
	Bendamustine, Days 1-2	£0.00	£394.17	£0.00	
	Cytarabine, Days 1-3	£0.00	£0.00	£394.17	
Key: R-BAC, rituximab, bendamustine and cytarabine; SoC, standard of care.					

Table 36: Number of regimen administrations and calculated total SoC administration cost per model cycle

Regimen	Model cycle 1	Model cycle 2	Model cycle 3
R-BAC	1	1	2
Total SoC administration cost per model cycle (undiscounted)	£1,182.50	£1,182.50	£2,364.99
Key: R-BAC, rituximab, bendamustine and cytarabine; SoC, standard of care.			

Table 37: Total SoC cost

Treatment	Model cycle 1	Model cycle 2	Model cycle 3
SoC	£2,544.67	£2,544.67	£5,089.33
Key: SoC, standard of care.			

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

Medical resource use required is dependent on progression status and is thus modelled by applying a cost to the proportion of patients in each health state. Additionally, medical resource use is assumed to differ for patients who are deemed to experience long-term survivorship (LTS). Model inputs are described below.

An update to the systematic literature review on the healthcare cost and resource utilisation only retrieved studies conducted in the United States which were not considered appropriate for this technical appraisal (Appendix I). In line with the original submission, resource use in each health state was derived from TA502[52], where a survey was designed to obtain the types and frequency of medical resource use (including visits, procedures, and tests) for an average MCL patient. A total of 52 participants (15 oncologists, 19 haematologists and 18 haematologist oncologists) provided responses. The outcomes from the survey are presented below in Table 38. As TA502 reports resource use according to stable disease, partial response, complete response and post-progression survivors, it is assumed that resource use for patients with stable disease would apply to pre-progression patients.

Table 38: Frequency of resource use by health state as reported in TA502 and applied in the model

Resource type	Frequency / model cycle (pre-progression, up to LTS timepoint)	Frequency / model cycle (post-progression)	Reference
Full blood count	0.39	0.78	TA502
X ray	0.06	0.06	
Blood glucose	0.02	0.00	
Lactate dehydrogenase	0.26	0.44	
Lymphocyte counts	0.39	0.78	
Bone Marrow Exam	0.06	0.00	
Office visit	0.39	0.78	
Inpatient stay	0.03	0.17	
Biopsy	0.04	0.00	
Blood transfusion	0.07	0.33	
Platelet infusion	0.00	0.17	
CT-Scan	0.00	0.00	Assumption
PET Scan	0.00	0.00	Assumption
Note: For pre-progression beyond LTS timepoint, only office visit twice a year is assumed.			

The most recent NHS reference costs (2023–2024)[123] were used to derive costs for each of the resource use components, as presented in Table 39.

Table 39: Resource use unit costs

Resource type	Code	Description/setting	Unit cost
Full blood count	PATH05 (Haematology)	DAPS	£3.10
X ray	PF (Plain film)	DADS	£43.13
Blood glucose	PATH04 (Clinical biochemistry)	DAPS	£1.53
Lactate dehydrogenase	PATH04 (Clinical biochemistry)	DAPS	£1.53
Lymphocyte counts	PATH05 (Haematology)	DAPS	£3.10
Bone Marrow Exam	SA33Z - Diagnostic Bone Marrow Extraction	Outpatient procedures	£451.84
Office visit	Outpatient Care, Clinical Haematology Service, Non-Admitted Visits, First/Follow Up Attendance. Weighted average of WF01A to WF01D	Outpatient care	£182.39
Inpatient stay	SA31A to SA31F - Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's	Total	£3,106.70
Biopsy	Weighted average of FF50A-C, FF51A-E, and WH54A-B: Complex General Abdominal Procedures Major General Abdominal Procedures, 19 years and over Procedures on the Lymphatic System	Total	£6,741.96
Blood transfusion	SA44A - Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over	Outpatient procedures	£398.79

Platelet infusion	SA44A - Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over	Outpatient procedures	£398.79
CT-Scan	Computerised Tomography Scan of One Area, weighted average of RD20A and RD21A	Total	£113.27
PET Scan	RN07A - Positron Emission Tomography (PET), 19 years and over	Total	£613.44
Key: DADS, directly accessed diagnostic services; DAPS, directly accessed pathology services			

The resulting costs per cycle for the pre-progression (< 48 months) and post-progression health states were £517 and £867, respectively.

Pre-progression patients surviving for longer than 48 months, are assumed to incur costs for clinical haematologist visit twice a year (Refer to “office visit” in Table 39)

B.3.5.4. Adverse event costs

AE costs are only applied to the brexu-cel treatment arm; these were included in the one-off cost of £41,101 (described in section B.3.5.2.1), with the exception of hypogammaglobulinaemia, which is associated with ongoing treatment costs. This is aligned with TA559 and Hettle et al.[119] and the approach taken in the previous submission. The approach to costing hypogammaglobulinaemia is detailed below.

B.3.5.4.1. Hypogammaglobulinaemia

Hypogammaglobulinaemia was not included in the lump-sum cost because it requires ongoing treatment over a relatively long period of time. The percentage of patients experiencing hypogammaglobulinaemia with a grade ≥3 in ZUMA-2 is [redacted].

Cost per gram of IVIG was assumed to be £69.00, derived based upon the cost of 20g Kiovig vials (BNF 2024) with no wastage assumed.

In line with the assumptions in the original submission (which were based on Hettle et al[119]) a dose of 0.5g/kg every 4 weeks was assumed. Furthermore, IVIG is assumed to be administered to patients for a duration of 12 months, consistent with the original assumptions[117]. During validation of the original submission, NHS Consultants agreed that both the dosing regimen and assumed duration was sensible, and added that there is awareness in clinical practice of the cost of IVIG therapy, and as a result, wastage is likely to be minimised,[83] therefore, no wastage was assumed when costing IVIG; this assumption is also applied here.

Table 40: IVIG dosing parameters

IVIG therapy	Dose (g/kg)	Frequency	Duration	Source
Kiovig	0.5	Every 4 weeks	12 months	TA559, Hettle et al., Clinical expert opinion[83,119,124]
Key: IVIG, intravenous immunoglobulin				

As the model considers a monthly cycle length, the treatment cost was adjusted from a 4-weekly cost to a monthly cost, using the following formula:

$$Cost\ per\ dose * \frac{365.25/12}{4 * 7}$$

Considering the proportion of patients experiencing hypogammaglobulinaemia with a grade ≥3 (■) and the cost of treatment, the weighted average monthly cost of IVIG treatment is £45.22.

B.3.5.5. Miscellaneous unit costs and resource use

B.3.5.5.1. Allogeneic stem cell transplant

As described in Section B.2.7, ■ patients in the mITT analysis set had an allo-SCT, while in a brexu-cel induced remission. The costs of allo-SCT is therefore applied to ■ of patients in the brexu-cel arm of the model (note that in practice, alloSCT would not be expected after brexu-cel). A scenario analysis was performed where alloSCT was removed from the costs calculation for the brexu-cel arm (B.3.11.3).

Based on McCulloch 2020 [27], it is assumed that 31% of patients on the SoC arm would receive allo-SCT (reflecting the uptake of alloSCT in this patient group.[83] A range of assumptions are explored in the scenario analysis in Section B.3.11.3.

The cost of allo-SCT was taken from the NHS reference costs (2023-24)[123] as presented in Table 41.

Table 41: Cost of allo-SCT

Currency code	Currency description	Unit cost
SA39A	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 19 years and over	£47,508.32

For simplicity, to avoid complexities arising from tracking time-dependencies in a cohort-level model, allo-SCT costs are assumed to occur at the start of the model.

B.3.5.6. End-of-life care

Patients with end-stage cancer typically incur costs at the end of life for palliative care. The cost for palliative care per day was estimated at £110.29, calculated based on the weighted average of N21AF and N21AN from the NHS national reference cost schedule 2023-24 (Table 42). The number of days was assumed to be 37, based on the median duration of palliative care for cancer patients reported by Bennett et al [125]. End-of-life care costs are applied as a lump sum upon death.

Table 42: End-of-life care costs

Currency code	Currency description	Activity	Unit cost
N21AF	Specialist Nursing, Palliative/Respite Care, Adult, Face to face	473,262	£142
N21AN	Specialist Nursing, Palliative/Respite Care, Adult, Non face to face	438,954	£76

B.3.6. End of life criteria

Brexu-cel was originally assessed under end-of-life criteria. In TA677 the committee concluded that treatment with autologous anti-CD19-transduced CD3+ cells meets criteria to be considered a life-extending treatment at the end of life (the EoL criteria)[66]. Post BTKi r/r MCL patients continue to meet these EoL criteria.

Additional note

Brexucabtagene autoleucel entered the managed access agreement (MAA) in February 2021 for the treatment of relapsed or refractory mantle cell lymphoma in adults who have previously had a Bruton's tyrosine kinase inhibitor (BTKi). This was under the understanding that the process and methodology for exiting the CDF would be substantially the same as that in place when signing the agreement, i.e. a 'Cancer Drugs Fund guidance review' by NICE under the technology appraisal process as set out in the NICE Guide to the process of technology appraisal – Process and methods (PMG19). Gilead relied upon the defined procedure which included the arrangements for how the technology would be assessed following completion of the MAA, when we agreed to the arrangements for participation in the CDF.

As clearly mentioned in the MAA and NICE Guide, this exit process should be considered a reappraisal based on additional evidence listed in the data collection agreement, intended to answer the clinical uncertainty raised by the NICE Appraisal Committee. The 2018 Addendum to the NICE Technology Appraisal Methods Guide to support the new Cancer Drugs Fund arrangements, referred to "a subsequent update of the guidance" (paragraph 6.5.3) at the end of the MAA period.

The current review of brexucabtagene autoleucel therefore forms the conclusion of the original appraisal rather than a de novo STA and to alter NICE's procedures retrospectively, applying substantially different methodology would be inconsistent with standards of procedural fairness.

B.3.7. Uncertainty

We believe there are no published or ongoing randomised trials comparing brexu-cel with pre-existing standard of care in patients with r/r mantle cell lymphoma after 2 or more lines of treatment including a BTKi who are fit enough to receive it. The company has presented a dossier based on a single arm study supported by relevant RWE. If the committee believes that additional data would reduce uncertainty then further follow up of existing trial data (ZUMA-2) or RWE are data collection routes available. As brexu-cel is now accepted in UK and international guidelines as the recommended therapy for this population, there is no plausible prospect of a randomised trial being conducted against pre-existing standard of care.

B.3.8. Managed access proposal

Brexu-cel has been available through the Cancer Drugs Fund since 2021.

The company believes that further follow-up or additional analysis of SACT data already collected might further reduce uncertainty in this appraisal.

B.3.9. Summary of base case analysis inputs and assumptions

B.3.9.1. Summary of base case analysis inputs

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

B.3.9.2. Assumptions

The approach to modelling has been designed to make the best use of the available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal. In the absence of key data, key assumptions have been necessary, these are summarised in Table 46.

Table 43: Summary of key assumptions of the economic analysis

#	Assumption	Likely bias direction	Justification
1	The economic model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS/PSS costs.	None	Section B.3.2 The model type and structure is consistent with those accepted for decision making in the only previous TA in R/R MCL (TA502) and the previous submission of brexu-cel (TA677)
2	The expected absolute clinical effectiveness of brexu-cel in terms of disease delay and survival is captured by ZUMA-2 mITT PFS and OS KM data captured and extrapolated over a lifetime perspective using log-normal survival modelling.	None	Sections B.3.3.1 to B.3.3.3 This approach captures the relevant pivotal regulatory trial data. The approach for survival modelling is consistent with both NICE DSU TSD guidance [107] and previous NICE appraisals, including decision-making analyses for the three previous CAR-T TAs (TA554, TA559 and TA567). The approach was viewed as consistent with the data and mechanism of action at NHS Consultant review.[83]
3	Patients in the brexu-cel arm are assumed long-term survivors (LTS) after 48 months and follow age-adjusted ONS general population survival data, adjusted by a standardised mortality ratio of 1.09	Uncertain	Sections B.3.3.1 and B.3.3.3 Likelihood of disease re-emergence >48 months post brexu-cel is low and mortality risk after this point is best modelled on the basis of age, adjusted by a standardised mortality ratio relevant to LTS Brexu-cel represents a step change in management of r/r MCL post BTKi. Other models of CAR T have changed to LTS between 2 and 5 years after treatment; the correct time for the change to LTS will not be known until further follow up is available
3	The expected absolute clinical effectiveness of SoC in terms of disease delay and survival is captured by the post-ibrutinib PFS and OS KM data available from McCulloch 2020 [27], and extrapolated over a lifetime perspective using lognormal survival modelling.	None	Sections B.3.3.1 to B.3.3.3 This approach captures the available OS and PFS KM data in the post-ibrutinib setting, identified through systematic review. The approach for survival modelling is consistent with NICE DSU TSD guidance [107] and previous NICE appraisals. Projections for SoC PFS and OS over time are consistent with NHS Consultant expectations.[83]

#	Assumption	Likely bias direction	Justification
5	The patient utility associated with PFS after brexu-cel is reflected by that observed in patient EQ-5D data from ZUMA-2, with the HRQL impact of Grade 3 and 4 AEs separately accounted for within the model	None	Sections B.3.4.1, B.3.4.4 and B.3.4.5. The use of patient-reported EQ-5D-5L data from the relevant ZUMA-2 patient group, cross-walked to produce EQ-5D-3L-equivalent utility data, is consistent both with the NICE Reference Case [99] and the October 2019 Position Statement on the use of EQ-5D-5L data.[112]
6	The patient utility associated with PFS with SoC is similar to observed in patient EQ-5D data from ZUMA-2	In favour of SoC	Sections B.3.4.1, B.3.4.4 and B.3.4.5. It is possible that the use of ZUMA-2 patient utility data as proxy data for SoC PFS utility overestimates utility on the comparator arm;.
7	Patient utility and health care resource use for brexu-cel patients who are predicted to be progression-free 48-months are expected to be similar to age-matched general population utility estimates for England, with the exception of regular but infrequent GP visits	None	Sections B.3.4.5. and B.3.5.3 This approach is consistent with NHS Consultant expectations and the decision-making approach in the original submission, where long-term survivors were assumed to have utility and NHS resources similar to age-matched general population estimates. .
8	The patient utility associated with PPS is assumed to be reflected by data used to inform decision making in TA502, synthesised as described in Section B.3.4.5 and calculated as a decrement compared to PFS utility	None	Sections B.3.4.3 and B.3.4.5. This approach is used to harness the data used for decision-making in TA502, the most recent NICE TA in released or refractory MCL, in absence of more suitable data from ZUMA-2, and in consideration of all evidence identified though systematic review of the available literature.
9	NHS resource use associated with disease management is assumed to follow that assumed for decision making in TA502.	None	Sections B.3.5.1 and B.3.5.3 This approach is used to harness the data and assumptions used for decision-making in TA502, the most recent NICE TA in released or refractory MCL, in consideration of all evidence identified though systematic review of the available literature.

Key: AE, adverse event; CAR-T, chimeric antigen receptor-T; DLBCL, diffuse large B-cell lymphoma; DSU, decision support unit; EQ-5D-5L, EuroQol 5-dimenison 5-level; GP, general practitioner; HRQL, health-related quality of life; KM, Kaplan-Meier; MCL, mantle cell lymphoma; mITT, modified intention-to-treat; NHS, National Health Service; NICE, National Institute for Health

#	Assumption	Likely bias direction	Justification
and Care Excellence; ONS, Office for National Statistics; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSS, personal social services; R-BAC, rituximab, bendamustine and cytarabine; SoC, Standard of Care; TA, technology appraisal; TSD, technical support document.			

B.3.10. Base case results

Table 47 reports base case outputs. All cost-effectiveness results presented, reflect the discounted price of [redacted] for brexu-cel. Figure 21 and Figure 22 show base case Markov traces for the respective cost-effectiveness model arms. Time-preference discounting, as described in Section B.3.2.2, is applied to all cost and QALY outcomes shown, but not life year estimates, unless otherwise stated.

According to the modelled basecase, brexu-cel is expected to result in [redacted] additional years of life, and an additional [redacted] discounted QALYs, versus R-BAC when modelled over a lifetime time horizon. These gains are achieved at an expected additional cost of [redacted] resulting in an estimated incremental cost-effectiveness ratio (ICER) of £54,366 per QALY gained. This ICER is close to the willingness to pay (WTP) threshold applied in the previous submission (based on end of life criteria), and is lower than the ICER estimated in TA677 (£58,302).

Table 44: Base-case deterministic cost-effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ROBABILIT (£/QALY)
R-BAC	[redacted]	[redacted]	[redacted]				
brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,366
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.							

Figure 19: Lifetime Markov trace for brexu-cel

Figure 20: Lifetime Markov trace for SoC

Key: SoC, standard of care

Estimates of clinical outcomes compared with ZUMA-2 trial results and full disaggregated results for brexu-cel and R-BAC are presented in Appendix H.

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

PSA results for the base case analysis are summarised across Table 48, Figure 23 and Figure 24. The PSA results shown are based on 1000 random draws from uncertain input parameter distributions.

PSA indicates that brexu-cel is consistently associated with QALY benefit versus SoC at a positive incremental cost, as shown in Figure 24. Relative to the deterministic results, the PSA outputs result in a slightly higher mean ICER. Figure 23 demonstrates a [redacted] % probability of being cost-effective at a WTP of £50,000.

Table 45: Mean PSA base case results

Technologies	Mean costs	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline
SoC	[redacted]	[redacted]			
brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SoC, standard of care.

Figure 21: Cost-effectiveness acceptability curve, from base case probabilistic results

Key: SoC, Standard of Care

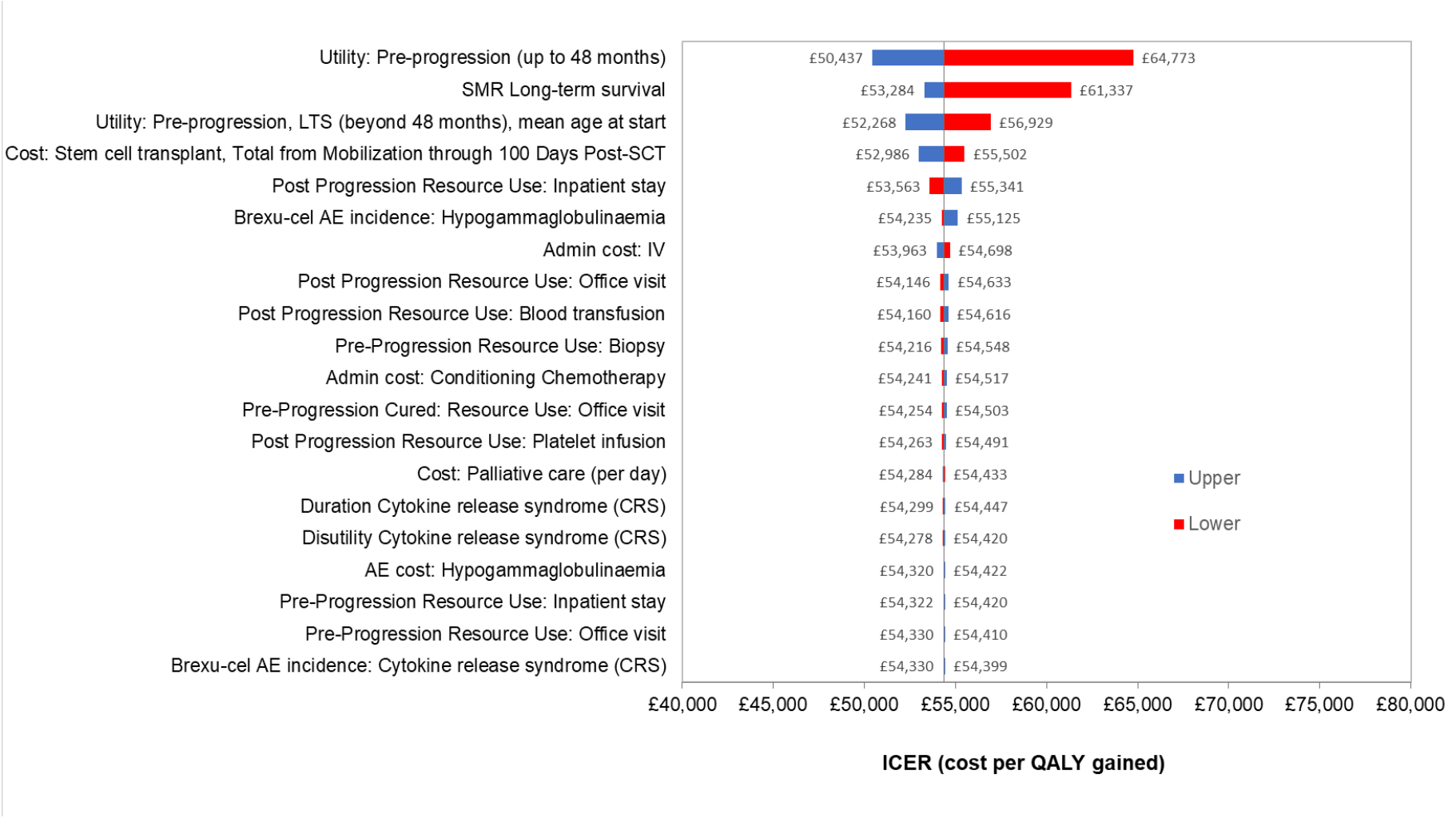
Figure 22: PSA Scatterplot, brexu-cel vs SoC, from base case PSA results

Key: PSA, probabilistic sensitivity analysis; SoC, Standard of Care; WTP, willingness to pay

B.3.11.2. Deterministic sensitivity analysis

Figure 25 shows a tornado diagram depicting the 20 parameters that have the greatest influence on the ICER versus SoC in one-way sensitivity analyses (OWSA). For OWSA, values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the confidence intervals reported in Appendix M. In this analysis, the ICER was most sensitive to parameter uncertainty around the pre-progression utility estimate from ZUMA-2 EQ-5D data described in Section B.3.4; and assumed uncertainty around the SMR applied to long-term survivorship predictions for PFS and OS in the base case, as described in Section B.3.3.

Figure 23: Tornado diagram showing OWSA results



Key: EOL, end of life; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin, OWSA, one-way sensitivity analysis; SCT, stem cell transplant; SoC, standard of care.

B.3.11.3. Scenario analysis

The scenario analyses test the sensitivity of cost-effectiveness results to methodological, parameter and structural uncertainties in the cost-effectiveness analysis. Table 49 describes different scenarios tested, the rationale behind each, and documents the ICER associated with each scenario. Summary results are generally robust to changes tested across the broad range of scenarios. The most impactful scenarios are those associated with discount rate assumptions, the model time horizon and the scenario where we explore the SACT-reported median age.

Table 46: Scenario analyses impact summary

Base case equivalent	Scenario detail	Brief rationale	ICER	IMPACT
Base case			54,366	-
Time horizon: 50 years	Time horizon: 20 years	Alternative time horizons	60,419	+11%
	Time horizon: 30 years		54,696	+1%
	Time horizon: 40 years		54,368	0%
Discount rate 3.5%	Annual discount rate for costs 1.5%; QALYs 1.5%	Alternative discount rates	45,155	-17%
	Annual discount rate for costs 6.0%; QALYs 6.0%		67,056	+23%
Long-term survivor for brexu-cel at: 48 months	LTS for brexu-cel patients at 36 months	Alternative LTS assumptions	43,946	-19%
	LTS for brexu-cel patients at 60 months		60,309	+11%
SMR of 1.09 applied to general population survival data for LTS	No SMR adjustment (general population survival)	Alternative LTS assumptions	53,284	-2%
Proportion of patients receiving subsequent alloSCT, SoC: 31%	Patients receiving allo-SCT, SoC: 15.0%	Alternative SoC subsequent allo-SCT assumptions	56,200	+3%
	Patients receiving allo-SCT, SoC: 40.0%		53,335	-2%
Proportion of patients receiving alloSCT, brexu-cel: 2.9%	Patients receiving alloSCT, brexu-cel: 0%	Alternative assumption	54,034	-1%
Mean age: 63.2 years	SACT-based age: 67.5 years (pre-progression utility also age-adjusted)	Consideration of RWE	£63,631	+17%

Key: alloSCT, allogeneic stem cell transplant; ICER, incremental cost-effectiveness ratio; LTS, long term survival; QALY, quality-adjusted life year; SACT, Systematic Anti-Cancer Therapy; SMR, standardised mortality ratio; SoC, standard of care.

B.3.11.4. Summary of sensitivity analyses results

While there is inherent uncertainty around the precise clinical- and cost-effectiveness of brexu-cel for relapsed or refractory MCL patients, the expected incremental benefit of this treatment remains substantial across plausible scenarios. Scenario analyses suggest that the ICER per QALY gained is relatively robust, ranging between £45,155 (-17% vs base case) and £67,056 (+23%) for all reasonable scenarios. The probabilistic sensitivity analysis (PSA) accounts for uncertainty in the assumptions and model parameters, and the probabilistic ICER's proximity to the base case ICER provides support for its plausibility.

Sensitivity analysis of individual model drivers confirmed that the main uncertainty of the analysis lies within the pre-progression utility estimate from ZUMA-2 EQ-5D (described in Section B.3.4) and around the SMR applied to long-term survivorship. Considering the relatively few patients from ZUMA-2 for which mature data was available, substantial uncertainties for these parameters are expected, though the scenario analysis can yield an idea of how the cost-effectiveness of treatment with brexu-cel could shift depending on this data.

B.3.12. Subgroup analysis

Subgroup analysis has not been conducted, the ZUMA-2 Cohort 1 primary outcome findings were consistent across pre-planned subgroups, including those defined by baseline demographics, clinical characteristics and treatment history. Beyond this, the sample size of ZUMA-2 subgroup data, and granularity of available comparator data, are prohibitive limitations for meaningful subgroup cost-effectiveness analysis.

B.3.13. Benefits not captured in the QALY calculation

Before the availability of CAR T-cell therapy, patients with post BTKi r/r MCL were subject to intense regimens of chemotherapy cycles in a hospital setting with little expectation of extended life. Moreover, when effective treatment options were exhausted, the mental strain on patients, their carers and family was excruciating[46,47,126], while not necessarily captured on HRQoL measures. With the availability of CAR T-cell therapy, the hope of potentially extended survival has substantially improved patient well-being through reduction in anxiety and stress.Patient and carer experience statements emphasise this, flagging that the

emotional burden of MCL can be higher than the physical burden in a pre CAR-T post-BTKi setting.[46] Arguably, this differentiation in outcome between patients on CAR-T versus patients on chemo-immunotherapy regimens with limited benefits is not captured in the current model.

The requested extension and updated analysis of the SACT data would also allow for further exploration of the QALY calculation reported here; we believe that there are uncaptured QALY survival benefits; an analysis of the later SACT population could reveal these and allow the benefits to be better captured in the modelling.

B.3.14. Validation

B.3.14.1. Validation of cost-effectiveness analysis

Base case deterministic cost-effectiveness results, presented in Section B.3.10, suggest mean life expectancy for post-ibrutinib MCL patients is [redacted] years following brexu-cel infusion and [redacted] years in absence of brexu-cel. In the absence of sufficient data maturity for a high enough number of patients, validation of absolute and relative survival estimates associated with brexu-cel is intrinsically difficult.

Since the introduction of brexu-cel through the Cancer drug fund (CDF), real-world data has routinely been collected as part of the Systemic Anti-Cancer Therapy (SACT) dataset, provided by the National Disease Registration Service, NHS England[86]. Between 19 January 2021 and 30 September 2023, 97 applications for brexu-cel were submitted, pertaining to 95 unique patients. 92 of these (97%) were reported in the data, having all been identified as receiving the single infusion. Out of these, complete data on relevant outcomes have been collected for 69 patients. The OS for these 69 patients is shown in Table 50, alongside the comparable survival estimates provided in this analysis.

Table 47: Comparison of estimated overall survival to validation data-set

Time period	OS (%), SACT data	OS (%), Model estimation
6 month	[redacted]	[redacted]
12 months	[redacted]	[redacted]

18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
Source: National Disease Registration Service (NDRS), 2024, Brexucabtagene autoleucel (was KTE-X19) for treating relapsed or refractory mantle cell lymphoma – data review[86]		

Compared to the survival associated with brexu-cel treatment recorded in the SACT dataset, the overall survival estimated in this study is consistently higher; though within the confidence intervals of the SACT data. However, there are reasons to suspect that the survival in the SACT data is lower than what should be expected from clinical practice. Production-related problems caused substantial delays to the start of treatment for many of the first patients who received brexu-cel. Since there is a strong associated between early treatment initiation and overall survival, this is likely to have impacted survival in the SACT dataset. Many of the later applicants for brexu-cel treatments (who did not experience production-related treatment delays) showed better overall survival. In addition, the SACT data collection spanned BSH guideline updates which might optimise CAR T outcome through earlier identification of potential CAR T candidates[16]. For this reason, the fact that the OS presented in this analysis exceeds that of the SACT data is in line with clinical expectations (see Section B.2.13.5 for company requests for additional SACT analysis) .

The structure, inputs and assumptions of the original cost-effectiveness analyses were reviewed during a 3 April 2020 meeting.[83] The updates made in this re-submission were reviewed by two further NHS clinicians and one health economist; the assumptions and input choices were considered defendable.

Prior to the original submission (in April 2020), the cost-effectiveness model was quality-assured by the internal processes of the external economists who built the economic model. In these processes, an economist not involved in model building reviewed the model for coding errors, inconsistencies and the plausibility of inputs; this was done as a thorough sheet-by-sheet check. The model was also subject to review against a checklist of known modelling errors and questioning of

assumptions; the checklist followed was based on publicly available and peer-reviewed checklists.[127-129] This was not repeated for the re-submission model.

B.3.15. Interpretation and conclusions of economic evidence

The economic analysis reports substantial increases in life years and quality-adjusted life years through management of r/r MCL patients with brexu-cel in preference to R-BAC, with incremental gains estimated at [redacted] LYs and [redacted] QALYs respectively. These gains were achieved at an expected additional cost of [redacted] resulting in an estimated ICER of £54,366 per additional QALY gained.

In common with the original submission, key drivers of uncertainty in the analysis were pre-progression utility estimates, SMR assumptions, and patient age. Scenario and sensitivity analyses suggest robust results when parameters are varied within their feasible range.

A key strength of the economic evaluation is in its provision of a transparent and flexible framework to explore the potential cost-effectiveness of brexu-cel in a UK setting. Other haematologic oncology models have defined "cure" points at 24 months or later, after which patient mortality is no longer driven by active disease. The concept of cure is not yet proven in MCL: in this model long-term survivors is only considered among those patients who have reached a stage after treatment where MCL mortality is no longer the main cause of death. The data available suggest this point may be reached beyond 36 months after treatment in MCL. Further follow up of these patients will allow the transition point to LTS to be placed more accurately.

The model reflects the longest follow-up of any cohort treated after r/r MCL, with a median of 67.8 months follow up reported in the ZUMA-2 dataset. This confirmed the assumptions made in TA677 that treatment with brexu-cel is associated with high rates of durable response, and long-term survival resulting in substantial QALY gain. Uncertainty has been reduced now that longer follow up is available and a body of RWE from the UK and elsewhere confirms that the high response rates and promising survival seen in ZUMA-2 are being replicated in broader practice[25,61,68,69].

Despite the extended duration of clinical follow-up, even now, follow up to ZUMA-2 is insufficient to fully predict long-term mortality, as most patients who survived 48 months after treatment are still alive, with their data censored. Further follow-up (through ongoing data collection in ZUMA-2) will allow us to confirm assumptions about late-stage mortality and long-term survival. There were also no new data on utility retrieved. Our SLR did not identify additional relevant data sources and ZUMA-2 follow up will not generate any more utility, so the EQ-5D values collected in the trial and reported in the original submission remain the best available utility data source.

The ability to define an appropriate comparator remains challenging; brexu-cel is now the established standard of care for CAR-T eligible patients who relapse on BTKi[16]. In line with the decision problem, the comparator for this submission is defined as rituximab-containing therapy (specifically R-BAC) given as a third-line or beyond following BTKi. Similar to the previous submission, no comparative evidence is available comparing brexu-cel against R-BAC in this setting and comparator data were taken from a historical cohort (McCulloch 2020). Given that there have been no updates to management options for this patient group (apart from the introduction of CAR-T), the comparator choice was defendable, approved by the clinicians consulted for the project and representative of the best available evidence.

In the absence of patient-based utility estimates for post progression health states, these estimates are limited to the pre progression health state. The ZUMA-2 EQ 5D 3L data represent a robust source of MCL evidence, with utilities estimated according to the NICE Reference Case preferred methods. However, use of these data in the model to inform pre progression states for both brexu-cel and R-BAC while in line with the Reference Case, may overestimate expected HR-QOL in the R-BAC patients. This means estimates of brexu-cel benefit may be conservative.

The generalisability of the economic findings to UK clinical practice has been provisionally supported by cross-reference to the outputs of the SACT database analysis (despite the limitations of this database). While the survival benefits estimated in the model are higher than those seen in SACT, predicted OS estimates sit within the confidence limits estimated around the OS observed in SACT. There is also a clinical rationale for believing that the SACT data underestimates the

expected benefit of treatment with brexu-cel. Production-related problems caused substantial delays to the start of treatment for many of the first patients who received brexu-cel in the SACT database and more importantly, enrolment of patients into the SACT study spanned the introduction of material changes to the BSH guidelines[16].

Real-world evidence supports substantial improvement in experience with brexu-cel over time[25], suggesting that an analysis of the SACT dataset by different time periods would be prudent, with the potential to capture overall survival gains resulting from this change in practice. Further exploration of the SACT data would allow for a more detailed validation of model outcomes. It would also allow for a more comprehensive approach to our real world scenario analysis. Currently we do not use SACT clinical evidence in the model due to the limitations outlined.

The cost-effectiveness analysis reported here supports a case for continued access to brexu-cel in this patient group. In addition, the off-model benefits of continued access to brexu-cel are substantial, with brexu-cel introducing a step-change to the management and outcomes for this previous high unmet need population. Key uncertainties remain but this is to be expected in a dynamic field where guidelines are constantly updated. As clinicians become more familiar with CAR-T options and the patient group becomes better defined, increasing offsets can be expected.

To conclude, removal of access to brexu-cel would reverse recent advances for this post BTKi r/r MCL patient group. The analysis reported here forms the conclusion to the original appraisal and the original claims of cost-effectiveness are supported.

B.4. References

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As requested by NICE during the meeting with Gilead on 11 June 2025, and to support collaborative efforts in maintaining continued access to brexucabtagene autoleucel (brexu-cel) for patients with r/r MCL, the table below reports severity analyses based on the York QALY shortfall calculator.

Table.7_.Severity.analysis

Parameter	Input	Reference
Age	63.2 years	Zuma-2[a]
% female in the patient population	16%	Zuma-2[a]
QALYs of patients untreated	1.39	Company base case
Discount rate	3.5%	NICE Methods
Remaining QALYs		
Without the disease	11.90	
With the disease	1.39	
Absolute shortfall	10.51	
Proportional shortfall	88.32%	

[a] Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N.Engl.J.Med. Apr 2 2020;382(14):1331-1342. doi:10.1056/NEJMoa1914347

We would like to reiterate our concerns about the application of the severity modifier in this appraisal and the impact that the removal of the end of life (EoL) modifier has had upon access to treatments for blood cancers more generally.

During the original appraisal (TA677) in 2021, brexu-cel qualified for the EoL modifier. Had the new NICE Methods and severity modifier been in place at that time, brexu-cel would likely not have met the lower willingness to pay threshold, and England would not have gained access to this innovative treatment that has resulted in a step-change in life expectancy for mantle cell lymphoma patients.

NICE have stated that the EoL criteria will not be applied in ID6325, however it was confirmed that NICE can potentially offer flexibility in its application of the severity modifier, and we would urge the Committee to exercise its discretion in this regard. There are examples of NICE applying flexibility in its application of the decision modifiers, including in order to allow continued access to a highly effective treatment option after 4 years of managed access within the CDF (TA509). Taking a

similar approach in this appraisal and using discretion to apply a higher Severity weighting would ensure that the NHS is able to continue to offer brexu-cel, the accepted SoC[1], to patients with severe disease who have limited alternative treatment options.

a) Severity modifier is ageist in principal

The severity modifier disproportionately impacts access to treatments for diseases which have higher prevalence in older populations. Previously many blood cancer therapies qualified for the EoL modifier and therefore a £50k willingness-to-pay (WTP) threshold. However, under the new NICE Methods, few of these therapies qualify for the severity modifier, and fewer meet the criteria for the higher weighting (£51k WTP), due to the limited remaining life years that can accrue benefit, in turn reducing the shortfall gain.

When analysing all TAs published by NICE since August 2019, it is reported that only 56% of blood cancer appraisals have been approved for use, when including appraisals that have been terminated, demonstrating the access challenges faced in England specifically for treatments for blood cancers[2]. This is compared to 74% approval reported across the TAs for other oncology indications.

Blood cancers predominantly impact the elderly and, due to their advanced age and reduced remaining life years, there is rarely an opportunity to achieve the higher weighting modifier even for the most severe diseases (in the instance of MCL, OS is reported to be 5-12.5 months in the 3L+ setting)[3]. However, had a younger patient with a similar disease be proceeding through the severity evaluation, they would arrive at different severity weightings, and thus modification to the willingness-to-pay threshold. This suggests a violation of the principal of horizontal equity[4] (individuals are being treated differently, even though their costs and prospects are the same) in the application of the severity modifier, and against NICE's stated principle 9 to aim to reduce health inequalities.

b) The thresholds to achieve higher weighting should be lowered

Furthermore, the severity weightings that are applied for the proportional shortfall (PS) and absolute shortfall (AS) are significantly higher than those applied in other European countries where a severity modifier, or similar, are in use.

NICE Severity modifier weightings		
Willingness-to-pay (WTP) modifier	Proportional shortfall (PS)	Absolute shortfall (AS)
1	>0.85	>12
1.2	0.85-0.95	12-18

1.7	<0.95	<18

Two other European countries that have adopted a severity weighting principle in their Health Technology Assessment, Norway and The Netherlands, have far lower weightings, meaning the opportunity for patients to access innovative medicines is higher.

The Netherlands		Norway	
PS	WTP modifier	AS	WTP modifier
0.1-0.4	1.0	0-3.9	1.0
		4-7.9	1.4
0.41-0.7	2.5	8-11.9	1.8
		12-15.9	2.2
0.71-1.0	4.0	16-20	2.6
		>20	3.0

As demonstrated, not only does NICE apply the strictest severity weighting, but it also applies the most restrictive WTP modification based on each of these levels, prohibiting innovation and leading to access inequalities across the UK and Europe.

c) Impact of discounting

Discounting of health effects, with a reference case set at 3.5%, has a more acute impact with the Severity modifier, than the impact of discounting on the EoL modifier.

The value of weighting in the severity modifier is dictated by the QALY gain, and discounting will have been directly applied to the QALY benefit when calculating shortfall.

The clinical information was the main factor that influenced the EoL modification in the WTP level. Therefore, when applying the severity modifier to the WTP thresholds, the evaluation should be made on the basis of undiscounted ICERS to ensure treatments that provide long-term benefits are not unfairly disadvantaged. To do otherwise leaves the risk that treatments for severe diseases, especially those with long-term benefits such as CAR-T, are undervalued, potentially resulting in limited or no access to innovative treatments.

[1] Eyre TA, Bishton MJ, McCulloch R, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. *British journal of haematology*. Jan 2024;204(1):108-126. doi:10.1111/bjh.19131

[2] BCA & Costello Medical. (n.d.). *Barriers to access to new blood cancer treatments*. Retrieved June, 2025, from https://crow-tomato-

25sm.squarespace.com/access#:~:text=BCA%20and%20Costello%20Medical%20Research%20Report%3A%20Barriers%20to%20Access%20to%20New%20Blood%20Cancer%20Treatments

[3] McCulloch R, Visco C, Eyre TA, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. *British journal of haematology*. Feb 3 2020;doi:10.1111/bjh.16416

[4] Hausman, D. M. (2024). Problems with NICE's severity weights. *Social Science & Medicine, 348*, 116833. https://doi.org/10.1016/j.socscimed.2024.116833

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma [ID6325]

Summary of Information for Patients (SIP)

February 2025

File name	Version	Contains confidential information	Date
ID6325_Brexu-cel RR MCL_NICE STA SIP	1.0	Yes	07/02/25

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Brand/Trade name: Tecartus Generic name: brexucabtagene autoleucel (brexu-cel)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) after two or more lines of therapy, including a Bruton's tyrosine kinase inhibitor (BTKi).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

EMA approval on 25/01/2021 https://www.ema.eropa.eu/en/medicines/human/EPAR/tecartus

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

In 2024/5 Gilead provided arm's length project grant funding to, and/or paid for consultancy services from the patient groups listed below, to support innovation and best practices in caring

for people living with blood cancer. Full details of the financial support provided to patient groups by Gilead can be found at https://www.gilead.co.uk/about/transparency

- African Caribbean Leukaemia Trust
- Anthony Nolan
- Blood Cancer UK
- Cancer52
- Leukaemia Care
- Leukaemia UK
- Lymphoma Action
- Macmillan Cancer Support
- Maggie's Centres

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Mantle cell lymphoma (MCL) is a rare blood cancer that is a type of non-Hodgkin lymphoma (NHL). NHLs are a group of different blood cancers originating primarily in white blood cells, which control our immune system. MCL specifically begins in the white blood cells located in "mantle zones" of lymph nodes which are small structures of tissue in the body that contain white blood cells to fight infection. The cancer typically affects people between age 60 to 70 years of age, and is three times more likely in men than women.

MCL begins slowly but later grows rapidly. At advanced stages the cancer can spread from the lymph nodes to bloodstream, bone marrow and digestive organs. Although early stage MCL typically has no symptoms, at a later stage the symptoms start with painless swollen lymph nodes in the neck, armpit and groin, night sweats, high temperatures, weight loss and itching. Once the cancer spreads, people may experience appetite loss, diarrhoea, sickness, anaemia and fatigue.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

During the early stages of MCL, most people do not exhibit any outward signs or symptoms; hence the disease is "silent" and often only discovered during regular blood tests which will reveal a high number of lymphocytes in the blood. Other times, a person's MCL is discovered during a physical examination, and the doctor discovers a swollen lymph node.

Formal diagnosis of MCL requires the removal and testing of a sample of lymph node tissue from the patient (referred to as a 'biopsy'). The tissue sample is then sent to a laboratory for testing. Once the MCL is diagnosed, the cancer is staged (stages I to IV) based on how many lymph nodes in the body are affected.

There are no additional diagnostic tests required for brexu-cel treatment.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

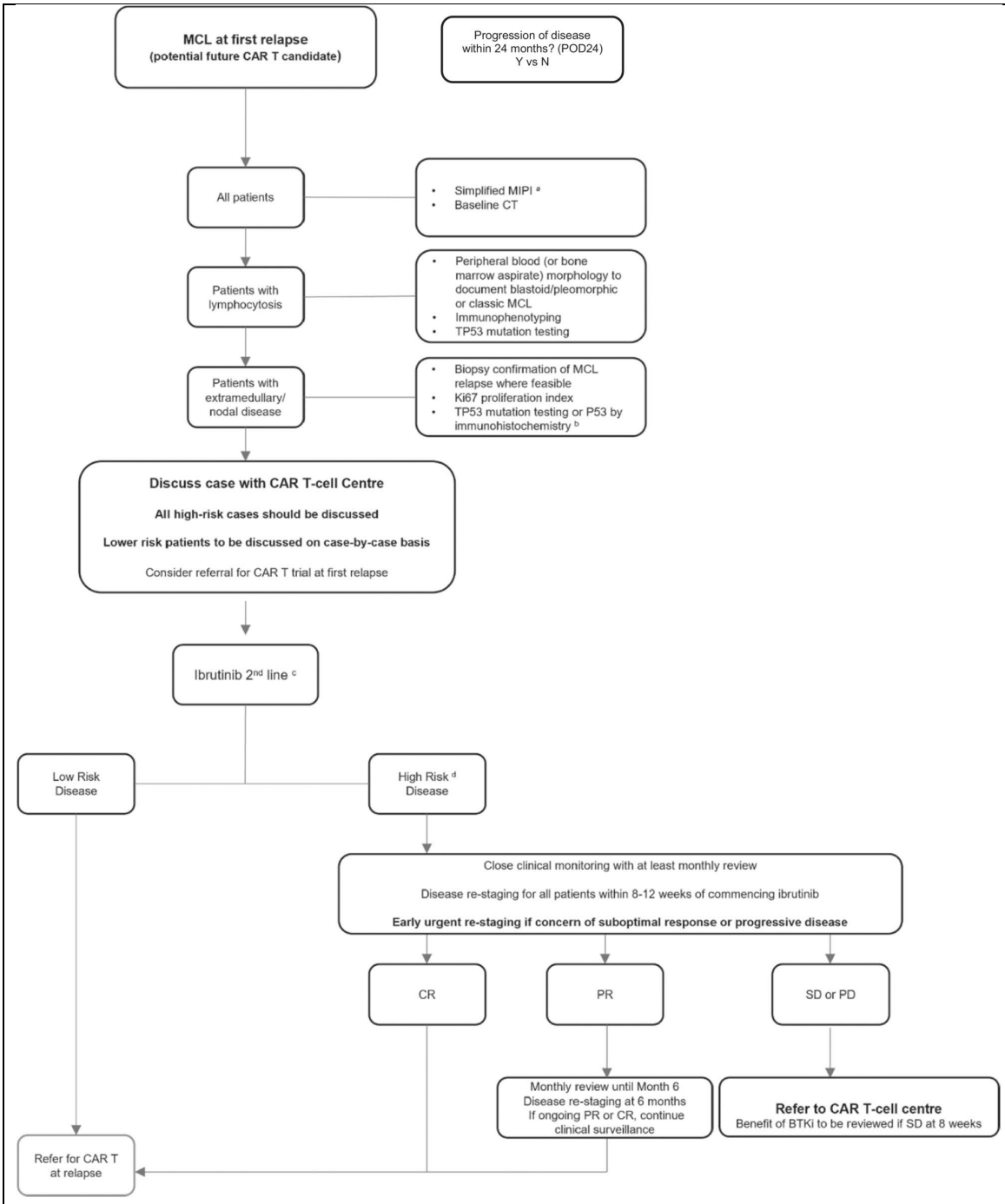
- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The most common treatment practice for MCL is outlined in the British Society of Haematology (BSH) guidelines(1). If the cancer does not respond to 1L therapy (refractory) or it comes back after an initial response (relapse), patients who are eligible for it are given a treatment known as a Bruton's tyrosine kinase inhibitor (BTKi; ibrutinib). At this point, those who are at high risk of MCL progression are immediately monitored for relapse to ensure prompt referral to CAR T third-line therapy if they relapse a second time. BSH guidelines now recommend CAR T therapy as the established treatment option for these post BTKi CAR T-eligible patients (Figure 1).

- These patients with r/r MCL whose disease returns after, or is not responsive to, a BTKi and at least one other line of treatment are the focus of this NICE CDF exit submission.

The prognosis for survival in patients who do not respond to BTKis has traditionally been extremely poor due to the lack of a promising further line of therapies; but in those patients eligible for CAR T therapy, the use of the treatment has improved this outlook substantially (see section 3e for more information on this). However, how someone's cancer may respond to the treatment depends upon many factors, such as the specific type and stage of their disease, along with other factors, including their age, other medical conditions and tumour genetics.

Figure 1. BSH Treatment Guidelines for MCL



Key: CAR, chimeric antigen receptor; CR, complete response; MCL, mantle cell lymphoma; PR, partial response; SCT, stem cell transplant **Source:** BSH MCL guidelines, 2024(2)

Brexu-cel is the only CAR-T that is licensed for relapsed/refractory MCL, and has been made temporarily available to the NHS since 2021 through the cancer drug fund (CDF). Since then, its effectiveness is being established through follow-up studies of r/r MCL patients in a UK setting(3).

Before the availability of CAR T-cell therapy, patients with relapsed/refractory MCL needed intense regimens of chemotherapy cycles in a hospital setting with little expectation of extended life. CAR T (brexu-cel) has provided a step change in outlook for this previously underserved patient group and is an established part of MCL management in a standard UK setting. In the absence of CAR T, the options for patients would be very limited as no new therapies have entered the UK health care setting after the introduction of CAR T in 2021.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

No patient-based evidence was generated for this submission however, before the availability of CAR T-cell therapy, patients with relapse after being treated with BTKi had to undergo intense regimens of chemotherapy cycles in a hospital setting with little expectation of extended life. Once all effective treatment options were exhausted, the mental strain on patients, their carers and family was high, while not necessarily captured on formal quality of life measures.

With the availability of CAR T-cell therapy, the possibility of potentially extended survival has substantially improved the outlook for patients who relapse after treatment with ibrutinib.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

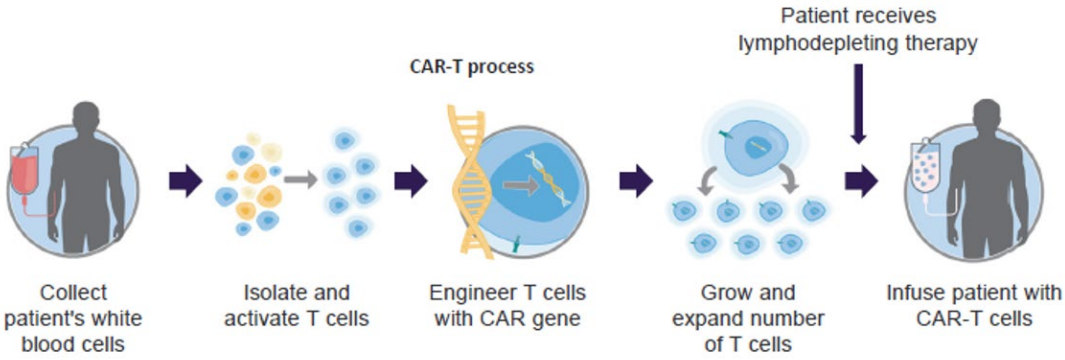
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

CAR T therapy is a gene cell medicine. It is used when other medicines have stopped working (that is, in relapsed or refractory disease). CAR T-cell therapy uses a person's own white blood cells (T-cells) to fight the cancer. The cells are taken from a person and sent to a lab for "reprogramming" so that they can kill the cancer cells. The "reprogrammed" cells are then put back into the same person through an infusion. This is a highly innovative approach that tailors the treatment to the specific patient and their disease (illustrated in Figure 2).

Brexu-cel is a single-infusion product for intravenous (administered into the vein) use only. This means it is delivered in a hospital setting. There are clear administration benefits of a single treatment infusion versus the recurrent cyclic nature of pre- CAR T conventional chemotherapy.

Figure 2: Process of manufacturing and administering brexu-cel



Key: CAR, chimeric antigen receptor; CAR T, chimeric receptor antigen T-cell; Lymphodepleting therapy is also known as conditioning chemotherapy and is given in the days before infusion of the CAR-T cells.

The summary of product characteristics for brexu-cel can be found here.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Prior to being admitted into hospital for infusion with brexu-cel, patients are treated with low-dose chemotherapy. This chemotherapy regimen consists of two agents (called cyclophosphamide

and fludarabine) which are both administered intravenously in the days leading up to infusion of brexu-cel. Patients might also be given holding or bridging therapy (e.g. R-BAC) to try control the disease before the CAR T infusion. Patients are also given paracetamol and diphenhydramine (an antihistamine) approximately 1 hour before brexu-cel infusion.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

A single infusion of brexu-cel using a person's own engineered T-cells is administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg. Patients then need to be monitored closely for 7 days in a hospital setting to check and manage any adverse events.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The pivotal, regulatory evidence to support brexu-cel is the single-arm, Phase I/II study, called 'ZUMA-2', that started enrolment in 2015. A summary of ZUMA-2 is presented in Table 1.

Table 1: Overview of ZUMA-2(4)

Study	ZUMA-2 (NCT02601313)
Study design	ZUMA-2 is an ongoing, Phase II, multicentre, open-label, single-arm study evaluating the efficacy and safety of brexu-cel in relapsed/refractory MCL
Location	The study was conducted at 32 centres across the US, France, Germany and the Netherlands
Study participants	Adult patients with relapsed/refractory MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTKi (ibrutinib and/or acalabrutinib)
Intervention(s)	Brexucabtegene autoleucel (brexu-cel)
Comparator(s)	None (ZUMA-2 is a single-arm trial)

Key: BTKi: Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma; **Source:** Wang et al., 2020

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

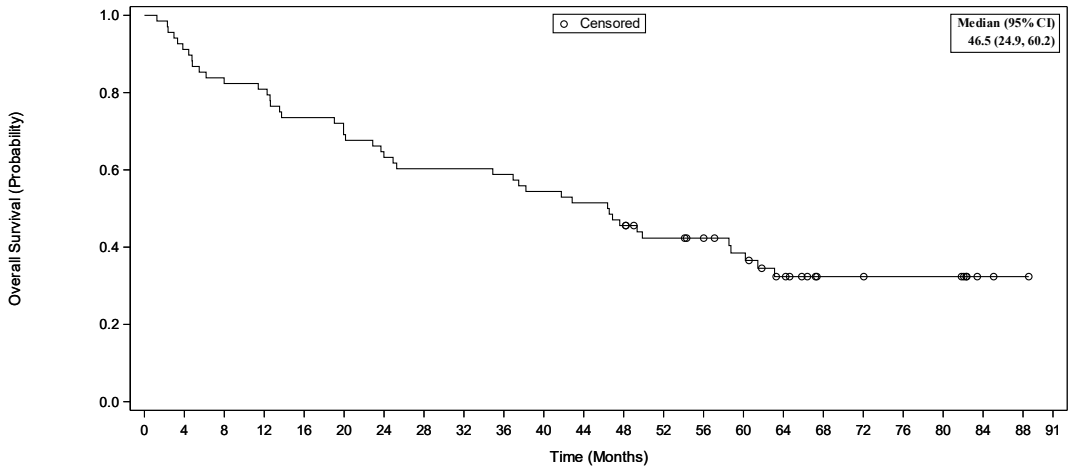
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

ZUMA-2 is a single-arm trial that does not include a comparator to brexu-cel.(4)

The primary aim of the ZUMA-2 trial was to look at overall response rate (how many patients respond to treatment) following brexu-cel infusion, defined as a complete (remission) or partial response to treatment per the International Working Group (IWG) response criteria for Malignant Lymphoma. This was evaluated 6 months after the brexu-cel infusion. Other key secondary efficacy outcomes included overall survival (how long a person survives), progression-free survival (how long until a person's cancer gets worse) and duration of their initial response to brexu -cel.

In the trial, over 80% of patients were alive at 12 months, with 30% of patients still alive at 5 years. The median overall survival, the point when half of patients were still alive, was 46.5 months. This is illustrated in Figure 3; a Kaplan-Meier survival curve based on the latest data.

Figure 3. Overall survival (patients from ZUMA-2)



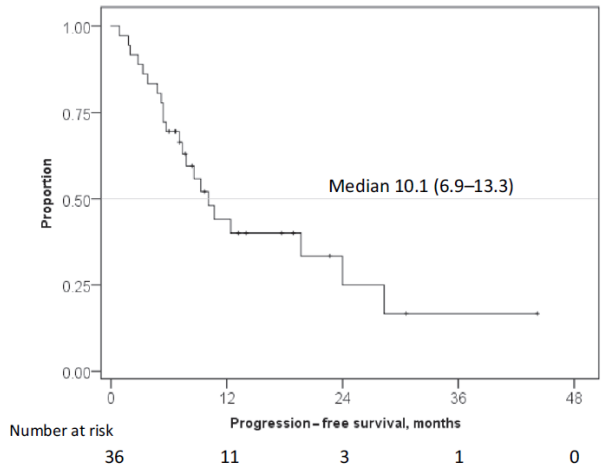
Key: CI, confidence interval; OS, overall survival; **Source:** Wang et al 2024(5)

The reported survival rates have not been seen before in the relapsed/refractory MCL setting. To put the ZUMA-2 results into perspective, observational studies pre CAR-T reported median overall survival at between 5.5 months (for patients who were not able to access subsequent treatment) up to 14.0 months (for patients on optimal pre CAR T management, for example early line R-BAC).

ZUMA-2 is a single-arm study, and comparator data for the economic analysis are sourced from the literature. In the previous submission, the committee concluded that data from a UK study by McCulloch(6) should be used to inform the clinical effectiveness evidence for the comparator. The evidence base has not changed since the previous appraisal (this is because since the initial submission, CAR T has become the established treatment choice in this patient setting so other treatment options are no longer explored). McCulloch reports survival outcomes for patients managed in a UK setting after two or more lines of therapy (one of which was a BTKi), that is, the same patient population that was enrolled and followed in the ZUMA-2 clinical trial.

The follow-up data for patients in the McCulloch study can be compared to the data reported above for brexu-cel. Figure 4 shows the same sort of survival curve as shown in Figure 3. In this study, only 30% of patients were alive at 12 months, with no patients alive by the end of follow-up. The median overall survival, the point when half of patients were still alive, was 10.1 months.

Figure 4. Overall survival (R-BAC patients from McCulloch)



These overall survival data (ZUMA-2 and McCulloch) are used along with the progression free survival data from these two studies (not reported here) to estimate how long patients stay progression free after receiving treatment and how long they stay alive. Survival curves are used to estimate outcomes over the longer time horizon included in the economic model. These approaches are described in section B.3.3 of the brexu-cel CDF exit submission.

Additional clinical evidence for brexu-cel includes the Systemic Anti-Cancer Therapy (SACT) database analysis(7). The SACT database collects systemic anti-cancer therapy treatment patterns

and outcomes on a national scale from all NHS England providers. SACT collected data on brexu-cel as part of the managed access agreement following entry of brexu-cel to the CDF in 2021.

Of the 92 patients in the SACT database who received brexu-cel, 51 (62%) patients survived to the end of the follow-up period (25 September 2024). OS at 24 months was 61%, and at 36 months was 45%. The data are not of good enough quality to include in the model but they help support the findings of both the ZUMA-2 study and the other long-term UK patient follow-up(3, 5).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The Euro-QoL 5 Dimension (EQ-5D) is a standardised measure of health-related quality of life (HRQoL) that was administered as a questionnaire to a group of patients (65) in ZUMA-2. The questionnaire was administered at different points in time to measure patients' HRQoL before (at enrollment) and after (at week 4 and month 3 and month 6) brexu-cel was administered.

These HRQoL scores decreased from baseline to Week 4 (reflecting the period when patients are most likely to experience acute treatment-related toxicity); however, scores in mobility, self-care, usual activities and overall health (according to the EQ-5D visual analogue scale [VAS]) improved by Month 3, with overall health returning to baseline status or better in most patients by Month 6. These data were converted into utility scores (a weighted measure of quality of life) and were used in the economic model (see B.3.4 in the submission).

A limitation of these data is that out of the 214 observations collected during EQ-5D follow-up, only three of these observations came from patients who had progressed on disease. This means that the data above are only useful to understand QOL in patients who have not progressed.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Most patients experience some side effects after CAR T therapy but the two events most linked to CAR T are cytokine release syndrome (CRS) and neurotoxicities (commonly known as ICANS)

CRS is characterised by symptoms such as high fever, low blood pressure, low oxygen levels in the blood, and may affect multiple organs in the body. Neurotoxicity can lead to symptoms of confusion and delirium in some patients, and possibly seizures and swelling of the brain.
The rates of these AEs are tracked carefully so that they can be managed as soon as they appear. They are classed by grade with AEs ≥ grade 3 most likely to have a serious impact on patients (for example resulting in admission to hospital, monitoring in an ICU setting or, very rarely, death). In the ZUMA-2 trial the rates of CRS and neurotoxicity ≥ grade 3 were estimated at 15% and 31% respectively. Other impactful events such as reduction in immune antibodies have a serious impact on patients and require long term management but are much rarer (1.5% in ZUMA-2).

There is a good deal of real-world evidence now from UK with brexu-cel showing that in a normal clinical setting the rates of Grade ≥ 3 CRS and neurological events are lower than those reported in the brexu-cel trial (12% versus 15% for CRS and 22% versus 31% for neurotoxicity)(3). These differences between trial and real-world settings suggest that CAR T centres are increasingly adept at preventing serious AEs and it is reasonable to expect a further improvement in the safety profile of brexu-cel with time. However, patients need to be monitored carefully for these events.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The main benefits of brexu-cel treatment include:

- Substantial survival benefits following brexu-cel treatment - the McCulloch study, conducted prior to the introduction of CAR T, showed that patients after their 2nd relapse had a median survival of 10.1 months(6); median survival at 5 years from ZUMA-2 was 46.5 months(5).
- Reduced need for repeated hospitalisations - brexu-cel is only one infusion; therefore, the patient does not have to go through several rounds of chemotherapy and hospital visits

- A step change in outlook for r/r MCL patients who have failed or relapsed on BTKis; prior to CAR T introduction there was no formal management option and outlook was extremely poor.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Key disadvantages relate to monitoring for adverse events. Patients must be carefully monitored, potentially within a hospital setting, for the first 7 days following their brexu-cel infusion for signs or symptoms of CRS or neurotoxicity. Patients must then stay within proximity of the treating hospital for at least the first month after brexu-cel infusion. Routine monitoring of these patients beyond the initial 7 days is recommended based on the opinion of the treating doctor.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic evaluation of brexu-cel was based on a mathematical model that simulated patients' disease experience over time. Models are designed as a simplification of the patient or disease pathway, and it is common in modelling different types of cancer for this to be focussed on disease progression. The model that was developed and submitted to NICE for brexu-cel had three health states: progression-free, progressed disease and death with all patients starting in a

progression-free health state. Patients' movement between health states in the model was based on efficacy data from ZUMA-2 (brexu-cel) and the McCulloch study (the comparator, R-BAC).

Each health state is associated with different levels of HRQoL and different costs (e.g. drug costs, cost to manage side effects, hospital stay costs). In addition, the side effects of brexu-cel treatment are captured in additional HRQoL calculations, with each side effect experienced assumed to result in a temporary reduction of HRQoL (no side effects were included for R-BAC).

To allow the condition to be modelled over a patient's lifetime, assumptions have to be made to overcome gaps in the evidence. A key gap is in the long-term survival and progression-free survival outcomes for patients treated with brexu-cel or R-BAC. Although 5-year outcomes from ZUMA-2 are available, the model needs to be able to estimate how these outcomes will look at 10, 20, 30 years following brexu-cel treatment. This is done by fitting curves to the observed trial or study data and selecting the curve that provides the best fit. Given the uncertainty around this, a variety of curves were tested before the curves that provided the best fit were selected.

The model showed that patients treated with brexu-cel experience a greater HRQoL because they have a greater life expectancy and remain in the progression-free health state for longer. This state has a greater HRQoL value compared with the progressed disease health state. Brexu-cel has a higher treatment cost compared to R-BAC and the benefits in avoiding progressive disease are not fully offset meaning that there is substantial overall cost impact. Balancing both the additional costs and quality of life gain, the model estimated the incremental cost per quality-adjusted life year gained (i.e. the incremental cost per QALY gained, NICE's preferred measure of cost-effectiveness). This was estimated at a similar level to the previous submission suggesting that brexu-cel should continue to be considered a cost-effective use of NHS resources.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Brexu-cel is an individualised and highly innovative medicine in which the patient's own T-cells are collected and genetically engineered ex vivo (outside the body) to express a CAR protein that programs them to target and kill cancer cells once returned to the patient via a single infusion.

Brexu-cel represents a breakthrough treatment in the relapsed/refractory NHL setting, offering the potential of long-term survival to patients who prior to introduction of CAR T had extremely poor life expectancy and for whom there was previously no defined standard of care.

While the main health-related benefits for brexu-cel are captured in the QALYs (quality-adjusted life years, which combine HRQoL with length of life), it is difficult to capture true innovation in such a calculation. The significant difference this treatment choice makes to patients, carers and healthcare services is such that continued brexu-cel access is, in the current clinical context, integral to the effective management of post BTKi relapsed or refractory MCL patients.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

No equality issues are foreseen.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- CAR T-cell therapy: an immunotherapy customised for each individual patient. The process involved collecting T-cell immune cells from the patient and re-engineering the immune cells to produce proteins called chimeric antigen receptors on the surface of the T-cells. These allow the T-cell to detect and attack cancer cells. These cells are then re-infused.
- QALY: quality-adjusted life year. A measure commonly used in economic models to value health outcomes. It combines quality and quantity of life.
- Refractory disease: cancer that has not responded to treatment.
- Relapsed disease: cancer that has previously responded to treatment, but then returns.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Fox CP, Chaganti S, McIlroy G, Barrington SF, Burton C, Cwynarski K, et al. The management of newly diagnosed large B-cell lymphoma: A British Society for Haematology Guideline. British journal of haematology. 2024;204(4):1178-92.
2. Eyre TA, Bishton MJ, McCulloch R, O'Reilly M, Sanderson R, Menon G, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. British journal of haematology. 2024;204(1):108-26.
3. O'Reilly MA, Wilson W, Burns D, Kuhnl A, Seymour F, Uttenthal B, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in the United Kingdom: A real-world intention-to-treat analysis. Hemasphere. 2024;8(6):e87.
4. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020;382(14):1331-42.
5. Wang M, Goy A, Munoz J, Locke FL, Jacobson CA, Hill BT, et al. Five-Year Outcomes of Patients (Pts) with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Treated with Brexucabtagene Autoleucel (Brexu-cel) in ZUMA-2 Cohorts 1 and 2. Blood. 2024;144(Supplement 1):4388-.
6. McCulloch R, Visco C, Eyre TA, Frewin R, Phillips N, Tucker DL, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. British journal of haematology. 2020.
7. NHS England. Brexucabtagene autoleucel (was KTE-X19) for treating relapsed or refractory mantle cell lymphoma - data review. 2024.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments (review of TA677) [ID6325]

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6325 Brexu-Cel EAG clarification questions_RESPONSE_CON	1.0	Yes	20/03/25

Notes for company

Highlighting in the template

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

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

ZUMA-2

A1. Please provide the original and most recent versions of the ZUMA-2 trial protocol.

We have provided the original ZUMA-2 trial protocol along with Amendment 9, which represents the most recent version of the protocol.

A2. Please confirm how the 5 people who were retreated were included in the efficacy and safety analyses. Was any censoring applied? Is re-treatment expected to be available for routine NHS use? Why was re-treatment required?

Disease assessments obtained after retreatment are not used in the primary summaries of objective response, best response, duration of response (DOR), and progression-free survival (PFS). For patients who undergo retreatment, disease assessments obtained after retreatment are included in the summaries of objective and best response to retreatment with anti-CD19 CAR T cells, as well as duration of response to retreatment (DORR). The subject's overall survival (OS) time is derived from the last known date they were alive, regardless of retreatment status.

Two patients in Cohort 1 who had disease progression after having an objective response to KTE-X19 were retreated, receiving a second infusion of KTE-X19 approximately 1 year and 1.3 years after the initial infusion. Following retreatment, [redacted] had a best overall response of [redacted] (using central assessment per Lugano classification) with a median DOR of [redacted] months; the other had [redacted]. Re-treatment is not expected to occur in NHS clinical practice

A3. The company submission makes reasonable reference to ZUMA-2 Cohort 2, but it is unclear if any information from this cohort actually informs the company submission. Please confirm.

Cohort 2 does not inform the company submission. The existence of that cohort was mentioned in the submission for completeness. Cohort 1 informs the submission.

A4. PRIORITY: Please provide safety and efficacy results (e.g. sections B.2.6.1 – B.2.6.3 and B.2.11) for the leukapheresed population of Cohort 1, Cohort 3, and the combined leukapheresed populations of Cohorts 1 and 3, from point of leukapheresis.

The leukapheresed population is not a pre-defined safety population. As per protocol, patients enrolled but not infused were followed for AEs up to 30 days post-procedure, making their AE follow-up different from the protocol-defined safety population. A separate AE table can be provided for these patients if needed, but we do not recommend combining them with the safety population.

For efficacy, we have FAS results for OS in Cohort 1 and can provide DOR and PFS upon request. Cohort 3 is not relevant to this assessment and includes BTKi-naïve patients, making it off-label in the EU; we do not recommend providing this analysis.

A5. The median time between leukapheresis and delivery to the site was 16 days, while the median time between leukapheresis and infusion was 27 days (CS B.2.4.2). Please clarify the reasons for the delay between delivery and infusion.

The delay between delivery and infusion is primarily due to investigator discretion, as Gilead/Kite has no control over the infusion date once the product is delivered. In

Cohort 1, 28 patients received bridging therapy, and infusion timing was determined based on clinical considerations, such as completing bridging chemotherapy.

A6. Based on the CS B.2.6.5, minimal residual disease (MRD) has been evaluated only in 29 patients. Could you please clarify how these patients were selected and whether MRD assessments have been defined and discussed as part of the ZUMA-2 protocol?

MRD was assessed as an exploratory analysis using a sensitivity threshold of 1 in 100,000 cells. Cryopreserved peripheral blood mononuclear cells were obtained at baseline and at months 1, 3, and 6, and MRD was analysed using next-generation sequencing with the clonoSEQ assay (Adaptive Biotechnologies). This assessment was conducted on an ad hoc basis using archived samples, with 29 samples deemed suitable for analysis. Further details can be found in the Wang et al. 2020.

A7. For the ZUMA-2 Cohort 1 enrolled and infused populations, please confirm how many patients showed blood circulating tumour cells (CTCs), both before and after bridging therapy.

Based on the protocol, ctDNA was not analysed in ZUMA-2 so we do not have this.

A8. Please clarify how many patients had their infusion delayed by more than 2 weeks and received additional conditioning chemotherapy.

There were no patients who had their infusion delayed by more than 2 weeks .

A9. Please provide details of the frequencies for each exclusion criteria in excluding people from the ZUMA-2 trial.

This relates to patients excluded at screening phase. These patients are not relevant to the appraisal. A full list of exclusion criteria is in the protocol (provided under A1).

A10. Please report the percentage of patients who had previous bendamustine at baseline based on the following timeline: <6 months, 6-24 months, ≥ 24 months, never.

We agreed a modified response to this at the clarification meeting. As reported in Wang 2020, 54% of patients received prior bendamustine; of these patients (n=36), n=12 (32%) received bendamustine <= 6months; n=26 (68%) at >6 months.

A11. In CS, Table 13, please report the updated list of all subsequent treatments patients received based on the latest data cutoff (April 2024).

An updated list of subsequent treatments is attached to this response.

A12. Please confirm when the next data-cut from ZUMA-2 Cohort 1 is anticipated?

There are no further data cutoffs planned.

A13. Please confirm original cohorts of people in LTFU, as the company submission appears to contain contradictory information.

The data relevant to this submission pertains exclusively to Cohort 1, and respective cohorts have been clearly specified in all tables, figures, and listings (TFLs).

A14. PRIORITY: If not already provided, please provide outcomes for the LTFU, only including people from Cohort 1.

The LTFU is the protocol used to collect long-term data for patients enrolled in the ZUMA-2 study. The long-term outcomes for cohort 1 include cohort 1 LTFU data.

A15. Please confirm in Figure 6 for example, how there are more people at risk beyond 24 months than there are enrolled in LTFU.

This discrepancy appears to be related to differences between central and investigator assessments. In the central assessment, which served as the basis for the Wang publication, the objective response rate (ORR) was 62%. Conversely, the ORR per investigator assessment was 60%. Since the latest data cutoff (DCO) includes only investigator assessments, the number reported in Figure 6 (based on central review) is higher than the corresponding number in the long-term follow-up (LTFU) analysis (based on investigator assessment).

A16. PRIORITY: Please confirm whether it is anticipated that people with prior allo-SCT would be eligible to receive brexu-cel (as per SACT), or not (as per ZUMA-2)

People with prior allo-SCT would be eligible to receive brexu-cel in the real world. Approximately 15% of all brexu-cel patients are expected to have received previous allo-SCT.

A17. Given that BTKi failure is a prerequisite for brexu-cel eligibility, please could the company explain the rationale of using BTKi as bridging therapy (~35% in Cohort 1)?

Given the aggressive nature of mantle cell lymphoma (MCL), symptoms can develop and progress rapidly. It is therefore important to maintain disease control until CAR T-cell therapy can be manufactured and administered. To achieve this, caution is exercised when discontinuing ongoing therapies, and bridging therapies are introduced as necessary. As Bruton's tyrosine kinase inhibitors (BTKis) are commonly used in MCL management, they were a preferred choice for bridging therapy in this context. Additionally, clinical guidelines advise against the abrupt discontinuation of ibrutinib due to the risk of rapid disease progression. Consequently, patients who had failed on ibrutinib often continued receiving it until CAR T-cell infusion to help control progressive disease.

A18. Please confirm the rationale behind the one patient who was not infused despite brexu-cel being successfully manufactured, due to atrial fibrillation.

One subject did not receive KTE-X19 after undergoing conditioning chemotherapy due to ongoing active atrial fibrillation (reported as "other"), which was identified by Kite after the initiation of the first day of conditioning chemotherapy. As per protocol, ongoing cardiac arrhythmias are an exclusion criterion; therefore, this patient did not receive the KTE-X19 infusion.

A19. In Section B.2.3.2 of the company submission, the company states: *"In line with the agreement in the previous submission, only the mITT population is reported."* Could the company please provide clarification on where, specifically, the Appraisal Committee explicitly stated a preference for using the mITT population over the ITT or enrolled population?

In TA677 the modified ITT was accepted by the committee as sufficient to demonstrate the effectiveness of brexu-cel (FAD section 3.3). The company model based on the modified ITT was accepted as appropriate for decision making (FAD section 3.9) after the company had implemented all ERG amendments with the exception of long term mortality (FAD section 3.7). No new information is available

about these patients, the ZUMA-2 cohort is the same as in TA677. The mITT population presented is consistent with the analysis and discussion in TA677.

A20. Please report the percentages of treatment-emergent adverse events (TEAEs) grade 3 and above for all patients regardless of frequency of occurrence based on the latest data cutoff (April 2024).

Please see most recent table for treatment-emergent adverse events (T14.3.3.1.1a). This has a data cut off OCT 2023; no AEs reported between this DCO and April 24.

A21. Please report the baseline characteristics, remission rates, DOR, PFS, and OS for the subgroups of patients with and without bridging therapy (e.g. condensed version of sections B.2.3.2 and B.2.6.1 - B.2.6.3). Include outcomes for patients whose disease was uncontrolled post-bridging therapy and whether they were infused despite progression.

The additional data is provided with this response but with the modification agreed at the clarification meeting (i.e limited to OS and PS for most recent datacuts available).

SACT

A22. Please confirm reasons for n=45 who did not apply for brexu-cel infusion. Please provide a breakdown, e.g. manufacturing failure = X, ineligible=X, death=X. Please provide an overview of the reasons for ineligibility.

We believe this specific breakdown does not exist, nor can our data be analysed in this manner. However, we can make certain assumptions based on the progression of manufacturing failure over the years. In 2021, the manufacturing failure rate was 23%, decreasing to 11% in 2022, and further declining to 2-4% in 2023-2024. Patients who did not receive brexu-cel due to manufacturing failure were either ineligible for treatment at the outset or became ineligible over time. Brexu-cel is invoiced at the point of delivery, so there would be no change for patients with manufacturing failure. Note that the company only has the same report as the EAG.

A23. Please explain the perceived impact of each change to the BSH guidelines on the brexu-cel outcomes..

The impact of the BSH guideline on clinical practice and subsequently brexu-cel outcomes is expected to be substantial.

MCL is an aggressive cancer. Symptoms develop and progress rapidly, making the prognosis of patients that relapse on Bruton Kinase Inhibitors (BTKis) and do not move quickly to further lines of therapy particularly dismal.[1] Brexu-cel was reimbursed through the CDF in Feb-21 for relapsed/refractory (R/R) patients with MCL following failure of treatment with BTKis.

The initial UK real-world experience for brexu-cel was reported at the American Society of Haematology (ASH) conference in Dec-22 by O'Reilly et al.[2] In this analysis, 82 patients with R/R MCL [intention-to-treat (ITT) population] were approved between Feb-21 and Jul-22 to receive brexu-cel. Of note, in this initial UK cohort the number of patients receiving brexu-cel was lower than expected, with manufacturing failure and progressing disease being cited as the main reasons for this discrepancy. Specifically, 29 patients were approved for treatment but were not able proceed to infusion. Furthermore, the manufacturing failure rate of 24.6% was substantially higher compared to a 4% of manufacturing failure in the pivotal ZUMA-2 trial.[3]

The authors of the O'Reilly et al., study concluded that "earlier referral with lower disease burden and better bridging strategies may reduce ITT failures, improve manufacturing success and overall outcomes". The end of study data collection (Jul-22) coincided with the publication also by O'Reilly et al., of an addendum to the British Society of Haematology MCL Guidance.[4] The 'ASH Study' conclusions were in line with the key messages of the national BSH addendum. This addendum recommended a risk-based surveillance strategy aiming to identify patients at high-risk of early BTKi relapse, capture early refractory or progressive disease, and refer eligible patients rapidly for treatment with CAR T.[4] Following the publication of the BSH addendum, a substantial improvement has been noticed in the UK manufacturing success of brexu-cel, suggesting an impact of the guidance recommendations on clinical practice. Specifically, the manufacturing failure rate was reduced from 23% in 2021[4], to [redacted]% in 2022 and to [redacted]% in 2023-24[5]. Subsequently, it would be reasonable to assume that this change in clinical practice after an initial real-world experience that has already led to an improvement in manufacturing success will also translate into improvements in survival outcomes as centres become more familiar with the use of brexu-cel according to the principles of the guidelines, and patients receive brexu-cel at the earliest possible stage.

Indeed, this phenomenon of improved outcomes for CAR-T patients as centres become more experienced has already been demonstrated for 3L diffuse large B-cell lymphoma (DLBCL) patients treated with CAR-T in the UK. In a paper published in Oct-23, outcomes for 726 patients were compared with patients divided into patients approved for treatment between Dec-18 to Dec-19 (DLBCL-ERA-1) and patients approved for treatment between Jan-20 to June-22 (DLBCL-ERA-2).[6] Despite objectively poorer baseline characteristics in DLBCL-ERA-2 versus DLBCL-ERA-1, both efficacy and safety outcomes significantly improved in ERA-2. For example, the complete response (CR) rate was 42% in DLBCL-ERA-1 and 63% in DLBCL ERA-2. Of note, CR in DLBCL-ERA-2 was higher than the 52% CR reported in the pivotal ZUMA-1 trial indicating that key changes in real-word clinical practice could lead to better outcomes compared to the pivotal trials.[6-7] These initial improvements in CR rates between the two eras of treatment, were also reflected into longer-term responses at 12 months (OS: 40.3% for DLBL-ERA-1 vs. 59.6% for DLBCL-ERA-2.6 Similar observations were made for progression free survival (PFS) at 12 months.

In conclusion, a substantial change in clinical practice due to centres becoming progressively more experienced with brexu-cel since its launch has taken place. This change is primarily related to early identification of relapse on BTKis and rapid referral for treatment with brexu-cel resulting in lower disease burden at infusion, higher manufacturing success rate and fewer patients not receiving infusions.

A24. Please confirm the extent to which the populations of the NHS England SACT dataset overlaps with that of the O'Reilly 2024 brexu-cel RWE paper

There is a substantial overlap between the SACT data and the O'Reilly 2024 study. The O'Reilly 2024 study included all consecutive patients that were referred for brexu-cel between February 2021 and June 2023, while the SACT data included patients referred for brexu-cel over the period of January 2021 and September 2023.

A25. Please confirm how many people were leukapheresed out of the n=142 (or 135 after duplicate removal).

These data are only available from SACT. We have requested these data.

A26. Please provide a Kaplan Meier plot for Overall Survival from date of leukapheresis, for all leukapheresed patients.

These data are only available from SACT. We have requested these data.

A27. Please confirm the average time between leukapheresis and infusion for the SACT dataset.

These data are only available from SACT. We have requested these data.

Section B: Clarification on cost-effectiveness data

B1. In Section B.3.9.2 of the submission (CS, Document B), the company justifies Assumption 7 regarding the use of age-matched general population utility by stating: "This approach is consistent with NHS Consultant expectations and the decision-making approach in the original submission." Could the company specify the exact page in the Technology Appraisal Guidance for TA677 where this approach is explicitly confirmed?

Section 3.10 of the FAD for TA677 states: "The company's model assumed that people who had treatment with autologous anti-CD19-transduced CD3+ cells whose disease has not progressed after 5 years of treatment have the same health-related quality of life as the general population ... The ERG incorporated the company's assumption in its base-case analysis". Other analyses – unsupported by evidence – were also explored by ERG and discussed by committee.

B2. The health outcomes and associated costs for patients who did not receive brexu-cel are not included in the economic model. Could the company clarify this and provide a justification for its chosen approach?

The original submission is limited to the mITT population; this appraisal is the conclusion of this original submission therefore there is no change to this.

In TA677 the modified ITT was accepted by the committee as sufficient to demonstrate the effectiveness of brexu-cel (FAD section 3.3). The company model based on the modified ITT was accepted as appropriate for decision making (FAD section 3.9) after the company had implemented all ERG amendments with the exception of long term mortality (FAD section 3.7). No new information is available

about these patients, the ZUMA-2 cohort is the same as in TA677. The model presented is consistent with the analysis and discussion in TA677.

Patients who do not receive brexu-cel do not incur the costs or consequences of therapy. These patients may however undergo bridging therapy, leukapheresis and conditioning therapy which they may not have undergone in the absence of brexu-cel. We have estimated an additional cost for this.

The revised basecase and associated tables/figures are provided at the end of this response document (these revised tables and figures capture all the analysis changes made in response to clarification Qs).

B3. PRIORITY: As raised during the DPM, please could the company provide an economic model based on PFS and OS extrapolations from the time of leukapheresis for all patients from Cohort 1 (FAS). Accompanying Kaplan-Meier plots would also be helpful.

This novel modelling approach suggested by the EAG in the DPM is not relevant to this reappraisal of TA677.

In TA677 the modified ITT was accepted by the committee as sufficient to demonstrate the effectiveness of brexu-cel (FAD section 3.3). The company model based on the modified ITT was accepted as appropriate for decision making (FAD section 3.9) after the company had implemented all ERG amendments with the exception of long term mortality (FAD section 3.7). No new information is available about these patients, the ZUMA-2 cohort is the same as in TA677. The model presented is consistent with the analysis and discussion in TA677.

B4. Could the company clarify whether EQ-5D assessment data is available beyond six months following the infusion date? If no such data exists beyond this period, could the company justify stopping HRQoL data collection after six months?

The secondary objectives of this study included assessing the safety and tolerability of KTE-X19, additional efficacy endpoints, and the change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.

B5. Could the company please provide a revised economic model that includes functionality for permitting separate utility values based on different time periods from the screening point? These periods may include pre-treatment, screening to week 4, week 4 to month 3, month 3 to month 6, and beyond month 6, as outlined in Table 12 of CS, Document B, page 44.

Due to the way that data flows through the model is difficult to provide a model version where these options can be incorporated without through review. We provide an output below where we have manually overwritten the utility trace inputs for the time periods covered in the request above using the summary utility data reported in Table 24 of CS, Document B, page 83. After cycle 6, utility reverts to the mean value used in the submission ([redacted]). The impact on the basecase is summarised in the table below. There is minimal impact on outcome. We suggest these outputs indicate a fully coded change to these parameters would not impact analysis outcomes.

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ROBABILIT (£/QALY)
R-BAC	[redacted]	[redacted]	[redacted]	-	-	-	-
brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

The EAG can have access to this version of the model if required. Please note that reviewing the detail of the utility inputs has brought to light an overestimate of the se associated with pre and post progression utility. The company has corrected this to provide a more reasonable estimate of variability around the utility point estimates.

This impacts the PSA and DSA; revised tables/figures are provided at the end of the response (i.e capturing all the analysis changes made in response to clarification Qs).

B6. Could the company please clarify, if the utility value of pre-progression ([redacted]) is patient-based, how patients or the company differentiate between this utility value and the disutilities associated with adverse events, given that AE-related disutilities are incorporated separately into the model.

Thanks for the comment. The pre-progression utility value ([redacted]) used in the model was based on the output from a linear mixed-effects model fitted to data collected at screening, week 4, month 3, and month 6, with varying sample sizes over time. We agree with the reviewer that the pre-progression utility value may have partially captured the disutility due to AE; however, it does not fully account for the duration and incidence of each AE and the conservative approach was taken to compute the disutility of each AE as an additional component. Nonetheless, AE was not found to be a major driver of ICER as the total QALY loss due to AE was small.

B7. Please could the company comment on and justify their use of utility values (as seen in Table 24 and 27 in the CS, Document B) for patients in the pre-progression health state, and how it compares with the equivalent general population utility?

The pre-progression utility estimate, [redacted], is estimated from ZUMA-2 patient-reported EQ-5D-5L data, using regression analysis after applying the van Hout algorithm crosswalk to EQ-5D-3L-equivalent utility estimates, as described in Section B.3.4.1. In the absence of real-world data from eligible UK patients within the targeted indication, this utility value is considered the best available source of evidence for this submission.

The general population utility for UK submissions is frequently calculated using the Ara-Brazier formula:

$$Utility = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

For an average age of 63.2 years, and 84% share of male patients, the expected utility for the general population is 0.820, i.e. similar to – though slightly below – the pre-progression utility value of [redacted] estimated from ZUMA-2. Considering that the expected general population utility for this age group already accounts for morbidity, and that the patients targeted for brexu-cel therapy is generally in otherwise good

condition, we consider these values sufficiently compatible to retain the value from the ZUMA-2 trial data as the base case for this submission.

B8. Could the company please provide a justification for using the post-progression utility estimate of [redacted], derived from the difference between pre- and post-progression utilities in TA502, as stated in section B.3.4.5 of document B? Additionally, could the company clarify why using the absolute value from TA502 may not be the most appropriate approach, and why data from TA502 was chosen over other potential sources identified in the SLR?

The approach taken here is consistent with the original submission. The SLR identified no additional information relevant to this parameter so no changes made.

B9. Please could the company clarify why the long-term survivor assumption was not applied consistently across all arms for the same condition.

Long term survivorship means that the disease is no longer expected to be the driver of patient outcomes; brexu-cel provided a step change to patient outcomes in rrMCL; it is not controversial that this step change is not relevant to non-CAR-T options; there is no expectation of long-term-survivorship in patients not receiving brexu-cel.

B10. Please can the company update their analyses using the most up-to-date CAR T tariff cost, which the EAG understands to be £57,080 based on [ID3887].

We incorporated the tariff of £41,101 into our analyses, as this is the figure which was agreed for use in TA872 and has subsequently been used by NICE in TA895, TA893 and TA975. As previously stated, we do not agree with the approach taken by NICE in the recent appraisal of liso-cel (ID3887) when a significantly increased tariff was used without a detailed evidence base, consultation or sufficient transparency.

In the Final Appraisal Document (FAD) of TA872 the NICE committee noted that NHSE considered that “while the current tariff represents the high hospital costs of establishing the infrastructure of a CAR T-cell therapy service and delivering a relatively new type of treatment, economics of scale may be expected over time”. Therefore, we were surprised to see an increased, unevidenced figure of £57,080 referenced in ID3887.

We have not been provided with sufficient information about how this figure has been calculated by NHSE, the components included within the tariff and the specific costs associated with each. Therefore, if we included this updated tariff figure in our analyses we would risk including costs which are not directly attributable to use of the product. We find ourselves in the same position as in TA872 when the ERG stated they were "concerned about the methods used by NHS England to derive the tariff. It was unclear how individual trusts estimated expenditure and how this corresponded to quantities of resource use."

We have tried to obtain further details from NHSE through a Freedom of Information Request, but NHSE have claimed this information is exempt from disclosure for reasons of confidentiality. In order to truly estimate the incremental cost of delivering CAR T treatment to patients, NICE, the EAG and companies involved in cost-effectiveness appraisals need greater visibility of the data used by the NHSE CAR-T Tariff Review Working Group to calculate the new tariff. Therefore, we have submitted a complaint to the Information Commissioner's Office to challenge NHSE's refusal to provide sufficiently detailed information. Unfortunately, we do not anticipate the ICO's review will be completed in time for this appraisal and so would urge NICE and the EAG to seek greater transparency from NHSE.

In line with the Methods Guide, NICE must apply a clear and methodological approach that is evidence based and transparent. In the absence of a fully transparent, bottom up costing from NHSE, we believe the only approach that can be taken by NICE in its decision making process is to continue to use the figure of £41,101 which NICE has previously agreed "adequately captured a reasonable projection of the cost to the NHS of delivering CAR T-cell therapy" (TA872). To do otherwise may lead to a procedurally unfair and unevidenced decision.

B11. Please clarify why, for health-state unit costs and resource use, the company has not used data from the ZUMA-2 trial but instead prefers to use data from TA502 (Ibrutinib for treating r/r MCL)?

The costs in our model were extracted from the NHS national reference cost schedule 2023-24, BNF, and eMIT. We took the resource use per health state from TA502; the HCRU in this technology appraisal was calculated by surveying active practicing haematologists and oncologists in the NHS, and the results of the survey

were validated by UK hematologic experts. Thus, the data are more comprehensive and representative of the real-world clinical practice. These data were not collected in ZUMA-2 so there was not the option to refer directly to ZUMA-2 patient data.

B12. The model seems to incorporate an unconventional half-cycle correction which is based on using the average of month numbers (e.g. taking the midpoint of time between two cycles) rather than taking the average of respective costs and effects between two cycles. Please can the company clarify and justify its approach.

We applied the half-cycle correction to reflect that events can happen at the mid-point of the cycle, rather than strictly at the beginning or end of each cycle. The approach is not an unusual one. Given the model cycle is one month only, we do not expect the two approaches to give rise to any substantial discrepancy in the result.

B13. Please could the company clarify whether any adverse events (AEs) occurred beyond the first 100 days post-infusion? If such events did occur, could the company confirm that all associated costs for adverse events occurring after this period are included as additional costs to the CAR-T tariff

The company believe that the large majority of treatment related adverse events will occur within 100 days of infusion and will be covered by the tariff.

Brexu-cel is given as a single infusion, not as repeated rounds of treatment. Patients receiving brexu-cel and other CAR-T therapies are at risk of a range of treatment related adverse events in the days and weeks after infusion. However, as time passes it becomes less clear whether events are treatment related, rather than disease-related or unrelated to treatment or disease. Events occurring many months or years after brexu-cel infusion are much less likely to be directly related to treatment and so appropriate for inclusion the model.

As noted elsewhere in this response the derivation of the tariff is unclear, but our understanding is that the tariff is intended to include costs of managing treatment related AEs out to 100 days after infusion. It is reasonable to infer that 100 days was chosen as a timeframe because this is expected to be sufficient to cover the large majority of treatment related costs.

B14. The company used only the currency code SA39A for the cost of allo-SCT, which is not consistent with the subsequent allo-SCT cost in TA893 (including harvesting, procedure, and follow-up). It appears the company should use the comprehensive currency codes to estimate the costs of allo-SCT. Could the company please verify this and update the related cost, or provide a justification for maintaining the current value?

The company notes that code SA39A covers only the allo-SCT procedure and that the approach in TA893 including harvesting, procedure, and follow-up is a more complete and accurate way describe the full cost of giving allo-SCT.

We have updated our cost of allo-SCT to include additional cost for stem cell harvesting, and for follow-up. The new costs are shown below -

Component	Cost	Source
Stem cell harvesting	£1,927.09	As for leukapheresis for CAR-T
Allo-SCT procedure	£47,508.32	Unchanged from the company submission
Follow-up, up to 24 months post allo-SCT	£56,957.61	TA893, company submission Table 68 inflated to 2024/2025 GBP Original source: NHS blood and transplant

The allo-SCT harvesting and procedure costs here remain lower than in TA893 for two reasons. In costing stem cell harvest we have assumed a mix of day case and inpatient procedures and averaged the relevant codes: this is to be consistent with the approach taken for the costs of leukapheresis for CAR-T applied elsewhere.

This change in cost alters the cost-effectiveness. A revised cost-effectiveness estimate (base case and sensitivity analysis) reflecting this change and others made in response to EAG comments is presented at the end of this document.

B15. In Section B.2.7 of the submission, the company states: *"Two patients in the mITT group had an allo-SCT while in a brexu-cel-induced remission; a further [redacted] patients started a new anti-cancer therapy (non-SCT) prior to progressive disease post-brexu-cel."* Could the company provide clarification on the specific new anti-cancer therapy that these [redacted] patients received?

Were the associated costs included in the model? Additionally, could the company please explain the rationale behind its approach taken for modelling subsequent therapies.

Thanks for your comment. The costs associated with the subsequent new anti-cancer therapy prior to disease progression were not included in the current model.

There are no treatments currently indicated post brexu-cel; no treatment has been shown to be effective or is recommended by NICE in this setting. The company has followed the Reference Case by including all NICE-recommended treatments. No therapies have proven effect in this setting; we are confident that no important drug costs are missed as no drug would be funded/is recommended for use in the NHS.

Some patients went on to investigational trials – the cost for these treatments would not be incurred by the NHS and the health benefits are not established. This is however one of the benefits of CAR-T i.e. patients have the potential to go onto alternative treatments once their effectiveness has been established in a UK setting.

B16. PRIORITY: It is unclear to the EAG whether the model is working as intended, due to the presence of terms such as "#REF!" in the model: Inputs sheet (cells C41 and B150), Cost calcs sheet (cell B44), Costs total (cells O27, R27). Please could the company provide a revised model, or confirm model functionality is as intended.

Thanks for raising the issue. We confirm that the model functionality is as intended, and the entries with "#REF" do not affect the validity of the results. Those entries correspond to model components created during the initial stage of model development but are no longer applicable in the final version of the cost-effectiveness calculation, and hence can be safely ignored.

B17. The EAG notes that within the economic model, parameters such as trial number and female percentage are sourced from 'Labels & constants', yet age references 'Main board'!$E$53 despite static values in 'Labels & constants' for Inferential, ITT, and Safety populations, while its standard error (SE) reverts to 'Labels & constants'. Similarly, 'Cure Point (months)' has multiple input locations: 'Labels & constants'!$AP$4:$AP$7, 'Inputs'!$N$53, and the fixed Name Manager range PFS_curetimepoint (48). Adjusting 'Inputs'!$N$53 alters

costs but not PFS_curetimepoint, a pattern also observed for OS and utilities, potentially affecting other parameters. Furthermore, the nomenclature for key parameters exhibits inconsistency. Certain parameters are assigned specific names within Excel's Name Manager, while others rely on direct cell references. Adopting defined names for critical parameters, such as cost/effect discount rates, starting age, and time horizon etc… could enhance clarity and usability.

Please could the company provide a model with improved consistency.

We acknowledge that there are some inconsistencies in the model structure and parameters names, and that these may cause inconvenience when reviewing the model. However, we also want to point out that these inconsistencies do not affect the functionality of the model or the validity of its results. Inconsistencies in big models such as this stem from the model having been developed in stages, with new functionalities sometimes added at later stages upon request from clinical experts or model reviewers; in this case the model is an adaptation of the model used for the original submission, which was subsequently updated following EAG feedback. In many cases, these inconsistencies unfortunately cannot be rectified without bigger overhauls to the model's structure, which always comes at the risk of causing unintended changes to the model. For this reason, we recommend no changes are applied. However, we acknowledge that it would have been neater to use a more consistent structure in the first place.

B18. PRIORITY: In section B.3.6. the company states that brexu-cel meets the end-of-life criteria. The EAG understands that these criteria no longer apply since NICE introduced the severity modifier in January 2022 as part of an update to its health technology evaluation manual. This change replaced the previous "end-of-life" (EOL) criteria. Can the company clarify how the severity modifier is incorporated into the economic model and submission? If missing, please add this functionality into the economic model.

Brexucabtagene autoleucel entered the Cancer Drugs Fund under a managed access agreement (MAA) in February 2021 for the treatment of relapsed or refractory mantle cell lymphoma in adults who have previously had a Bruton's tyrosine kinase inhibitor (BTKi). This was under the understanding that the process and methodology for exiting the CDF would be substantially the same as that in

place when signing the agreement, i.e. a ‘Cancer Drugs Fund guidance review’ by NICE under the technology appraisal process as set out in the NICE Guide to the process of technology appraisal – Process and methods (PMG19). Gilead relied upon the defined procedure which included the arrangements for how the technology would be assessed following completion of the MAA, when we agreed to the arrangements for participation in the CDF.

As clearly mentioned in the MAA and NICE Guide, this exit process should be considered a reappraisal based on additional evidence listed in the data collection agreement, intended to answer the clinical uncertainty raised by the NICE Appraisal Committee. The 2018 Addendum to the NICE Technology Appraisal Methods Guide to support the new Cancer Drugs Fund arrangements, referred to “a subsequent update of the guidance” (paragraph 6.5.3) at the end of the MAA period.

The current review of brexucabtagene autoleucel therefore forms the conclusion of the original appraisal rather than a de novo STA and to alter NICE’s procedures retrospectively, applying substantially different methodology would be inconsistent with standards of procedural fairness.

Section C: Textual clarification and additional points

References, Documentation and Searches

C1. Please provide the complete sources for references 80 and 102, which are incomplete or missing in the currently provided reference pack.

Reference 80 is a duplicate of reference 79 so only one reference is provided; The company does not have reference 102 in-house; we have reached out to the original consultancy who conducted the advisory board but have not heard back from them.

C2. Please provide a clear mapping of the data on file references used in the company submission, and the references provided in the reference pack. There are occasions where the reference number is not provided (e.g. pages

12, 40, 42, 44), or unclear (page 41). If any referenced files have not been provided, please provide these.

We have cross-checked the data on file references and ensured alignment with the reference pack. The only changes are as above (provision of reference 102).

C3. Please could the company provide unredacted versions of their complete submission (main dossier, appendices, economic model) for the original appraisal of brexu-cel (TA677).

The unredacted versions of the complete submission (main dossier, appendices, economic model) for the original appraisal have been submitted in our response.

C4. Please provide as a standalone file the Excel spreadsheet of included and excluded studies at secondary screening from the updated 2024 SLR mentioned in the company appendices (page 51). The EAG are unable to access the embedded file.

The Excel spreadsheet of included and excluded studies at secondary screening from the updated 2024 SLR is submitted as a standalone file in our response.

C5. Please can the company provide the information relating to the search terms and numbers of records identified for the 'other data sources searched' including conference abstracts and clinical trial registers for the identification of clinical evidence, cost-effectiveness studies, health-related quality-of-life studies and cost and healthcare resource identification, measurement and valuation.

‘Other data sources searched’ was included as part of the original submission and included searches within the listed databases, websites and societies; no search terms were recorded for this. The searches for ‘other data sources searched’ was not repeated for the 2024 searches, which were limited to the SLRs reported. In addition to the reported SLRs, pragmatic searches for relevant studies were performed to ensure that no relevant studies or decisions within the target indication had been published after 2020. These pragmatic searches included NICE, but no relevant studies beyond those identified through the SLRs were identified.

C6. CS Appendix G, Updated SLR: Search strategy and databases searched (Page 86) states that the same databases and grey literature resources were

searched as the original search. The databases reported in Appendix G include MEDLINE, Embase, MEDLINE In-Process, the Cochrane Library, HTA database, EconLIT, EconPapers and the CEA Registry. The databases reported for the updated searches for published cost-effectiveness studies include PubMed, Embase and the Cochrane Library (Table 50), PubMed, Embase, the Cochrane library and EconLit for the Health-Related Quality of Life searches (Table 68) and the Cost and healthcare resource identification, measurement and valuation searches (Table 93). Please confirm whether the additional databases were searched. If they were searched, please provide the search strategies used, and the number of records identified.

Thank you for identifying this incorrect phrasing. The updated SLRs focused only on the databases reported in Tables 8, 50, 68 and 93 of the Appendices. The search terms and strategies for these are reported in the appendices, tables 5-8, 47-49, 64-67 and 90-92, respectively. These searches were designed to align with the original searches. In addition to this, pragmatic searches were used to search the other databases included in the original SLRs, but no new relevant studies were identified through these searches, and no record of search terms was kept.

C7. CS Appendices Table 17, Could you clarify why the table lists *"Rai et al. 2022. Pirtobrutinib, a Non-Covalent (reversible) BTK Inhibitor, in Mantle Cell Outcomes for Recurrent Mantle Cell Lymphoma Post-Ibrutinib Therapy: A Retrospective Cohort Study from a Japanese Administrative Database"* while the corresponding PDF provided has the title *"Outcomes for Recurrent Mantle Cell Lymphoma Post-Ibrutinib Therapy: A Retrospective Cohort Study from a Japanese Administrative Database"?* Additionally, can you confirm that the Song et al. 2023 paper provided matches the intended study? Lastly, the Wang et al. 2022 study listed in the table does not appear to have a corresponding PDF – could you clarify if this was an omission or if the document is available?

Appendices Table 17 has the wrong title for Rai et al. 2022. The study reviewed for the SLR is consistent with the corresponding PDF provided, titled “Outcomes for Recurrent Mantle Cell Lymphoma Post-Ibrutinib Therapy: A Retrospective Cohort Study from a Japanese Administrative Database”. The Song et al. 2023 paper was wrongly attached, the correct paper is provided in our response. Wang et al. 2022 has a full text available and is also provided in our response to these clarification Qs.

References (for response to A23)

1. McCullogh et al., Br J Haematol. 2021 Apr;193(2):290-298. Doi: 10.1111/bjh.17363
2. O'Reilly et al., Blood (2022) 140 (Supplement 1): 7519–7521. https://doi.org/10.1182/blood-2022-165031. ASH 2022 presentation.
3. Shah et al., Lancet. 2021 Aug 7;398(10299):491-502. Doi: 10.1016/S0140-6736(21)01222-8
4. O'Reilly et al., Br J Haematol. 2022 Oct;199(1):40-44. doi: 10.1111/bjh.18378. Epub 2022 Jul 27
5. Gilead Sciences, Data on file, 2024
6. Boyle et al., Br J Haematol. 2024 Feb;204(2):507-513. doi: 10.1111/bjh.19157. Epub 2023 Oct 17
7. Neelapu et al., N Engl J Med. 2017 Dec 28;377(26):2531-2544. doi: 10.1056/NEJMoa1707447

Updated analyses

The model has been updated to reflect:

- A weighting to account for pre-infusion costs in pts not infused, under the assumption that these may be related to brexu-cel (see response to B2)
- A correction of the uncertainty estimate around pre and post-progression utility (see response to B5)
- An updated approach to the costing of AlloSCT (adding harvesting and follow up) (see response to B14)

Revised tables and figures for key outcomes are provided below.

Table 1: Base-case deterministic cost-effectiveness results (updated)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	PROBABILIT (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,270

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

Table 2: Mean PSA base case results (updated)

Technologies	Mean costs	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline
SoC	[redacted]	[redacted]			
brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	£52,663

Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SoC, standard of care.

Figure 1: PSA Scatterplot, brexu-cel vs SoC (updated)

Key: EOL, end of life; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; SCT, stem cell transplant; SoC, standard of care

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments [ID6325]

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

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

Information on completing this submission

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

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	**Susannah Wood** **Harveen Ubhi**
2. Name of organisation	Lymphoma Action Anthony Nolan
3. Job title or position	Health Information Officer Policy and Public Affairs Manager
4a. Provide a brief description of the organisation. How many members does it have?	**Lymphoma Action** Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare

	companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. **Anthony Nolan** Anthony Nolan is a charity with 50 years of expertise in uniting science and people to push the boundaries of what can be achieved for blood cancer and blood disorder patients. Our stem cell register matches potential donors to patients in need of transplants. We carry out cell and gene therapy research to improve the outcomes from cell therapy and support patients through their treatment journeys. We are funded by a combination of income sources as detailed in our annual report.

4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]
If so, please state the name of company, amount, and purpose of funding.
	Lymphoma Action
	Gilead Sciences Ltd £15,000
	Contribution towards our Peer Support Services.
	
	BeiGene UK £20,561.34
	Contribution towards our Lymphoma Essentials and Preparing for Treatment provision and sponsorship of Lymphoma Management course for HCPs.
	Payment for patient volunteer expenses to attend BeiGene event.
	
	Roche £20,000
	Contributed towards our Helpline, Information Provision and Preparing for Treatment project.
	
	Anthony Nolan
	• **Autolus Therapeutics:**
	  ○ £50,000 commercial income for the provision of cord blood for cell and gene therapy research and development in immunotherapy/oncology
	  ○ £10,000 donation towards Anthony Nolan's CAR-T CNS
	• **Kite, Gilead:** £18,200 research grant towards the Anthony Nolan CAR-T Patient Experience Study

	• **Sanofi:** £20,000 grant to support the development of a report highlighting the psychological impact of stem cell transplant and CAR-T on patients and families
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to members of our community to understand their experiences of living with r/r Mantle Cell Lymphoma. We combined the information gathered from this, along with our experiences of working with these patients and their carers, with a questionnaire response from a patient who had been given brexucabtagene.

Section 2 Living with the condition and current treatment

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

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and	Lymphoma is a type of blood cancer, where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most common type, with around 14,200 people diagnosed each year in the UK. There are around 60 different types of NHL which can be classified in two main ways. Firstly, they can be grouped into low-grade and high-grade based on how fast they grow. Secondly, they can be grouped depending on the type of lymphocyte they developed from: B cells or T cells. B-cell lymphomas are much more common, accounting for 90% of cases. Mantle cell lymphoma (MCL) is a type of NHL which develops from B cells found in the mantle zone of lymph nodes. It mainly affects lymph nodes but can also spread to other parts of the body such as bone marrow, spleen, bowel and liver.

social life. Is there any impact on their siblings?	MCL is a rare cancer with around 600 people being diagnosed each year in the UK. It tends to be a cancer of later years, with most people diagnosed being middle-aged or older. MCL often grows very quickly, which means symptoms can develop fast. These can include swollen lymph nodes, abdominal pain or a feeling of fullness due to an enlarged spleen, or symptoms arising from lymphoma cells invading the bone marrow. This can include bruising or bleeding, being more prone to infections, or symptoms of anaemia. Some people also have what is known as B-symptoms which can include weight loss, night sweats or fever. Fatigue is also a common symptom of mantle cell lymphoma, but one which is often overlooked. *"Before having the treatment, life was very difficult. I lost my hearing completely in one ear, had no appetite, and no energy. I went from being a very active person to someone who couldn't do anything."* MCL unfortunately almost always relapses at some point after initial treatment, and then multiple times after this. Most people with MCL will require more than one line of treatment, and often the aim is to achieve as much time as possible cancer free in between these treatments. The psychological impact of a diagnosis of MCL is enormous. Patients have described insomnia, anxiety and a constant fear of dying to us. Much of this fear is due to this high risk of relapse and running out of viable treatment options. Patients and those close to them live with this fear which obviously adds to this impact. *"The diagnosis has been very difficult to deal with, mainly due to the short overall survival statistics and the uncertainty surrounding response to chemo because of the heterogeneity of the disease and the unknown remission duration. I have young children, and I am scared to leave them without a father."*

7. What do carers experience when caring for someone with the condition?	The family and friends of people with MCL also have their lives turned upside down and can struggle with the diagnosis given to their loved one. *"Caring for my husband was very worrying. The emotional side was tough, but you had to be very truthful to each other and talk about your worries."* Carers have to be there emotionally but also practically, often taking on the burden of day-to-day activities, "*My wife will have a lot to deal with, looking after the children and picking up the things that I won't be able to help with during my very aggressive treatment"*. Carers can feel powerless to help, especially as MCL is a cancer which is likely to come back despite responding to treatment – one of our patients talked about the "*inevitable relapse*".
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	The treatment for MCL varies according to several factors which include the stage, prognostic score or symptoms of the lymphoma, along with the patient's age and overall health. In some cases, for example when patients have very few symptoms as the lymphoma is growing slowly, no active treatment is required. This is called active monitoring, or 'watch and wait'. If treatment is required, in most cases this is chemotherapy in combination with immunotherapy such as rituximab. If patients are fit enough, they will be given an intensive regimen including cytarabine. This can be effective and helps to prevent the MCL from spreading, but it can be incredibly difficult to endure. *"The side-effects (of my chemotherapy) were insomnia and extreme tiredness plus hair loss".* If patients are less fit, they may be offered an alternative chemotherapy regimen such as R-CHOP (rituximab, cyclophosphamide, doxorubicin (or hydroxydaunorubicin), vincristine (Oncovin®) and prednisolone), bendamustine plus rituximab or VR-CAP (a version of R-CHOP which includes a targeted drug called bortezomib).

	If patients respond well to chemotherapy, they may be offered an autologous stem cell transplant (SCT). This requires intensive chemotherapy and patients have to be fit enough which is often not the case. In almost all cases, despite treatment MCL will unfortunately relapse. This can happen on multiple occasions, requiring many different treatment regimens. Possible treatments at this point include the targeted treatment ibrutinib, a different chemotherapy regimen to the one previously received, CAR-T therapy, a donor stem cell transplant or taking part in a clinical trial. Not all of these treatments are suitable options for everyone and patients and their carers worry about running out of options.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	MCL is a very difficult cancer to live with. It can act like a high-grade lymphoma by growing quickly and causing significant symptoms, but also like a low-grade lymphoma often relapsing after treatment requiring various treatment regimens, "*It is very hard to live with this type of lymphoma, as although I am in remission I know it will come back at some point".* Therefore, patients want multiple treatment options open to them, especially ones which can be tolerated by most patients. They feel that there is currently an unmet need for this, which adds to the fear that the treatment options that they are offered will either not provide a long-term remission or will cause intolerable side effects. This is confirmed by the recent 2024 Lymphoma Coalition survey, which shows that 72% of patient respondents and 80% of carer respondents (total respondents 1204; 3% MCL) rated fewer side effects/more tolerable side effects during treatment as important, or very important. *"Yes, there is an unmet need. The perfect treatment would be something with relatively little side effects."*

	"*We need as many treatments at our disposal as possible given the high relapse rate. This is especially important for younger patients.*" *"I think the more options for treatment for this condition there are the better, so that clinicians can help patients decide which treatment is best tailored to their personal life at the time".* *"Obviously we'd all hope for a cure with a treatment that did not endanger life and had fewer side effect."*

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	Receiving this treatment is certainly challenging in many ways, for example, requiring long periods of time away from home if you do not live near a treatment centre. However, patients are often happy to make sacrifices such as this if they have the opportunity for a successful treatment. We heard from a patient who had this treatment 100 miles from their home, in January 2023. They describe it as a *"last resort"* and despite the upheaval on their life and that of their family they could not praise it highly enough: *"The treatment was intense, hard at times, but with the amazing help and support of staff and our immediate family we got through it. I cannot praise this treatment enough, this to us is the perfect treatment. I would go through it all again as the outcome is marvellous."* One of the reasons that people are happy to potentially travel so far, and stay away from home, is that they are at a point where they have very few options left to them. The patient described what a lifeline it was, and how it changed his life:

	"Since having the treatment, I have my life back. At first, I had to be very careful about mixing with people, as the treatment severely reduced my immunity. I caught a cold, and it quickly turned to pneumonia. I am at the moment taking a precautionary antibiotic three times a week. I can mix more normally now and am getting back to a near normal life."
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	As MCL is a disease which will often relapse multiple times patients need to receive many different lines of treatment. Unfortunately, many will reach a point where there a no options left for them. Brexucabtagene offers them a further option at a time when they are running out of hope. The patient we spoke to was incredibly grateful for this and also found that the treatment gave him very few side effects, which was an additional advantage: *"The advantage is I am more or less cured. The treatment itself does come with side effects as was thoroughly explained to us numerous times. I was very lucky as I sailed through the treatment. The only side effect was 3 weeks after treatment I had a mild episode of neurotoxicity. I went straight into the hospital and was treated overnight."*
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	The patient we heard from felt that there were no real disadvantages. There is the issue that it needs to be given at specific treatment centres and that patients need to remain near to those centres for a number of weeks after the treatment. However, patients and their carers are almost always willing to accept this for a potentially curative treatment option such as brexucabtagene.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	The patient we spoke to who had received brexucabtagene felt that it had a definite place as a treatment option for patients who had not responded to multiple other treatments: *"I think people who have the same diagnosis as me will definitely benefit from this treatment. It has given me my life back."*

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	We received no information from patients to answer this question effectively.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	We received no information from patients to answer this question effectively.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	We received no information from patients to answer this question effectively.

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	We received no information from patients to answer this question effectively.

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Without brexucabtagene, which is the only CAR-T option currently available for patients, there will be an increase in unmet need for patients for patients who have relapsed after an auto transplant and who may not be able to find a donor match on the stem cell transplant register. Without a CAR-T option at this stage, the only option left is likely to be palliative care.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	N/K

Section 6 Equality

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

None that we are aware of.

Section 7 Other issues

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

Section 8 Key messages

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

- MCL is a complex lymphoma where relapse is common
- There are currently few treatment options available for third line treatment
- The psychological impact of relapsing multiple times is incredibly tough for patients and their carers and having a further treatment option would make a huge difference
- The patient we spoke to found brexucabtagene relatively easy to receive and described it as a lifeline.

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.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Guidance review following a period of managed access

Clinical expert statement

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments [ID6325]

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	**Sunil Iyengar**

2. Name of organisation	**The Royal Marsden NHS Foundation Trust**
3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with 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.) I have not seen the company's submission.

6. Do you have a conflict of interest that you wish to declare[1]?	Direct– I have been on advisory boards, received speaker fees and conference support from Gilead.
7. 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	
8. What is the main aim of treatment?	For cancer drugs please delete as appropriate: curative / stop progression / palliative Other, please describe – Non-Hodgkin lymphomas such as mantle cell lymphoma are not generally treated with curative intent apart from the small number of patients who are suitable for and benefit from allogeneic stem cell transplantation. The aim of treatment therefore is largely to reverse disease related symptoms and provide the longest possible remission. Currently available therapies at various lines, including CAR-T therapy with Brexucabtagene autoleucel, can achieve this aim. Although treatment is not curative, 'stopping progression' or 'palliation' are not terms that are used when discussing treatment intention with patients

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

	unless standard therapies have been exhausted or the patient is deemed clinically unfit to receive treatment.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Induction of a partial or complete response according to the Lugano criteria for response assessment in Non-Hodgkin lymphoma is considered a clinically significant treatment response.
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Please delete as appropriate: Increased survival Y Increased time to progression Y Improved QOL Y Does the new technology provide other substantial health related benefits not included in the QALY calculation? Y/N, please explain: No. Non-health benefits. Please delete as appropriate: Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y/N, please explain:

	Yes. Potentially a greater proportion of patients will be able to return to work and / or their carers will have an improved QoL as a result of a good response and prolonged remission with treatment, when compared to other treatments at third line. Improved accessibility to patients Y/N, please explain: Not applicable as already accessible on CDF. Implications for delivery of the NHS service Y/N, please explain: As this statement is for transition for CDF to NICE there are no new implications for delivery of service if approved.
11. Are there any recognised side effects of the technology?	If yes, please explain how they may affect the patient's quality of life There are recognised side-effects of this technology including cytokine release syndrome (CRS), immune effector cell associated neurological syndrome (ICANS), infections and low counts in the first month following treatment. Fatigue, low blood counts (immune effector cell associated haematotoxicity) and risk of infection can persist following completion of treatment for several months.
12.Are there any important outcome data that were not	Data on QoL and non-health related benefits.

collected during the managed access period?	
13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	Mantle cell lymphoma relapsing post Ibrutinib therapy presents a significant challenge. CAR-T therapy is currently approved on the CDF in the 3rd line setting, following second line treatment with Ibrutinib. Although there is no randomised evidence in the post BTK inhibitor setting, CAR-T therapy appears to be the most effective treatment available for this cohort of patients and the outcomes for those who relapse following Ibrutinib therapy is poor with standard, non-CAR-T therapies. In the absence of CAR-T therapy, clinicians will have to revert to standard chemotherapy agents or rely on clinical trials for access to novel therapies for these patients. There is also likely to be an increase in the number of allogeneic transplants performed if CAR-T therapy is not available.
14. 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?	CAR-T therapy is an innovative cellular immunotherapy treatment. Although there are challenges with getting patients to the point of cell infusion (30% of approved and 20% of harvested patients did not proceed with CAR-T therapy in the UK real world data), and there is an unmet need with bridging therapy, patients who make it to CAR-T infusion have high response rates (87% in the UK real world data) and very respectable outcomes (median PFS 21 months, median OS not reached). There is no randomised evidence to show benefit over non CAR-T interventions but there are a couple of published comparisons (Wu et al Leuk Lymphoma 2024 and Hess et al BJH 2022) that suggest CAR-T therapy improves survival of patients.
15. Are there any groups of patients who might	It is not clear currently if there are any particular groups of patients who benefit more or less based on pre-treatment. There is some evidence to suggest that patients with high-risk disease such as TP53 mutated mantle cell lymphoma, blastoid morphology and high proliferation can also benefit from this technology.

benefit more or less from the technology than others?	
What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Mantle cell lymphoma is treated as per the British Society of Haematology guidelines. Link below Y/N, please provide a link: https://doi.org/10.1111/bjh.19131
17. Are there other clinical pathways used in England other than those recommended in the guideline?	Y/N, please explain important differences and why they occur: No
18. Would the new technology require a change in the clinical pathway?	No as already in use under the CDF.
19. Will the technology introduce new costs to the	No as already in use under the CDF.

NHS or patients other than for the technology itself?	
20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	This is a one-off treatment so criteria for starting or stopping are not applicable to this treatment. However, there is a short waiting period of a few weeks between collection of cells from the patient for product manufacture and administration of treatment. During this time a minority of patients have progressive disease and the clinician may decide not to proceed with infusion of the CAR-T product or it may not be possible to proceed for other reasons. In the UK real-world data 21 out of 104 patients did not proceed to CAR-T infusion with reasons listed as below – Progressive disease-9, Manufacturing failure with progressive disease-7, manufacturing failure and referred for another therapy-2, COVID death -1, New cancer diagnosis -1, Poor performance status -1.
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: One-off treatment, high response rates in infused patients – at our centre 5 out of 6 achieved CR and 1 patient achieved a PR). Positive benefits for patients who respond well with prolonged remissions. More efficient referral pathway to reduce 'brain to vein time' as a result of experience with the technology on the CDF and addendum to the BSH guideline for management of MCL (O'Reilly et al. BJH 2022).

	Negative: Challenges with bridging patient/controlling disease due to limited effective therapies in the 3rd line setting. Increased rates of CRS and ICANS with higher risk of CCU admission, compared to Axi-cel in DLBCL, but comparable to published data with ZUMA-2. More risk of steroid refractory toxicities and non relapse mortatlity in older patients.
22. Did any people decline treatment? What were their reasons why?	We have not had any patients decline treatment at our institution. In the UK real world data there was one patient who declined treatment out of the 119 patients approved by the national panel. The reasons are not known.
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	No unexpected issues. Some patients need more frequent monitoring in the immediate post treatment period but in general 3 monthly monitoring in the first year with blood counts, lymphocyte subsets and immunoglobulins. Routine outcome is collected routinely on our internal databases and fed through to the national data collection and to EBMT.
24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	No.

25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	Better patient selection and screening, better referral pathways, faster time to infusion for eligible patients. Better control of disease before apheresis (better control of wcc in patients with lymphocytosis). Better knowledge and education on management of toxicity based on experience from other centres and published data during this period. Prophylaxis with anakinra or dexamethasone for high-risk CAR haematotox patients is another measure that may potentially reduce toxicity but this needs formal evaluation.
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: ZUMA-2, cohort 2 0.5x10^6 /kg, more patients could proceed with treatment even if cell dose less than 2x10^6 with similar outcomes. Paper: Five-Year Outcomes of Patients (Pts) with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Treated with Brexucabtagene Autoleucel (Brexu-cel) in ZUMA-2 Cohorts 1 and 2. Yes for the comparator, please give link:
Equality	
31a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	

Thank you for your time.

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Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments (review of TA677): EAG Report [ID6325]

Produced by	*Centre for Evidence and Implementation Science*
Authors	*Amin Mehrabian, Research Fellow, University of Birmingham* *Mehdi Yousefi, Research Fellow, University of Birmingham* *Angela Mwape, Research Fellow, University of Birmingham* *Naila Dracup, Information Specialist, University of Birmingham* *Daniel Gallacher, Assistant Professor, University of Birmingham*
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Date completed	*Date completed (17/04/2025)*

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 17/42/44.

Declared competing interests of the authors
The authors of this report have no conflicts to declare.
The EAG's clinical advisor has participated in advisory boards and received honoraria from Kite Gilead.

Acknowledgements
We are grateful to a haematologist with extensive CAR-T experience in the UK but wishes to remain anonymous who provided expert clinical advice on this appraisal, and to Professor Aileen Clarke who quality appraised this report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Mehrabian A., Yousefi M., Mwape A., Dracup N., Gallacher D., Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments (review of TA677) EAG Report: A Single Technology Appraisal. Centre for Evidence and Implementation Science, 2025.

Contributions of authors
AMe led the critique of the clinical effectiveness evidence. MY led the critique of the cost-effectiveness evidence and implemented the EAG analyses. AMw supported the critique of the clinical effectiveness evidence. ND led the critique of the company's search strategy. DG led the EAG in the production of this report. All authors reviewed the final copy of this report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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0 Executive summary

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

Section 0.1 provides an overview of the key issues. Section 0.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 0.3 to 0.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (starting at section 1).

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

0.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID6325	Summary of issue	Report sections
1	Generalisability of ZUMA-2 trial to NHS care and choice of data source for extrapolating brexu-cel PFS and OS	2.2, 3.2.3, 3.2.6
2	Choice of population for extrapolating R-BAC PFS and OS relative to subsequent alloSCT	2.4.2, 3.2.3
3	Modelling of pre-infusion period for brexu-cel	2.4.4, 3.2.3
4	Implementation of cure assumption (timing and magnitude)	3.2.2
5	Utility values for health states	3.2.7
6	CAR-T Tariff application and ICU costs	3.2.8
7	Underestimation of IVIg costs	3.2.8.3
8	Costs and usage of alloSCT	3.2.8.4

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

Brexu-cel: The main source of information to inform the brexu-cel progression-free and overall survival extrapolations, and when to apply the long-term survivor assumption. Other differences include whether to capture the pre-infusion period in the economic modelling, and the subsequent rate and duration of IVIg, and application of CAR-T tariff and ICU costs.

R-BAC: Whether to remove the effects of subsequent alloSCT from the preferred source of efficacy for R-BAC, and the subsequent rate of alloSCT for costs.

0.2 *Overview of key model outcomes*

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

Overall, the technology is modelled to affect QALYs by:

- Extending both the time spent in pre-progression health state and the average survival time with a potential for cure
- Having a different side effect profile

Overall, the technology is modelled to affect costs by:

- Having a different cost of acquisition, administration and aftercare.

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

- The decision to include the pre-infusion period and broaden the population of brexu-cel considered in the economic model
- Whether to use RWE or trial data to extrapolate for brexu-cel, and choice of overall survival extrapolation
- When and how to apply the cure assumption for brexu-cel
- Whether to include effects of alloSCT in R-BAC data source
- The proportion of people receiving subsequent alloSCT

0.3 *The decision problem: summary of the EAG's key issues*

The EAG did not identify any key issues relating to the decision problem.

0.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

The EAG identified the following issues related to the clinical effectiveness evidence:

Issue 1: Generalisability of ZUMA-2 trial to NHS care and choice of data source for extrapolating brexu-cel PFS and OS

Report section	2.2, 3.2.3, 3.2.6
Description of issue and why the EAG has identified it as important	The EAG is concerned that available real-world evidence suggests that ZUMA-2 overestimates the efficacy of brexu-cel relative to the real-world studies. The company uses ZUMA-2 data in a naïve comparison to real-world data for the comparator. The EAG is concerned about the high potential for bias from the company's approach.
What alternative approach has the EAG suggested?	The EAG combines data from the RWE sources to inform the efficacy of brexu-cel, whilst utilising the longer follow-up from ZUMA-2 to inform the shape of the extrapolation, and uses baseline characteristics from SACT dataset. Whilst this approach still relies on a naïve comparison, it avoids comparing trial evidence to real-world evidence.
What is the expected effect on the cost-effectiveness estimates?	The EAG approach reduces the costs and QALYs associated with brexu-cel, increasing the ICER.
What additional evidence or analyses might help to resolve this key issue?	Longer real-world follow-up would reduce the uncertainty of the long-term efficacy of brexu-cel in real-world use, but the EAG considers that reliance on a naïve comparison is unavoidable, making all estimates of relative efficacy highly uncertain.

Issue 2: Choice of population for extrapolating R-BAC PFS and OS relative to subsequent alloSCT

Report section	2.4.2
Description of issue and why the EAG has identified it as important	The EAG's clinical adviser stated that the outcomes for R-BAC from McCulloch 2020 were likely to overestimate the real-world efficacy of R-BAC. The McCulloch study authors highlighted the potential for selection bias within the cohort, noting that younger, fitter patients were chosen and deemed eligible for alloSCT. It also had a higher than expected rate of subsequent alloSCT (~30%).
What alternative approach has the EAG suggested?	The EAG has been able to remove the survival outcomes of people who received subsequent alloSCT from the data, meaning it is able to extrapolate using a more realistic set of data.
What is the expected effect on the cost-effectiveness estimates?	The EAG approach reduces the QALYs associated with R-BAC, which decreases the ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional reporting of historic outcomes for the wider patient population could inform on R-BAC efficacy. New data is unlikely given the current patient access to brexu-cel through managed access.

0.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

The EAG identified the following issues related to the cost-effectiveness evidence:

Issue 3: Modelling of pre-infusion period for brexu-cel

Report section	2.4.4, 3.2.3
Description of issue and why the EAG has identified it as important	The company base case does not account for the outcomes of people who are leukapheresed but not infused with brexu-cel, only their costs.
What alternative approach has the EAG suggested?	The EAG models separately the costs and QALYs gained in this period for both people who are infused with brexu-cel and those who are not, using information from the DESCAR-T study for non-infused people. The EAG combines these in a weighted average based on information from O'Reilly et al., where 83 out of 104 leukapheresed people were infused, to represent the overall population. The EAG also explores the impact of including the period of assessment for leukapheresis, however the associated costs are not accounted for.
What is the expected effect on the cost-effectiveness estimates?	Starting from the point of leukapheresis lowers both the average costs and QALYs of brexu-cel, and causes the ICER to increase.
What additional evidence or analyses might help to resolve this key issue?	More detailed information of patient costs and outcomes in this period specific to UK use of brexu-cel would improve the generalisability of this analysis. Establishing when in the CAR-T process is a fair starting point for comparison to non-CAR-T therapies.

Issue 4: Implementation of cure assumption (timing and magnitude)

Report section	3.2.2
Description of issue and why the EAG has identified it as important	The company assumes that people who receive brexu-cel who remain alive beyond 48 months are effectively cured, and apply a mortality rate of 1.09 times the general population mortality.
What alternative approach has the EAG suggested?	The EAG considers that this assumption is inconsistent with the longer follow-up of ZUMA-2, and that the cure assumption should be applied from 60 months. The EAG also recommends applying a mortality rate of 3.00, consistent with TA893 (brexu-cel for B-ALL). A higher rate is support by a comparison of post-60 month follow-up from ZUMA-2 and background mortality.
What is the expected effect on the cost-effectiveness estimates?	Applying a higher mortality rate decreases the QALYs associated with brexu-cel and increases the ICER.

What additional evidence or analyses might help to resolve this key issue?	Additional longer follow-up from ZUMA-2 and real-world sources is required to resolve uncertainty around this assumption.

Issue 5: Utility values for health states

Report section	3.2.7
Description of issue and why the EAG has identified it as important	The company use utility values derived from ZUMA-2, however some of these are higher than the UK general population, which the EAG considers implausible.
What alternative approach has the EAG suggested?	Where values exceed those for the general population, the EAG instead uses the general population values, however the EAG also explores applying utility values from other technology appraisals for this condition.
What is the expected effect on the cost-effectiveness estimates?	This approach reduces the QALYs associated with brexu-cel, which has a small increase on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Alternative or real-world utility data is required to reduce this uncertainty.

Issue 6: CAR-T Tariff application and ICU costs

Report section	3.2.8
Description of issue and why the EAG has identified it as important	The company uses an old CAR-T tariff cost (£41,101), and does not add in costs for ICU, which the EAG understands are not included in the CAR-T tariff cost.
What alternative approach has the EAG suggested?	The EAG uses the updated tariff cost (£58,964) and adds additional costs relating to ICU use following administration of brexu-cel. The EAG also costed up the individual components of CAR-T infusion using available information which produced an estimate similar to the updated tariff cost.
What is the expected effect on the cost-effectiveness estimates?	These changes increase the costs associated with brexu-cel, which also increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	Real-world data relating to ICU use could further reduce the uncertainty on this issue.

Issue 7: Underestimation of IVIg costs

Report section	3.2.8.3
Description of issue and why the EAG has identified it as important	IVIg is administered for the management of adverse events, including hypogammaglobulinaemia, and the prevention of infections. The company assumes a rate of [redacted] use of IVIg for a duration of one year, derived from the percentage of grade ≥3 hypogammaglobulinaemia. The EAG clinical expert reported that this is lower than their expected total use of IVIg, which was anticipated to be in excess of 10%. A publication on the ZUMA-2 trial (Wang et al. 2023) reports an IVIg rate of 38% from 3 years of follow-up.
What alternative approach has the EAG suggested?	The EAG models using the rate of IVIg as reported in ZUMA-2, for a duration of one year, and explores alternative proportions and durations in scenario analyses.
What is the expected effect on the cost-effectiveness estimates?	This approach increases the costs associated with brexu-cel, which increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	Reporting of real-world use of IVIg following CAR-T use in the NHS would improve the accuracy of the modelling of costs relating to use of IVIg.

Issue 8: Costs and usage of alloSCT

Report section	3.2.8.4
Description of issue and why the EAG has identified it as important	For R-BAC, the company model a subsequent rate of alloSCT of ~30%, as was reported by the study informing the efficacy of R-BAC (McCulloch 2020). EAG considers this rate to be too high, and inconsistent with other sources.
What alternative approach has the EAG suggested?	Whilst the true value of this parameter remains an area of uncertainty, the EAG's clinical expert stated it was not clear why this rate would differ from the rate of alloSCT following brexu-cel. Hence the EAG models the same rate ([redacted]%) for both arms when estimating subsequent treatment costs. This approach is also somewhat consistent with the EAG's approach to removing the effects of subsequent alloSCT from the R-BAC source.
What is the expected effect on the cost-effectiveness estimates?	This approach reduces the costs associated with R-BAC, which the EAG consider to improve the plausibility of the modelling. The EAG's clinical expert stated that if brexu-cel was not available, alloSCT would likely be performed earlier but it has not been possible to capture this in the model.
What additional evidence or analyses might help to resolve this key issue?	Additional reporting of historic outcomes for the wider patient population could inform on R-BAC efficacy. New data is unlikely given the current patient access to brexu-cel through managed access.

0.6 *Other key issues: summary of the EAG's view*

No other key issues were identified by the EAG. However the EAG made several other changes relating to less influential model parameters or features: the source of AE information, and the model's time horizon and half cycle correction.

0.7 *Summary of EAG's preferred assumptions and resulting ICER*

Table 2: Summary of EAG's preferred assumptions and ICER

	EAG preferred assumption		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Impact on ICER
	Company's base case		[redacted]	[redacted]	**£54,366**	-
1	Population approach	Using the ITT population (leukapheresed patients) from real world databases, and removing SCT effects from R-BAC source	[redacted]	[redacted]	£68,352	+25.73%
2	Time horizon	Using the 100 years minus the starting age as a time horizon	[redacted]	[redacted]	£54,378	+0.02%
3	half-cycle correction	Use of average health state occupancy for half-cycle correction	[redacted]	[redacted]	£54,428	+0.11%
4	Cure time point	Using the 60-month LTS timepoint	[redacted]	[redacted]	£60,309	+10.93%
5	Proportion receiving alloSCT and associated costs	Including alloSCT in both arms (xxx% in brexu-cel and xxx% in R-BAC) with updated costs	[redacted]	[redacted]	£57,586	+5.92%
6	Mortality Rate Adjustment Factor (MRAF)	Using the MRAF of 3.00	[redacted]	[redacted]	£72,483	+33.32%
7	IVIg Therapy Needs	Using 38% for patients requiring IVIg therapy for a period of one years	[redacted]	[redacted]	£57,618	+5.98%
8	Adverse events (AEs) source	Using the most updated incidence rates of AEs	[redacted]	[redacted]	£54,818	+0.83%
9	CAR- T tariff costs	Using the tariff costs for CAR-T infusion and monitoring, valued at £58,964 + ICU costs (with 27% for ICU)	[redacted]	[redacted]	£61,819	+13.71%
10	Pre/Post-Progression, and LTS HRQoL Estimates	Pre-Progression; GPU, Post-Progression: Direct TA502 value (0.68), LTS: GPU	[redacted]	[redacted]	£56,114	+3.21%
Changes 1 through 10 (EAG base case)			[redacted]	[redacted]	£127,961	+135.37%

ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group; ITT: Intention to treat; GPU: general population utility; ICU: intensive care unit; IVIg:

Intravenous immunoglobulin; MRAF: mortality rate adjustment factor; EAG: external assessment group; LTS: long term survivorship; HRQoL: health related quality of life;

Acronyms Table

Abbreviation	Definition
AAT	alanine aminotransferase
AC	Appraisal Committee
AE	adverse event
AIC	Akaike information criterion
ALC	absolute lymphocyte count
AlloSCT	Allogeneic stem cell transplant
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under curve
AutoSCT	autologous stem cell transplant
Axi-cel	axicabtagene ciloleucel
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	best objective response
brexu-cel	brexucabtagene autoleucel
BSA	body surface area
BSH	British Society for Haematology
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T-cell
CDF	cancer drug fund
CEA	cost-effectiveness analysis
CEA Registry	Cost-Effectiveness Analysis Registry (Tufts Medical Center)
CI	confidence interval
cMCL	classical Mantle Cell Lymphoma
CNS	central nervous system
CQ	clarification question
CR	complete response
CRD	Centre for Review and Dissemination
CRi	complete response with incomplete bone marrow recovery
CRP	C-reactive protein
CRS	clinical release syndrome
CS	Company submission
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DADS	directly accessed diagnostic services
DAPS	directly accessed pathology services
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DVT	deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EMC	Electronic Medicines Compendium
EPAR	European public assessment report

Abbreviation	Definition
EQ-5D-5L	European Quality of Life – 5 Dimensions, Five-Level Version
EoL	End-of-Life
FACT-G	Functional Assessment of Chronic Illness Therapy – General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FAS	full analysis set
FCR	fludarabine, cyclophosphamide, rituximab
FDA	US Food and Drug Administration
FUP	Follow-up
HIV	human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HRG	health resource group
HRQoL	health-related quality of life
IAS	inferential analysis set
ICANS	immune effector cell-associated neurotoxicity syndrome
ICER	incremental cost-effectiveness ratio
IL	interleukin
INAHTA	International Network of Agencies for Health Technology Assessment
IPI	International Prognostic Index
IRRC	Independent Radiology Review Committee
IV	intravenous
IVIg	intravenous immunoglobulin
IWG	International Working Group
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LTS	long term survival
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MCM	mixture-cure-model
MedDRA	Medical Dictionary for Regulatory Activities
MIMS	Monthly Index of Medical Specialties
MIPI	MCL International Prognostic Index
mITT	modified intent-to-treat
MRD	Minimal residual disease
MRI	magnetic resonance imaging
NA	not applicable
NCCP	National CAR-T Clinical Panel
NCI	National Cancer Institute
NE	not estimable
NHL	non-Hodgkin’s lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	objective response rate
OS	overall survival
OWSA	One-way sensitivity analyses
PD	Progressive disease
PDS	personal demographics service
PET-CT	positron emission tomography-computed tomography

Abbreviation	Definition
PFS	progression-free survival
PO	per oral
PR	partial response
PRO	Patient-reported outcomes
PS	performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
R/R	relapsed or refractory
R-BAC	rituximab, bendamustine and cytarabine
R-bendamustine	Rituximab plus bendamustine
RC	rituximab plus chemotherapy
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
RCT	randomised controlled trial
R-CVP	rituximab, cyclophosphamide, vincristine, prednisolone
RR	Response rate
RWE	real-world evidence
SACT	systemic anti-Cancer therapy
SAE	serious adverse event
SCT	stem cell transplant
SD	standard deviation
SE	standard error
SLR	systematic literature review
SmPC	Summary of Product Characteristics
s-MIPI	simplified-Mantle Cell Lymphoma International Prognostic Index
SmPC	summary of product characteristics
SMR	standardised mortality ratio
SoC	standard of care
SPD	sum of the products of diameter
TA	technology appraisal
TFL	tables, figures and listings
ULN	upper limit of normal
VAS	visual analogue scale
VR-CAP	Rituximab, cyclophosphamide, doxorubicin, bortezomib, prednisolone
WBC	white blood cell

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

The EAG has reviewed and critiqued the company submission (CS) submitted to NICE by Gilead Sciences Ltd. This report contains a critique of the clinical and cost-effectiveness evidence of brexucabtagene autoleucel (brexu-cel) for treating relapsed or refractory (R/R) mantle cell lymphoma (MCL) after 2 or more systemic treatments. This appraisal is a review of TA677[1], as brexu-cel is emerging from a period in managed access. Brexu-cel treatment involves extracting a patient's T-cells and modifying them to include a gene which targets lymphoma cells enabling their destruction. These modified T cells are then infused back into the recipient.[2]

1.2 Background

The company provides a description of brexu-cel and of the relevant mechanism of action and health condition in sections B.1.2 and 1.3 of the CS. The EAG provides a critique of the submitted evidence pertaining to the disease overview, technology, brexu-cel positioning in the treatment pathway and additional input from the EAG clinical advisors.

1.2.1 Condition, epidemiology and symptoms

MCL is a rare and typically aggressive subtype of B-cell non-Hodgkin lymphoma (NHL). It originates from malignant B-lymphocytes in the mantle zone of lymph nodes, driven primarily by genetic mutations that promote the accumulation of abnormal B-cells.[3]

In their description of the health condition (CS, doc B, section 1.3.1), the company references earlier MCL classifications (World Health Organisation Haematological report 4 (WHO-HAEM4)), including Klener et al. (2019)[4] and Cheah et al. (2016)[5], which have since been replaced by the WHO-HAEM5 classification.[6]

1.2.1.1 WHO-HAEM5 Classification of MCL

The updated WHO-HAEM5 classification outlines three main subtypes of MCL: classical MCL (cMCL), leukaemic non-nodal MCL (nnMCL), and high-grade MCL[6].

- Classical MCL: The most common subtype, typically involving t(11;14) translocation and Cyclin D1 overexpression. It is often aggressive, with high-risk cases showing blastoid features, high Ki67 index, and TP53 mutations.
- Leukemic non-nodal MCL: A rarer, more indolent form involving mainly the blood and bone marrow. It usually lacks SOX11 expression and has a lower proliferation rate and better outcomes than classical MCL.
- High-grade MCL: Now recognised as a distinct entity, this subtype includes additional genetic alterations (e.g., TP53 mutations) and a high proliferation index. WHO-HAEM5 also introduces a section on high-grade transformation, acknowledging the progression of indolent lymphomas, including MCL.[6]

The CS collectively refer to all these types as MCL and the EAG clinical experts agree that in clinical practice, MCL subtypes are treated similarly.

1.2.1.2 Epidemiology and prognosis

MCL affects approximately 590 individuals annually in the UK, with a male-to-female ratio of around 3:1[7] [3].

The Lugano classification is commonly used for staging MCL as summarised in Table 5[8], with advanced stage associated with poor prognosis.

Table 3. Lugano staging of lymphomas adapted from Cheng et al.[8]

Stage	Criteria
Limited stage	
I	Single lymph node region or one extra-lymphatic site (no nodes)
II	Multiple nodal groups on the same side of the diaphragm, with or without localized extra-lymphatic spread
Advanced stage	
III	Nodes on both sides of the diaphragm, may involve spleen or specific nodes (e.g., para-aortic, mesenteric)
IV	Diffuse/disseminated extra-lymphatic involvement, with or without node involvement

Prognostic scoring

The simplified MCL international prognostic index (s-MIPI) is outlined in Table 4 (CS section B.1.3.2),which includes age, ECOG performance status, lactate dehydrogenase (LDH) levels, and white blood cell (WBC) count.[9] Patients are stratified into low (60% 5-year survival), intermediate (40%), or high-risk (15%)

categories. Additional prognostic markers include high Ki-67 (≥50%),TP53 mutations, bulky disease, and blastoid morphology.[10, 11] However, clinical advice to EAG suggests that the s-MIPI has only been validated for use in first-line MCL treatment, and there are no validated prognostic scores for patients undergoing third-line treatment. However, based on EAG clinical advice, individual components of the s-MIPI, such as age and ECOG score, remain important for determining prognosis after CAR-T therapy. Specifically, older patients are at higher risk for certain toxicities and non-relapse mortality (NRM), while those with impaired performance status (PS) tend to have poorer survival outcomes. The EAG clinical expert further emphasised that disease burden (including extra-nodal sites and bulky disease) is likely the most significant prognostic factor for MCL patients undergoing CAR-T therapy.

However, due to limited follow-up, it remains challenging to determine whether high-risk disease features, such as TP53 mutations or blastoid disease, independently impact survival outcomes post-CAR-T. These high-risk patients often present with bulky disease and multiple extra-nodal sites, making it difficult to adjust for these factors in smaller datasets. Despite this, it is likely that high-risk disease does play an important role in prognosis. The British Society for Haematology (BSH) guidelines also state that while s-MIPI score models are typically validated in patients receiving front-line therapy, they should not be used to clinically influence the initiation of frontline therapy in routine practice.[12]

1.2.1.3 Outcomes in R/R MCL

The EAG checked the references in CS, section B.1.3.2 on R/R MCL outcomes. The EAG clinical advisor commented that R/R MCL is generally incurable, with treatment focused on disease management and prolonging survival.[13, 14] The introduction of Bruton tyrosine kinase inhibitor (BTKi) therapy has improved median overall survival (OS) in second-line treatment from 8 months (2004 – 2011) to 16.8 months (2012 – 2015).[15] UK real-world data from Haematological Malignancy Research Network (HMRN) supports this trend but also shows that median OS drops to under two months for R/R MCL patients receiving fifth-line therapy post-BTKi failure.[15]

1.2.1.4 Health-relate quality of life (HRQoL)

CS section B.1.3.3 addresses the HRQoL burden in R/R MCL, appropriately stating that quality of life declines over time.[16] However, some referenced studies (e.g., Holzner, 2004; Nolte, 2019) examine broader cancer populations rather than R/R MCL specifically.

- R/R MCL-Specific Data: Carter et al.[17] found a correlation between performance status and HRQoL, while international prognostic index (IPI) scores had no significant baseline impact. Hess et al.[18] reported better HRQoL with ibrutinib (a BTKi) than temsirolimus.
- Other Studies: Byrd et al.[19] observed improved HRQoL with ibrutinib in chronic lymphocytic leukaemia. While informative, this was not MCL-specific.

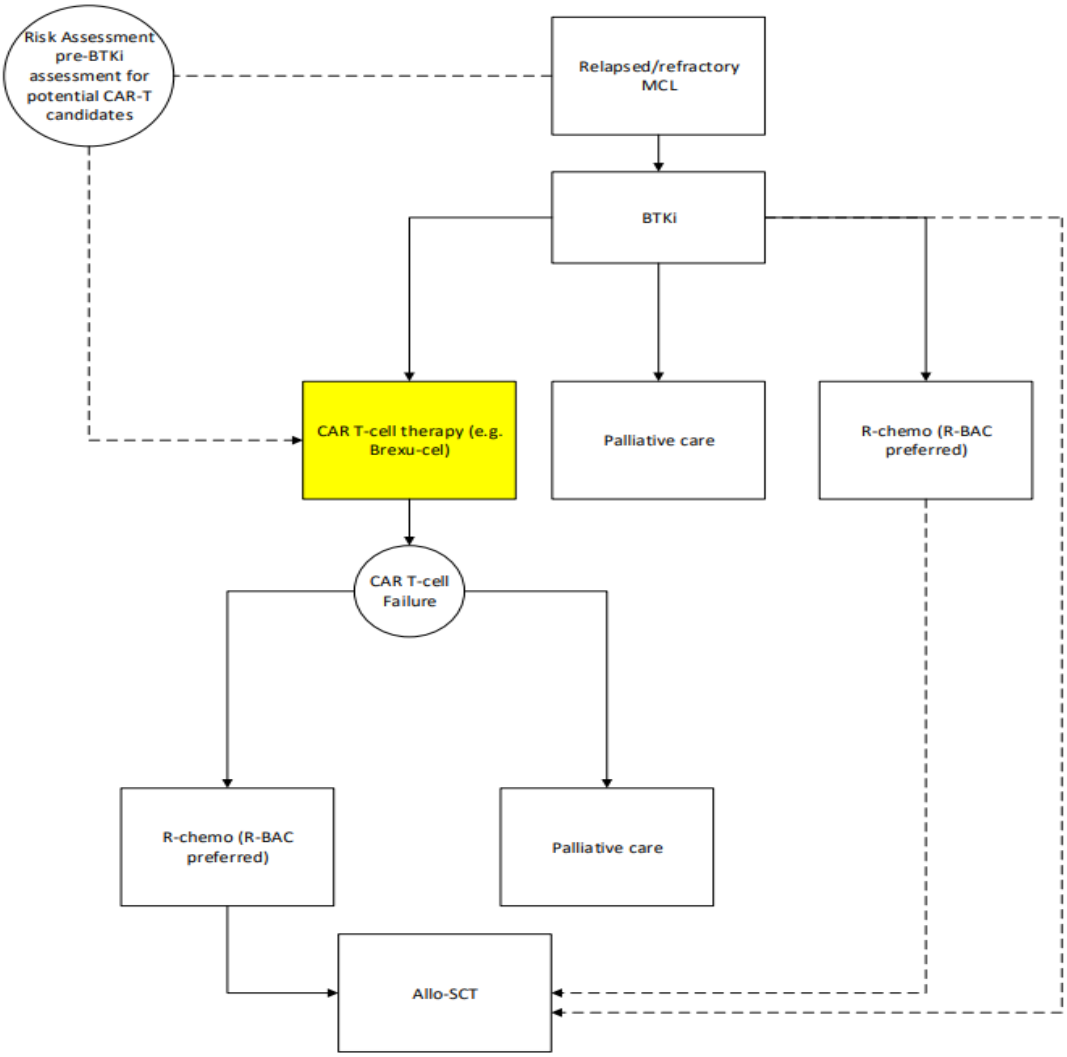
Post-BTKi failure and CAR-T therapy, HRQoL data are scarce. A simulation study suggests tumour burden, CAR-T side effects, and psychosocial stressors influence HRQoL.[20] Reducing treatment delays may mitigate early decline.[20]

1.2.2 Position of brexu-cel in treatment pathway

The CS positions brexu-cel as a third line therapy for R/R MCL post BTKi failure. The EAG finds the company's description of the technology and mechanism of action appropriate (CS section B.1.2). The CS summaries the treatment pathway for CAR-T eligible patients after first relapse and the proposed position of brexu-cel (CS section B.1.4.3, Figure 2).

1.2.2.1 EAG consideration on the treatment pathway

Based on EAG clinical advice, the EAG mapped brexu-cel's position in the NHS treatment pathway (Figure 1). For R/R MCL patients post BTKi failure without re-access to ibrutinib post CAR-T failure, brexu-cel is an option alongside Rituximab chemotherapy (primarily Rituximab-Bendamustine Cytarabine (R-BAC) R-chemo) and palliative care. Due to high rates of CAR-T-cell failure rates, palliative care following such failures remains common. Additionally, administering R-chemo is challenging because of post-CAR-T blood count issues. Allogeneic stem cell transplant (alloSCT) post-CART-T failure is extremely rare in the UK. As a result, most patients who fail CAR-T therapy have limited treatment options, emphasising the need for further therapeutic advancements.



Abbreviations: Allo-SCT, Allogeneic Stem Cell Transplant; Brexu-cel, Brexucabtagene Autoleucel; BTKi, Bruton's Tyrosine Kinase inhibitor; CAR T-cell, Chimeric Antigen Receptor T-cell; MCL, Mantle Cell Lymphoma; r/r MCL, relapsed/refractory Mantle Cell Lymphoma; R-BAC, Rituximab, Bendamustine, and Cytarabine; R-chemo, Rituximab-based chemotherapy

Figure 1. Expected positioning of brexu-cel in the NHS care for the r/r MCL

1.2.3 Unmet need

CS section B.1.3.5 highlights poor survival outcomes for R/R MCL patients post-BTKi failure. The CS states that additional treatment lines impact HRQoL, though only one simulation model specifically examined HRQoL post-BTKi failure in CAR-T patients. The CS argues that brexu-cel addresses this unmet need by improving survival outcomes, summarizing key long-term data from ZUMA-2 and additional SACT data (see Section 2.2).

1.3 *Critique of company's definition of decision problem*

The EAG's comments on the company's decision problem are in Table 6. While some differences exist between the company's decision problem and NICE's final scope, the EAG has no major concerns. The CS evidence for brexu-cel aligns with the decision problem population.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with relapsed or refractory mantle cell lymphoma who have had at least 2 previous lines of therapy including a Bruton's tyrosine kinase (BTK) inhibitor	Adult patients with r/r MCL who have previously received two or more lines of therapy including a BTKi	Minor word changes to reflect the adult population and the licensed indication	The company's population aligns with the NICE final scope. The minor wording change to specify the "adult population" reflects the licensed indication and is appropriate. However, the EAG clinical advisor agreed that the CS population in the ZUMA-2 trial is unlikely to be representative of clinical practice in England as real-world patients are less fit.
Intervention	Brexucabtagene autoleucel	Brexucabtagene autoleucel	Not applicable	The company's intervention aligns with the NICE final scope. This is reflective of the application for marketing authorisation with EMA which was submitted on 9 January 2020 with regulatory approval granted in December 2020 for adult patients with R/R MCL who have previously received two or more lines of systemic therapy including BTKi.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Comparator(s)	Established clinical management including but not limited to: • Chemotherapy with or without rituximab • Zanubrutinib (subject to NICE evaluation) Allogeneic haemopoietic stem cell transplant	Established clinical management including but not limited to: Chemotherapy with or without rituximab	AlloSCT is not a relevant comparator. AlloSCT may be used to consolidate a response to BTKi treatment in a minority of responding patients. In contrast, brexu-cel is positioned as a third-line treatment after BTKi failure. While Zanubrutinib is currently being appraised by NICE for the management of MCL, with the main study supporting its use in BTKi-naive MCL patients, brexu-cel is positioned as a third-line treatment following BTKi failure, in contrast to Zanubrutinib.	The company appropriately justifies the exclusion of alloSCT as a relevant comparator. alloSCT is typically used for consolidation after BTKi response, not post-BTKi failure. The EAG clinical advisors also note that alloSCT after brexu-cel is rare, as most patients are too old or unfit, with no available options to bridge to alloSCT. The exclusion of zanubrutinib is also appropriate, as it has not been appraised by NICE and is used in BTKi-naive patients, whereas brexu-cel is positioned post-BTKi failure. However, the EAG clinical advisors state that patient's ineligible for brexu-cel treatment will receive combination R-chemo – R-BAC if reasonably robust, or a gentler regimen if not.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment health-related quality of life.	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	Not applicable	The company's outcomes align with the NICE scope. The EAG notes that the health-related quality of life data is limited and not reflective of intended population with only specific HRQoL data reported in the pivotal trial of the submission (ZUMA-2).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for	The company submission addresses the decision problem outlined in the NICE final scope, focusing on evaluating the clinical and cost effectiveness of the intervention in the relevant patient population. However, the company's modelling approach includes certain deviations that may influence the assessment of long-term benefits and resource use.	While the submission aligns broadly with the NICE final scope, it diverges in several key areas. Notably, the company does not apply the updated severity modifier, instead continuing with the legacy end-of-life criteria. The model also assumes a highly extended time horizon—exceeding 100 years—which is atypical for NICE appraisals. Furthermore, cost inputs, such as the CAR-T tariff, are not drawn from the most current data sources. The model also omits some costs and outcomes	The EAG is likely to raise concerns regarding the company's methodological choices. The exclusion of the severity modifier and reliance on outdated cost data may limit the model's relevance and accuracy. The extended time horizon may overestimate long-term benefits, and the omission of pretreatment costs could understate the total cost impact. These factors could lead to uncertainty in the cost-effectiveness estimates and warrant further scrutiny or adjustment.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		linked to the pretreatment phase beginning with leukapheresis.	
Subgroups	NA	NA	NA	The NICE final scope has not considered any subgroups for this population. Based on the literature[21] and EAG clinical expert, there are subgroups and prognostic factors that affect the treatment and prognosis of patients that should be considered. The CS explored the ongoing response rate for a range of subgroups, and none were statistically significantly below the 40% target response rate, though the small sample size meant the uncertainty remained high.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic	Not addressed	Not provided	No equity issues were identified by the EAG.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

The EAG reviewed the methods used by the company to assess the eligibility criteria, identify, extract, assess risk of bias and synthesise the evidence on the safety and efficacy for treatment of adult patients with R/R MCL after two or more lines of therapy, including a BTKi. Study types included, ranged from RCTs to observational studies. The review initially included a population of adult (≥ 18 years) patients with R/R MCL who have received at least one previous line of therapy; this population was then refined to adult (≥ 18 years) patients with R/R MCL who have received at least two previous lines of therapy, including a BTK inhibitor, which was updated to reflect the approved indication for brexu-cel based on TA677.[1] The SLR was then refined to focus on the NICE decision problem as discussed further below.

2.1.1 Searches

A more detailed EAG critique is in the appendix (section 6.1).

Reasonably comprehensive searches in relevant bibliographic databases were undertaken in February 2019, which were updated and re-ran in January 2020 and November 2024 and reported in CS Appendix B. The EAG has some concerns over the reporting of the non-database (conference abstracts, clinical trial registries, hand-searching of relevant HTA organisations and reference checking) searches as the search terms applied, and numbers of results are not reported. Non-database searches are reported to have been carried out in February 2019 and January 2020 only (CS Appendix 1.1), which the company confirmed in the clarification responses. Rather 'pragmatic searches' were carried out for studies relating to the intervention of interest published after 2020, which yielded no additional studies for inclusion (CS clarification questions). The PRISMA flow diagram of the 2024 SLR Update reports that two studies were identified 'through other methods', but those methods are not reported (CS Appendix 1.1 Figure 3: PRISMA flow diagram (Updated SLR 2024).

Not reporting the search terms or numbers of results reduces the transparency and reproducibility of the systematic literature review. Only conference proceedings from 2018 onwards were searched and it is not reported how these were searched, i.e. via the conference websites or via a database, such as Embase. A search of older

conference proceedings may have identified further trials that were never published, to counter publication bias.

The updated SLR search carried out in November 2024 is in line with the previous SLR search strategy. However, the search was only run for records between 2020 to 2024. The EAG believe that the update searches should not have been limited by date, given the addition of patients that have received at least two previous lines of therapy, including a BTK inhibitor to the existing population. Furthermore, the search terms for disease state, for example ‘relapsed’ or ‘refractory’ is limited. The EAG note that limiting the searches to studies published after 2020 could have resulted in potentially relevant studies published prior to 2020 being missed. The searches were limited to studies published in English, which could introduce language bias.

2.1.2 Systematic Literature Review (SLR) methodology

A summary of the EAG’s quality assessment of the company’s systematic literature review (SLR) using the modified Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) is presented in Table 5. The full EAG assessment using the modified ROBIS is in the EAG Appendix, section 6.4. Overall, the EAG has some concerns over the risk of bias.

Table 5. Summary of the EAG's critique of the company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS Appendix B, section D.1.1, Tables 13 and 16	Low concern
Searches and selection of studies	CS Appendix B, section B.1.1	Low concern
Data extraction and risk of bias assessment	CS Appendix B, section B.1.1, Tables 18 - 21	Unclear concern
Evidence synthesis	CS Document B, section B.2.1 – 2.2, 2.9 – 2.10	Unknown

Eligibility criteria

There are substantial concerns regarding the restrictive study selection regarding exclusion of relevant studies, unclear eligibility criteria, and a lack of transparency in study selection.

Searches and selection

The EAG checked all included and excluded studies and found that some of these were not in line with the eligibility and some disagreement on the reasons for exclusion. Only one study with two included reports originally identified by the SLR was eventually included in the CS as it was in line with the NICE decision scope.

Data extraction and risk of bias assessment

The review was independently screened for relevance by two reviewers, and a third resolving any disagreements.

The method of data extraction is unclear, including whether a second reviewer checked for accuracy. The company used the quality Critical Appraisal Skills Programme (CASP) framework for the risk of bias assessment. While the CASP framework is in line with NICE guideline recommendations for quality assessment of systematic reviews, it focuses on broader appraisal and quality assessment. Therefore, the ROBIS tool is preferred for systematic reviews due to its greater validity and reliability[22] The EAG is unclear whether two reviewers independently conducted the risk of bias assessment.

Evidence synthesis

The company did not include all identified studies, and no predefined analyses were specified in the CS. Furthermore, only three eligible non-randomized RCTs were identified to inform clinical effectiveness. As a result, no indirect or mixed treatment comparisons were conducted (CS Document B, section B.2.10). While subgroup analyses based on baseline characteristics were performed, potential confounders were not reported or adjusted for. Consequently, the study population was not representative of real-world clinical settings, as the patients appeared to be young and generally healthy.

2.2 *Critique of studies of the technology of interest, the company's analysis and interpretation*

The pivotal trial providing safety and efficacy information for this indication of brexu-cel is ZUMA-2.

2.2.1 Trial design (ZUMA-2)

The EAG's summary of the key features of the ZUMA-2 trial, based on the company' submitted information, is summarised in Table 6. At clarification, the company submitted two protocols version 1.0 and version 9, the EAG in this report unless stated or otherwise refers to protocol version 1.0 which is supplemented in ZUMA-2 publication by Wang et al. 2020[23] due to the comprehensiveness of the protocol.

An overview of ZUMA-2 is provided in Table 6, combining information from the CS and trial protocol. Table 7 contains the pre-specified outcomes of ZUMA-2. The EAG notes that the trial infused 68 people with CAR-T product out of 74 leukapheresed participants,

[redacted]. Five people were also retreated with brexu-cel, potentially incurring additional benefit that is not expected to be available on NHS.

Table 6. EAG Summary of ZUMA-2 trial design

Method step	Summary of the approach used	Section(s) of CS of relevance or other source
Method of randomisation	ZUMA-2 is a multicentre (16 sites in the US, 2 sites in France, 1 site in the Netherlands, 1 site in Germany), open-label, phase 2, *single-arm trial* evaluating the efficacy of brexu-cel in subjects with relapsed refractory mantle cell lymphoma	CS Document B, Section B.2.2, Table 6 and Table 7 Company study protocol v 1.0 Wang et al 2020 [23], Clinicaltrials.gov[24]
Eligibility criteria	Participants were 18y or older with histologically confirmed mantle cell lymphoma with either cyclin D1 overexpression or presence of the translocation t(11;14), had diseases that was either *relapsed or refractory to up to five previous lines of treatment* (including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody, and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib and/or acalabrutinib), with absolute lymphocyte count ≥ 100/μL and eastern cooperative oncology group performance status (ECOG PS) of 0 or 1 Exclusions were history of allogeneic stem cell transplant (alloSCT), recent malignancies other than nonmelanomatous skin cancer or carcinoma	CS Document B, Section B.2.2, Table 7 Company study protocol v 1.0 Wang et al 2020[23]

	in situ, prior CAR-T, pregnancy, specific viral infections (HIV, Hepatitis B), autoimmune disease, presence of any in-dwelling line or drain, detectable cerebrospinal fluid (CSF) malignant cells or brain metastases or with a history of CNS lymphoma, history or presence of CNS disorder, cardiovascular-related conditions, or investigator judgement of patient being unlikely to complete all protocol-required study visits A complete list of inclusion and exclusion criteria is reported in the CS, protocol sections 5.2 and CS Document B, Section B.2.2, Table 7	
Treatment stages	All patients went through the following stages: • Screening (within 28 days of enrolment) Enrolment/Leukapheresis (within approx. 5 days of eligibility confirmation) • Bridging therapy if applicable* (within 5 days prior to conditioning chemotherapy) • Conditioning chemotherapy** (day -5, -4, -3, -2, -1) • Investigational product (IP) treatment (day 0, 1 – 7) • Post-treatment assessment (week 2 ± 2 days, week 4 ± 3 days, month 2 ± 1 week, month 3 ± 1 week) • Long-term follow-up period (month 6 ± 2w, month 9 ± 2w, month 12 ± 2w, month 15 ± 2w, month 18 ± 2w, month 24 ± 1m, month 30± 1m, month 36 ± 1m, month 42 ± 1m, month 48 ± 1m, month 54 ± 1m, month 60 ± 1m, month 72 ± 3m and annually, thereafter up to 15 years)	Company study protocol v 1.0 Wang et al 2020[23]
Treatment regimens	The target dose for brexu-cel was 2 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells per kg body weight	CS Document B, Section B.2.3.1
Measured outcomes	**Primary outcomes** • Objective response rate (ORR): Complete response [CR] + partial response [PR]) per the Lugano Classification[25] **Secondary outcomes** • Duration of response (DOR) • Best objective response (BOR) • Overall response rate (ORR) as determined by study investigators • Progression-free survival (PFS)	CS Document B, Section B.2.6.1 – 2.6.5 Company study protocol v1.0

	• Overall survival • Incidence of adverse events (AEs) and clinically significant changes in laboratory values • Incidence of anti-CD19 CAR-T antibodies • Levels of anti-CD19 CAR-T cells in blood • Levels of cytokines in serum • Changes over time in the European Quality of Life-5 Dimensions (EQ-5D) scale score and visual analogue scale score	
Statistical analysis	A target 50% ORR per independent review against a null hypothesis that the ORR is 25% or less	CS Document B, Section B.2.4 Company study protocol v1.0

*At the discretion of the investigator and after discussion with the medical monitor, bridging therapy was considered for any subject, particularly those with high disease burden at screening (eg, > 25% marrow involvement and/or ≥ 1,000 leukemic phase mantle cells/mm3 in the peripheral circulation). Bridging therapy was allowed with (1) dexamethasone or other corticosteroid, (2) ibrutinib, or (3) acalabrutinib. If prescribed, bridging therapy was administered after leukapheresis and completed at least 5 days prior to initiating conditioning chemotherapy.

** conditioning chemotherapy regimen consisted of fludarabine 30 mg/m2/day and cyclophosphamide 500 mg/m2/day, administered x 3 days

Table 7. EAG summary of the company's stated key endpoints for (ZUMA-2) based on submitted information

Objectives	Endpoint Description	Assessment	Chosen assessment time points	Incorporated into the economic analyses
Primary	ORR (CR + Cri) based on revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007)	Assessed by IRRC review and study investigators.	Every 3 months up until Month 72 and annually thereafter	No
Secondary: Efficacy	DOR, BOR, ORR per IRRC, PFS, OS, Minimal residual disease (MRD)	ORR per IRRC assessed by IRRC DOR is derived using disease assessments obtained on study prior to initiation of new	DOR, BOR, ORR per IRRC, PFS, OS: Every 3 months up until Month 72 and annually thereafter, MRD: 1, 3. 6 months	Yes – PFS and OS only

		anticancer therapy (including SCT) PFS assessed by investigator or IRRC MRD was assessed as an exploratory analysis		
Secondary: PROs	To evaluate the changes in scores from baseline to month 6 in the five-level version of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire	Assessed using the EQ-5D 5L questionnaire at screening (for baseline scores)	Week 4 (± 3 days), Month 3 (± 1 week) and Month 6 (during the long-term follow-up period) before any other assessments or procedures)	Yes – through health state utility values derived from ZUMA-2 EQ-5D-5L data by mapping to EQ-5D-3L
Safety	To assess Incidence of AEs and clinically significant changes in laboratory values, Incidence of anti-KTE-C19 antibodies, levels of anti-CD19 CAR+ T cells in blood and levels of cytokines in serum	AEs - observed by investigator or reported by patient Laboratory tests - graded according to NCI Common Toxicity Criteria CAR-T cells	AEs and Laboratory tests: every 3 months up to 48 months CAR-T cells: Day 7, week 2, week 4, month 3, month 6, month 12, and month 24	Yes

ORR (Objective Response Rate), CR (Complete Response), CRi (Complete Response with Incomplete Bone Marrow Recovery), IWG (International Working Group), IRRC (Independent Radiologic Review Committee), DOR (Duration of Response), BOR (Best Objective Response), PFS (Progression-Free Survival), OS (Overall Survival), MRD (Minimal Residual Disease), SCT (Stem Cell Transplant), PROs (Patient-Reported Outcomes), EQ-5D 5L (European Quality of Life – 5 Dimensions, Five-Level Version), AEs (Adverse Events), NCI (National Cancer Institute), and CAR-T (Chimeric Antigen Receptor T-cell).

2.2.2 Risk of bias for the trial (ZUMA-2)

The CS (Appendix B, section 1.3, Table 22) conducted the quality assessment of ZUMA-2 and 16 other studies from the updated SLR (Nov 2024). However, only

three studies were included, in line with the final NICE scope; ZUMA-2 (a single arm, non-randomised trial) and two follow-up studies (CS Document B, section B.2.2, Table 5).

For non-randomized and non-controlled studies, the CASP framework was used, following NICE guidelines. However, the EAG notes that the CS did not provide a narrative rationale for its quality assessment decisions. Additionally, in the previous submission,[1] the company used the Downs and Black checklist for ZUMA-2.

Given that key aspects of the ZUMA-2 trial remain unchanged, the EAG considers the Downs and Black checklist more appropriate, consistent with TA677.[1] This checklist offers a more comprehensive and quantitative assessment, covering internal and external validity as well as reporting quality.[26] Therefore, in addition to CASP, the EAG independently conducted a Downs and Black assessment for ZUMA-2 (see section 6.3).

The company reported that it was unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited. However, the EAG notes that the subjects recruited were relatively fit patients with low ECOG PS and did not include patients with controlled viral infections. Clinical advice to the EAG states that such a population is not reflective of clinical practice. Furthermore, the EAG is unable to ascertain if treatment centres were reflective of UK NHS practice.

The EAG notes that patients were selected based on specific eligibility criteria, which may limit how well the results apply to the wider R/R MCL patients

2.2.3 Sources of real-world evidence for brexu-cel

The EAG utilises a comprehensive array of real-world evidence (RWE) in this appraisal to provide an extensive overview of generalisability, prognosis, and clinical effectiveness, in conjunction with the latest follow-up data from ZUMA-2. This evidence encompasses four main sources: 1) the England Systemic Anti-Cancer Therapy (SACT) dataset for the Cancer Drugs Fund (CDF) NHS population, 2) a study by O'Reilly et al. (2024)[27] representing the UK, 3) the DESCAR-T registry from France under the European Medicines Agency approval label,[28] and 4) the US lymphoma CAR-T Consortium.[29] The EAG briefly introduces each source:

SACT population (NHS England)

Between 19 January 2021 and 30 September 2023, 142 CDF funding applications for leukapheresis were submitted, involving 137 unique patients. NHS England assessed the real-world effectiveness using the Systemic Anti-Cancer Therapy (SACT) dataset, demonstrating the potential for real-world data to inform decision-making and facilitate earlier patient access to treatments. The eligibility criteria were broader than ZUMA-2 and similar to the national CAR-T Cell panel used in the O'Reilly et al. study.[27] Of these, 92 unique patients who received treatment were included in the analyses.[30]

Addendum to the British Society for Haematology Guideline

In 2022 an addendum[31] was issued by the British Society for Haematology for haematologists regarding the investigation of Mantle Cell Lymphoma (MCL) patients for potential future CAR-T-cell therapy. In the UK, MCL patients who progressed on ibrutinib before CAR-T-cell therapy were found to have poor outcomes, with a median overall survival of 1.4 months, and 0.4 months for those unable to receive further therapy.[32] Consequently, the national approach has been revised to include early identification and monitoring of high-risk MCL patients at first relapse, aiming to capture early refractory disease or progression on second-line ibrutinib.

Early referral at the first indication of ibrutinib failure may enhance the accessibility and efficacy of CAR-T-cell therapy. High-risk patients are advised to be closely monitored and discussed with a CAR-T-cell centre, with frequent appointments and early re-imaging if symptoms persist. The company claims this may improve real-world efficacy of brexu-cel compared to what was observed in the SACT dataset, however a comparison of infusions before and after this date do not clearly support this (see section 2.4.3).

O’Reilly et al. study (England and Scotland)

The UK study by O’Reilly et al. reports on real-world ITT outcomes for brexu-cel in consecutively approved patients from 12 institutions between February 2021 and June 2023. Of the 119 approved patients, 104 underwent leukapheresis, and 83 received brexu-cel infusion. Progressive disease (PD) and manufacturing failure (MF) were the primary reasons for failure to reach harvest and infusion. The median follow-up was 13.3 months. The UK NCCP eligibility criteria were broader than

ZUMA-2, including patients with prior alloSCT, CNS involvement, flexible organ function requirements, comorbidities, and controlled viral infections such as hepatitis or HIV.[27]. Note that this population is believed to have considerable overlap with the SACT dataset, as confirmed by the EAG clinical advisor,[30] and they should not be considered independent studies or populations.

DESCAR registry (France; EMA)

The DESCAR registry details the intention-to-treat (ITT) population in France, enrolled during the tumour board review following European Medicines Agency approval. It includes 181 patients from 24 French centres, with 71.8% not meeting ZUMA-2 eligibility criteria due to reasons such as the necessity of a bridge other than corticosteroids or BTKi (61.1%), performance status (PS) ≥2 (12%), and prior malignancy (8.3%). The treated set comprised 152 patients, while the untreated set included 26 patients, with a median follow-up of 14.2 months.[28]

US Consortium (United States)

The US study involved patients who underwent leukapheresis between August 1, 2020, and December 31, 2021, at 16 institutions. Of the 189 patients who underwent leukapheresis, 168 received brexu-cel infusion. Among these patients, 79% did not meet ZUMA-2 eligibility criteria due to disease status (relapsed/refractory after five lines of therapy, alloSCT, anti-CD19 CAR cell therapy, CNS or cardiac involvement) or clinically significant comorbidities. BTKi naïve patients were not considered in this draft report.[29]

2.2.4 Sources for comparator arm

The main source of information for R-BAC was a paper by McCulloch et al. (2020).[33] An additional paper published a year later also contains information on R-BAC (McCulloch et al. (2021)), however, has a smaller relevant population size.[33] The EAG briefly introduces each population below.

2.2.4.1 McCulloch et al. (2020)

Methodology

This retrospective cohort study aimed to evaluate the efficacy and safety of the R-BAC regimen (rituximab, bendamustine, cytarabine) in patients with mantle cell lymphoma (MCL) who had progressed following treatment with Bruton’s tyrosine

kinase inhibitor (BTKi).[33] Eligible patients were identified through specialist MCL services in the UK and Italy.

Population

The study included 36 patients treated with R-BAC across 23 centres between October 2015 and March 2019. The median age was 66 years (range 43–81), and the median number of prior systemic therapies was 2 (range 1–6). The baseline characteristics are summarised in section 2.2.5.

Comparator and Results

The study compared the outcomes of R-BAC with those of other agents used in the post-BTK inhibitor setting, including chemotherapy, phosphoinositide 3-kinase inhibitors, lenalidomide, bortezomib, and single-agent venetoclax. Previous studies reported ORRs of 29–32% and median OS of 5.8–8.4 months for chemotherapy and other agents, and an ORR of 53%, median PFS of 3.2 months, and median OS of 9.4 months for venetoclax.

Intervention and Results

Patients received four to six cycles of R-BAC regimen. The response to treatment was assessed according to the Lugano 2014 classification, with imaging evaluations conducted at the discretion of the treating clinician. The study also explored the role of R-BAC as a bridge to alloSCT and its effectiveness in transplant-eligible patients.

The overall response rate (ORR) to R-BAC was 83%, with a CR rate of 60%. 31% of patients were bridged to alloSCT. The median PFS was 10.1 months [95% CI, 6.9-13.3], and the median OS was 12.5 months [95% CI, 11.0-14.0]. Among patients consolidated with alloSCT, only one patient relapsed.

2.2.4.2 McCulloch et al. (2021)

McCulloch et al. (2021)[34] provided further insights into post-ibrutinib outcomes in patients progressing through ibrutinib. Of the 100 patients discontinuing ibrutinib due to progressive disease, 57% received no additional systemic therapy, while 43% received at least one additional course of treatment.

Post-ibrutinib systemic therapy consisted of rituximab, bendamustine, cytarabine (R-BAC) in 50% (21/42), rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) in 12% (5/42), rituximab, bendamustine (R-B) in 10% (4/42),

and assorted chemotherapy combinations in 24% (10/42). Five patients (5/23; 21.7%) receiving R-BAC were consolidated with alloHSCT. Among 23 patients receiving post-ibrutinib R-BAC, the median post-ibrutinib OS was 14.0 months (95% CI 8.1–19.8) versus 3.6 months (95% CI 2.6–4.5) for those receiving other therapies. This group was younger than patients receiving other post-BTKi therapies.

2.2.4.3 EAG Comments on R-BAC Sources

The EAG acknowledges the potential uncertainties inherent in the McCulloch studies. The limited sample size in both publications reduces the robustness of any derived interpretations. The single-arm design, data retrieval processes, and retrospective nature of McCulloch et al. studies[33, 34] may introduce biases, particularly in the likelihood of selecting younger patients for treatment in McCulloch et al. (2020). The study, while not explicitly stating it objectives, aimed to evaluate the efficacy of R-BAC and address its associated challenges by proposing bridging to alloSCT as a solution. Specifically, the study focused on younger, transplant-eligible patients to demonstrate subsequent bridging to alloSCT. Given the short median PFS post-R-BAC (with an ORR of 83% and a median PFS of 10.1 months), this bridging was intended to sustain responses, resulting in a higher proportion of subsequent alloSCT (31% in 2020 and 21.7% in 2021). To achieve this objective and demonstrate the proposed solution, the recruitment of more transplant-eligible patients led to a higher proportion of patients being bridged to alloSCT..

The EAG's clinical advisor noted that within the NHS, patients with progressive disease, advanced age, comorbidities, and high-risk post-BTKi are less likely eligible for alloSCT post-3rd line of therapy. Only a small subset of young, fit patients with a suitable donor undergo alloSCT, typically in first remission or after responding to second-line BTK inhibitors. By the third line setting, most eligible patients would have already received alloSCT earlier in their treatment journey. Furthermore, the EAG's clinical expert acknowledged that the findings of McCulloch et al. (2020) may not accurately represent NHS patients, as the outcomes and survival rates are likely lower than those reported in McCulloch's small cohort, with a potential risk of selection bias.

McCulloch et al. (2020)[33] identifies potential selection bias, noting the preference for younger, fitter patients for alloSCT and McCulloch et al. (2021) advises cautious

interpretation of post-ibrutinib outcomes due to the older patient demographic and limited treatment options.[34] The study was restricted to patients from centres with access to ibrutinib. Given the limitations and the study's objectives towards evaluating R-BAC and post-alloSCT, the study's interpretations should be approached with caution.

Nevertheless, due to the absence of more suitable evidence, the EAG has utilized the McCulloch publications in this report. The EAG preference is to use McCulloch 2020 as the primary source, due to the McCulloch 2021 population having more optimistic outcomes than the McCulloch 2020 population which were already described as too optimistic by the EAG's clinical expert. See section 2.4.2 where the EAG removes the effects of subsequent alloSCT from McCulloch 2020.

2.2.5 Comparison of brexu-cel and R-BAC sources

A comparison of the baseline characteristics of the studies of brexu-cel is provided in Table 8, where information on the company's and EAG's preferred source for the comparator arm (introduced later) is also included.

Table 8: Baseline characteristics of ZUMA-2 trial compared with RWE studies of brexu-cel and R-BAC

		ZUMA-2 trial cohort 1 enrolled population (ITT; n =74)[23, 35]	O'Reilly et al. 2024 (n=119)[27]	CDF patients reported as SACT (n=92)[30]	DESCAR registry (n=152)[28]	US consortium (n=144)[29]	McCulloch 2020 (n=36)[33]
Age	Median (range), years	65 (38-79)	68 (41–80)	67.5 (41-78)	68.0 (39-83)	67 (34-89)	66 (43–81)
Male, n (%)		62 (84)	87 (73)	71 (77)	131 (86.2)	NR	29 (80.6)
ECOG performance status score, n (%)	0	47 (64)	42 (35)	15 (16)	125 (88.0)	NR	NR
	1	27 (36)	77 (65)	33 (36)		NR	NR
	≥ 2	0	0	2 (2)	17 (12)	18 (13)	7 (19.5)
	Missing	NA	NA	42 (46)	NR	NR	NR
Simplified MIPI, n (%)	Low risk	29 (39)	23 (23)	NR	27 (19.9)**	46 (32)	5 (13.9)**
	Intermediate risk	30 (41)	31 (31)	NR	54 (39.7)**	75 (52)	6 (16.7)**
	High risk	13 (18)	47 (47)	NR	55 (40.4)**	23 (16)	15 (41.7)**
	Missing	2 (3)	18 (15)	NR	16 (10.5)	NR	NR
Ki-67 proliferation index ≥ 30%, n (%)		40 (54.1)	49 (78)	NR	85 (79.4)	102 (70.8)	NR

		ZUMA-2 trial cohort 1 enrolled population (ITT; n =74)[23, 35]	O'Reilly et al. 2024 (n=119)[27]	CDF patients reported as SACT (n=92)[30]	DESCAR registry (n=152)[28]	US consortium (n=144)[29]	McCulloch 2020 (n=36)[33]
Morphology, n (%)	Blastoid	19 (26)	29 (37)	NR	41 (31.1)	59 (41)	7 (19.5)
	Pleomorphic	4 (5)	4 (5)	NR	NR		NR
TP53 mutation, n (%)		6 (8.1)	21 (17.6)	NR	29 (30.2)	54 (50)	NR
POD24, n (%)		33 (48.5)[a]	67 (57)	NR	NR	71 (49)	NR
Extranodal disease, n (%)		43 (58)	90 (76)	NR	NR	NR	NR
Prior therapy, n (%)	AutoSCT	31 (42)	40 (34)	25 (27)	60 (39.5)	NR	15 (41.7)
	AlloSCT	0 (0)	15 (13)	14 (15)	9 (5.9)	NR	2 (5.6)
Received bridging therapy, n (%)		28 (38)	94 (79)	84 (91)	126 (82.9)	NR	NA

Abbreviations: alloSCT, allogeneic stem cell transplant; autoSCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; mAb, monoclonal antibody; MCL, mantle cell lymphoma; mITT, modified intent-to-treat; PD, progressive disease; s MIPI, simplified-Mantle Cell Lymphoma International Prognostic Index.

[a]Calculated from mITT population with 68 patients.

**MIPI has been reported. For the McCulloch et al. (2020), MIPI at start of R-BAC has been used.

2.2.5.1 Comparison of brexu-cel sources

- **ECOG PS scores:**

In the ZUMA-2 study, it was observed that 64% of patients exhibited an ECOG performance status (PS) of 0, while 36% had a score of 1. In contrast in the SACT population, only 16% were recorded with a score of 0, and 36% with a score of 1, with 46% of patients having missing ECOG scores. In O'Reilly et al., 35% of patients were documented with a score of 0, and 65% with a score of 1. Additionally, in the DESCAR and US datasets, 12% and 13% of patients, respectively, were reported with scores ≥2, which were not observed in the ZUMA-2 study, highlighting a potential difference (lower (better) ECOG scores) between ZUMA-2 and real-world use of brexu-cel.

- **Simplified MIPI, Ki-67, TP53 mutation, and POD24:**

In the ZUMA-2 study, it was observed that 80% of patients were categorized into low- and intermediate-risk groups according to the simplified score-based international prognostic index (s-MIPI) criteria, with only 18% considered high-risk. Conversely, O'Reilly et al. reported that 54% of patients were in the low-intermediate risk group, while 47% were classified as high-risk with a poor prognosis.

O'Reilly et al., in comparison to ZUMA-2, documented higher proportions of patients with poor prognostic factors, including the Ki-67 proliferation index ≥ 30% (78% vs 54.1%), TP53 mutations (17.6% vs 8.1%), extranodal disease (76% vs 58%), and progression of disease within 24 months of first-line therapy (POD24; 57% vs 48.5%). Similarly, the DESCAR study indicated higher percentages in comparison to ZUMA-2.

The EAG's clinical advisor highlighted that Ki-67, TP53 mutation, and POD24 may be potential key markers of poor prognosis. Given the differences in the majority of these factors between ZUMA-2 and the RWE sources, it suggests that the ZUMA-2 trial may not be representative of real-world use of brexu-cel.[12, 36-38]

- **Previous stem cell transplant (SCT):**

In the ZUMA-2 trial, 42% of patients had undergone autologous stem cell transplant (auto-SCT), while no patients with allogeneic SCT (alloSCT) were included due to trial original protocol exclusion criteria (page 15). The SACT and O'Reilly et al.

studies reported 15% and 13% previous allogeneic SCT, respectively, in addition to fewer autologous SCT compared to the ZUMA-2 trial (27% and 34% for SACT and O'Reilly et al., respectively, compared to 42% in ZUMA-2).

EAG notes:

The EAG considers that the difference in patient groups, with fewer previous auto-SCTs and higher percentages of previous alloSCTs in the RWE, compared to the ZUMA-2 trial, introduces potential uncertainties regarding the generalisability of the ZUMA-2 trial results. In response to the EAG's inquiry about the possibility of brexu-cel administration to patients with prior alloSCT (clarification question A16), the company has confirmed eligibility in real-world settings.

- **Bridging therapy:**

It has been noted that 38% (28 out of 74) of patients participating in the ZUMA-2 trial were administered bridging therapy. Conversely, the SACT, O'Reilly et al., and DESCAR studies documented substantially higher percentages of patients receiving bridging therapy prior to infusion, attributed to the more aggressive and progressive characteristics of the disease, with figures of 91%, 79%, and 82.9%, respectively.

EAG notes:

The company suggested that bridging therapy might be provided to all patients, with special attention to those demonstrating a high disease burden during screening (original protocol page 57). Taking into account the discrepancies between RWE and ZUMA-2, it is conceivable that the ZUMA-2 trial population's lack of requirement for disease control prior to infusion may be due to a comparatively less severe disease state than that observed in RWE. This interpretation was supported by the EAG's clinical expert.

2.2.5.2 Comparison to McCulloch et al. (2020)

Due to the small number of patients included in the McCulloch et al. (2020)[33] study and the limited reporting on baseline characteristics, a consistent approach to comparing it with RWE studies individually was not feasible. However, certain key differences observed were collected and reported by the EAG.

When comparing the McCulloch 2020 study with ZUMA-2, it becomes evident that McCulloch's findings are more aligned with the real-world evidence (RWE) utilized by

EAG for brexu-cel. This alignment is mainly reflected in the inclusion of those with a history of alloSCT and patients with an ECOG performance status score of 2 or higher. Furthermore, McCulloch's cohort comprised a higher proportion of high-risk patients compared to ZUMA-2, which is consistent with the patient profiles observed in DESCAR and O'Reilly et al. 2024.

These discrepancies raise important questions about the generalizability of ZUMA-2's findings and suggest that RWE may provide a more comprehensive understanding of patient outcomes in a broader, more diverse population.

2.2.6 Efficacy outcomes for brexu-cel

2.2.6.1 Primary outcomes; objective response rate (ZUMA-2)

The response rates have been reported by the company in the CS dossier document, Table 11, and are replicated by the EAG in Table 9.

Table 9: Objective response rate (ZUMA-2)

	Brexu-cel
	mITT (n = 68)
Objective response rate (CR + PR), n (%) [95% CI]	62 (91) [50.1, 73.2]
Complete response rate, n (%) [95% CI]	46 (68) [55.2, 78.5]
Partial response, n (%) [95% CI]	16 (24) [14.1, 35.4]

Key: CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; IWG, International Working Group; mITT, modified intent-to-treat; PR, partial response.
Notes: CIs are reported as per the Clopper–Pearson method used for primary analyses.
Source: Wang 2023[35]

EAG notes that there is a variation in the confidence interval for the ORR between the company's data and the data reported by Wang et al. 2023, as cited in the CS dossier document, Table 11.[35] Wang et al. 2023, with a median follow-up (FUP) of 35.6 months (range, 25.9-56.3), reports the ORR with IRRC assessment as 91% [95% CI, 81.8 to 96.7].[35]

2.2.6.2 Secondary outcomes

2.2.6.2.1 Duration of response (ZUMA-2))

In protocol section 8.16.7.3,[23] it was noted that patients receiving only new anticancer treatments were censored. According to CS, Table 14.2.5.2.2a, only [redacted] patients ([redacted]%) were censored due to new anticancer therapy. By July 2019 (median follow-up of 12.3 months), [redacted] subsequent anticancer therapies had been administered to [redacted] patients ([redacted]%) (CS, main dossier, section B.2.7). By October 2023 (48 months data cutoff), this number had increased to [redacted] therapies for [redacted] patients ([redacted]%) (CQ A11). The observed discrepancy, with fewer reported censorings ([redacted] patients that had subsequent treatment vs. [redacted] patients with new anticancer therapies that were censored), suggests that the impact of subsequent treatments on endpoints, particularly the DOR, may not have been fully captured.

In the CS dossier document, section B.2.6.1, the duration of response (DOR) has been reported by the company for a period of three years. The EAG opted to utilise the most relevant and updated results available (April 2024 data cutoff). Figure 2 (sourced from company data on file, Figure 14.2.4.2a) illustrates the Kaplan-Meier (KM) Plot of DOR based on investigator assessments for [redacted] out of 68 infused patients from cohort 1 who achieved an objective response. The median DOR has been reported as [redacted].

It was observed that [redacted] experienced events, including [redacted] ([redacted]%) experiencing disease progression and [redacted] ([redacted]%) dying. Additionally, [redacted] received subsequent treatment and were censored. Table 14.2.5.2.2a reports a DOR of [redacted] at the 60-month time point. By the 60-month data cutoff, the KM plot had reached a plateau, indicating that the results reflect changes up to that time point. Beyond this time point, patients were censored.

Figure 2: Kaplan-Meier Plot illustrating the duration of response, as assessed by investigators, for the cohort 1 mITT analysis set (subjects with ORR, N = 60)

2.2.6.2.2 Overall Survival (ZUMA-2)

In Table 14.2.7.1.1a, the company reported the overall survival (OS) for cohort 1 infused patients (n=68) with a Kaplan-Meier (KM) median of 46.5 months [95% CI, 24.9-60.2]. Figure 3, compares the new OS follow-up from that submitted in the original appraisal.

By the data cutoff, it was observed that 44 patients (65%) had died, [redacted] had withdrawn, and [redacted] was lost to follow-up. According to the Kaplan-Meier (KM) estimates, there was a notable decline in survival from [redacted] at 30 months to [redacted] at 63 months. The most recent data indicated a survival rate of [redacted] at 66 months.

Censoring commenced after 48 months. The footnote of Table 14.2.7.1.1a indicates that patients were censored at their last contact date before the data cutoff date, except for those known to be alive or determined to have died after the data cutoff date, who were censored at the data cutoff date.

Figure 3: Kaplan-Meier plot of overall survival for old and current data-cuts of ZUMA-2

2.2.6.2.3 Progression-free survival (ZUMA-2)

Figure 4 compares the PFS follow-up in the current submission with the previous submission for 68 infused patients. The median follow-up period (FUP) for Figure 4 was 67.8 months (58.2-88.6).

The median PFS time has been reported as 25.3 months [95% CI, 12.7-46.6]. In total, 44 events (65%), including disease progression and death, as well as censoring for subsequent treatments ( ) such as stem cell transplant (SCT), non-SCT new anticancer therapy, and withdrawal or loss to follow-up, were reported.

According to Table 14.2.6.2.1.1a, the 63-month PFS rate was].

Figure 4: Kaplan-Meier plot of progression-free survival for old and current data-cuts of ZUMA-2

2.2.6.3 Health-related quality of life (ZUMA-2)

The company utilized the EQ-5D to evaluate patients' quality of life at enrolment (screening), post-infusion at week 4, months 3 and 6. The absence of further assessments raises concerns regarding the comprehensiveness of the data on patients' experiences. Potential adverse events (AEs) reported by Wang et al. (2023) after the initial data cut align with the EAG's critique.[35] Notably, AEs occurring after 6 months, late-onset AEs, and the impact of disease progression have not been documented.

The single-arm, non-randomized trial design may introduce bias, as patients, assessors, and analysts were all aware of the drug, potentially limiting the positive interpretation of outcomes. Deterioration in HRQoL (defined as worsening by at least 1 level on the 5-level scale by the company) continued from screening to the 6-month assessment, and as Table 10 shows, there is ongoing deterioration for some patients up until the 6-month assessment. Given the remaining deteriorations at each assessment, the accuracy of the presented data may be questionable. Furthermore, the gap between enrolment and infusion, during which patients

underwent leukapheresis, bridging, and conditioning therapy, was not covered in the assessments.

Table 10 (derived from company dossier document, Table 12) indicates a decline in quality of life by week 4, likely due to adverse effects and hospitalizations. Data shows inconsistent recovery by month 6, with persistent anxiety and depression. More frequent, refined long-term assessments would have alleviated the EAG's concerns and provided a more accurate depiction.

Table 10: EQ-5D summary by visit (Cohort 1 infused patients)

EQ-5D-5L Dimension	Screen	Week 4	Month 3	Month 6
Mobility				
N	62	51	54	40
Patients reporting no problems, n (%)	53 (85)	25 (49)	37 (69)	30 (75)
Patients with deterioration from screening[a], n (%)	-	21 (41)	13 (24)	8 (20)
Self-care				
N	62	52	54	40
Patients reporting no problems, n (%)	59 (95)	35 (67)	45 (83)	37 (93)
Patients with deterioration from screening[a], n (%)	-	16 (31)	9 (17)	3 (8)
Usual activity				
N	65	51	55	41
Patients reporting no problems, n (%)	53 (82)	22 (43)	38 (69)	30 (73)
Patients with deterioration from screening[a], n (%)	-	25 (49)	13 (24)	8 (20)
Pain / Discomfort				
N	65	54	55	42
Patients reporting no problems, n (%)	43 (66)	34 (63)	33 (60)	28 (67)
Patients with deterioration from screening[a], n (%)	-	9 (17)	13 (24)	5 (12)
Anxiety / Depression				
N	65	54	55	42
Patients reporting no problems, n (%)	49 (75)	36 (67)	38 (69)	26 (62)
Patients with deterioration from screening[a], n (%)	-	11 (20)	12 (22)	10 (24)
EQ-5D Visual Analogue Scale				
N	65	52	55	42
Mean (SD)	82.0 (15.4)	74.5 (15.6)	80.1 (15.6)	84.8 (17.5)
Median (range)	85 (75–95)	78 (60–89)	83 (70–92)	90 (80–95)
Patients with deterioration from screening[b], n (%)	-	26 (50)	16 (29)	5 (12)

Key: EQ-5D-5L, EuroQol-5 Dimension-5 Level; SD, standard deviation; VAS, visual analogue scale.

EQ-5D-5L Dimension	Screen	Week 4	Month 3	Month 6
Notes: [a], deterioration defined as worsening by at least 1 level on the 5-level scale; [b], deterioration defined as VAS reduction of ≥10 on the 0-100 scale where higher scores indicate better health. **Source:** Wang et al. 2020 (supplementary appendix).[23]				

2.2.7 Subgroup analysis (ZUMA-2)

The subgroup analysis (Figure 5), taken from CS appendices (Figure 4), is presented below and evaluated by the EAG using clarification question A6 and the trial protocol. This figure illustrates the proportion of individuals in each subgroup who sustained a response to brexu-cel at the 3-year follow-up (July 2021; median of 35.6 months).[35] Given that only [redacted] out of 68 people ([redacted]%) (CSR, Table 14.2.5.2.2a) exhibited an ongoing response according to the most recent data cut (01 April 2024), any interpretations of the subgroups should be approached with caution.

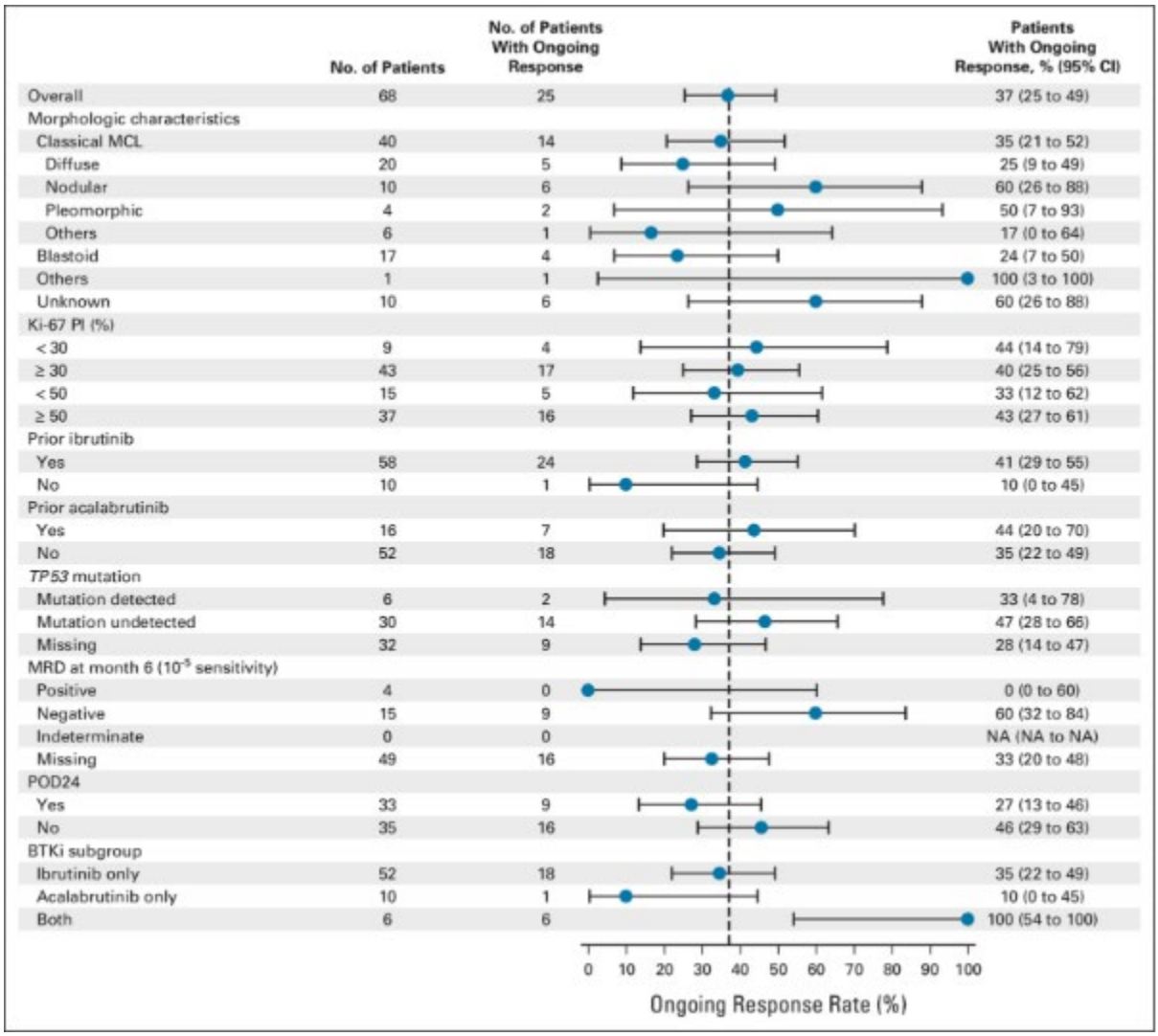


Figure 5: Subgroup analyses for ongoing response rate

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma; MRD, minimal residual disease; NA, not available; PI, proliferation index; POD24, progression of disease < 24 months after initial diagnosis; TP53, tumor protein p53 gene.

The interpretability of the results is limited by the small sample size and the broad confidence intervals for most covariates. The 95% confidence interval, calculated using the Clopper-Pearson method, lacks adjustment for multiplicity, complicating the interpretation further. This omission increases the risk of Type I errors, potentially leading to false positives and misleading conclusions.

The protocol (page 107) specifies that while the Clopper-Pearson interval provides adequate coverage probability (likelihood that the CI contains the true value of the parameter being estimated), results in wider-than-necessary intervals, leading to overly conservative estimates of the lower bound of the objective response rate (ongoing response). The EAG notes that such excessive caution can obscure the true precision of the estimates, resulting in a lack of clarity in data interpretation. This ambiguity can hinder informed decision-making, ultimately impacting clinical practice and policymaking.

Additionally, the EAG has observed that the TP53 mutation, POD24, and minimal residual disease (MRD) were not included among the pre-defined covariates for subgroup analysis in the trial protocol, section 4.2. The company noted in clarification question A6 that MRD assessments had an ad hoc and exploratory basis. The company has indicated in response to clarification question A6 that MRD assessments were conducted on an ad hoc and exploratory basis

2.2.8 Safety outcomes (ZUMA-2)

While the majority of events were documented at a median follow-up of 12.3 months (data cutoff July 2019; range, 7.0 to 32.3),[23] it was observed that 3% of long-term and late-onset events occurred up to 35.6 months (July 2021 data cutoff; range, 25.9-56.3). Wang et al. (2023) with a median follow-up of 35.6 months (25.9-56.3) noted that 3% of long-term and late-onset adverse events were reported during the extended follow-up period.[35] Additionally, ICU admissions in the RWE were higher compared to ZUMA-2.[28] Given the risk of secondary malignancies, close monitoring of patients has been recommended.[39-41]

In the ZUMA-2 protocol page 30,[23] non-serious adverse events reporting ends with new anticancer therapy initiation. By July 2019 (median follow-up of 12.3 months), [redacted] treatments were administered to [redacted] patients ([redacted]%) (CS, main dossier, section B.2.7). By October 2023, this increased to [redacted] treatments for [redacted] patients ([redacted]%) (clarification question A11). This raises the potential for biased reporting of non-serious long-term adverse events.

As a priority clarification question (Clarification question A4), the EAG sought the safety results for cohort 1, cohort 3, and their combined populations, given that both cohorts evaluate the same dosages for the MCL. However, these results were not provided by the company.

2.2.8.1 Retreatment, deaths and consent withdrawal

Subjects who achieved a response based on revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007), but experienced disease progression three months post-first infusion could be offered retreatment, including conditioning and brexu-cel infusion at a targeted dose of 2 x 10^6 anti-CD19 CAR-T cells/kg.[24]

In the ZUMA-2 cohort 1, five patients received the second dose although it is not practiced within the NHS, as highlighted by the EAG's clinical advisors and the company (Clarification question A1). All five patients succumbed within up to 5 years of follow-up. Three out of five patients experienced serious adverse events, including disseminated intravascular coagulation, pyrexia, Corynebacterium infection, sepsis, myelodysplastic syndrome, cerebrovascular accident, syncope, and hypotension.[24] Serious adverse events not included for concise reporting can be found in clinicaltrials.gov NCT02601313.[24]

Of the 74 patients who commenced the trial, 51 did not complete it. The reasons included death (44/74; 55.4%), enrolment without infusion (6/74; 8.1%), full consent withdrawal (3/74; 4.1%), and loss to follow-up (1/74; 1.4%).[24]

2.2.8.2 Hospitalisation and Intensive Care Unit (ICU) admission

The company did not report hospitalisations in the main dossier and appendices. The EAG sought this information in the CSR document, Table 14.4.8.1a. Hospitalisation durations occurred for [redacted] patients, ranging from [redacted] to [redacted] days, with a mean (StD) of [redacted] ([redacted]) days and a median of [redacted] days, based on the July 2019

data cutoff. For infusion purposes, all subjects were hospitalised for at least 7 days and discharged only if toxicities were improving or stabilised.

According to the CADTH Reimbursement Review,[27, 41] 22.7% of ZUMA-2 patients were reported as admitted to the hospital. However, O'Reilly et al. (2024) and the DESCAR registry indicate higher percentages, specifically 27% and 34.3%, respectively.[28] CADTH's clinical input suggests an approximate ICU proportion of 30%. Across all sources, the proposed ICU proportions exceed those reported for ZUMA-2.

2.2.8.3 Treatment-emergent adverse events (TEAE)

The EAG deemed the company's Table 15 in the CS main dossier document to be less appropriate for depicting brexu-cel's TEAEs, as it solely reported adverse events with a frequency of 30% or higher. This threshold was neither substantiated in the trial's original protocol nor the company dossier. The EAG requested the most recent safety data from the company in clarification question A20. The company confirmed that no adverse events had been reported since the October 2023 data cutoff (48 months data cut). Table T14.3.3.1.1a has been summarized in Table 11.

Table 11: ZUMA-2 cohort 1 (n=68) (October 2023 data cutoff) safety

	Any Grade (%)	Worst Grade ≥ 3 (%)
TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
CRS	[redacted]	[redacted]
Neurologic event	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Serious infection	[redacted]	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]
Tumour lysis syndrome	[redacted]	[redacted]

Abbreviations: CRS, cytokine release syndrome; TEAE, treatment-emergent adverse event.

In addition to the list provided, a published study using the FDA Adverse Event Reporting System (FAERS) database reported that cardiotoxicity emerged following the administration of CAR-T cells in the r/r MCL population. Among all evaluated

CAR-T therapies, brexu-cel was noted for having both the highest incidence of cardiotoxicity at 7.5% and the highest mortality rate at 2.35%. Similarly, another study based on the FAERS database indicated that patients administered with brexu-cel may experience renal toxicities.[42]

Some late-occurring events, reported between median follow-up periods of 12.3 and 35.6 months, were documented in 18 patients.[35] Of these, 14 patients (77.8%) experienced Grade ≥ 3 adverse events, with neutropenia being the most prevalent. Grade ≥ 3 serious adverse events included encephalopathy, pneumonia, upper respiratory tract infection, and influenza. Wang et al. (2023) highlighted that the compromised immune system of infused patients, potentially due to B-cell aplasia and previous therapies, may have contributed to the Grade 3 infections.[35]

Three new fatal adverse events were reported after 2 years post-infusion: Salmonella bacteraemia (24.9 months post-infusion), myelodysplastic syndrome (25.2 months post-infusion), and acute myeloid leukaemia (37.5 months post-infusion).

Intravenous immunoglobulin was administered to 26 patients (38%) by the 35.6-month follow-up period, compared to 22 patients (32%) by the 12.3-month follow-up period.

The Summary of Product Characteristics (SmPC) for Tecartus, as detailed in the electronic medicines compendium (EMC),[40] advises vigilance regarding the potential risk of secondary malignancies following infusion, which may emerge from several weeks to multiple years post-treatment. It is recommended that patients be closely monitored.

2.2.9 Comparison of time-to-event outcomes across sources.

The EAG sought to compare estimates of efficacy of brexu-cel from the various sources available.

For OS (Figure 6), the EAG notes high agreement between the available sources of RWE, which are all consistently lower than the OS from ZUMA-2.[28-30] For PFS, the agreement of the RWE studies is less strong, however they remain on average lower than the PFS from ZUMA-2.[27-29] Note, as SACT data were available for OS, it was included over data from O'Reilly as SACT data has a larger sample size and longer

follow-up. PFS data were not available for SACT and so O'Reilly data were used for this. The findings illustrate the anticipated observed differences in relation to the characteristics of the underlying different populations - see section 2.2.5.1.

Figure 6: Comparison of brexu-cel OS from ZUMA-2 and RWE sources

Figure 7: Comparison of brexu-cel PFS from ZUMA-2 and RWE sources

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

In the company submission for the original appraisal (pre-managed access), the company conducted a matching-adjusted indirect comparison (MAIC) to support their claim for clinical benefit over standard care. A MAIC was presented alongside other supporting evidence, which was accepted by the committee. This MAIC was limited by its small sample size and limited number of matching covariates.

In this latest submission, no updated MAIC was provided. However, as the MAIC did not previously inform the economic analyses, which instead are based on a naïve comparison, and as the extended follow-up of ZUMA 2 is somewhat consistent with the previous appraisal, the EAG does not consider this omission consequential.

2.4 *Additional work on clinical effectiveness undertaken by the EAG*

2.4.1 Additional EAG literature searching for alternative sources to inform R-BAC efficacy.

The EAG for the TA677 had suggested, and the committee concurred, that a combination of rituximab, bendamustine, and cytarabine (R-BAC), as outlined in TA677[1], was the most appropriate comparator to brexu-cel for patients with relapsed or refractory Mantle Cell Lymphoma (r/r MCL) who have progressed following treatment with Bruton's tyrosine kinase inhibitor (BTKi) within NHS practice. The EAG's clinical expert confirmed the suitability of R-BAC as a relevant comparator in clinical practice. Consequently, the EAG undertook an exhaustive search for randomized controlled trials (RCTs) pertaining to relapsed/refractory mantle cell lymphoma (r/r MCL) published post-2021, subsequent to the previous STA publication. A comprehensive search strategy was employed to ensure no potential comparators were overlooked. As a result, 320 studies were identified and meticulously evaluated to update the data on R-BAC or any potential comparators. Regrettably, no new studies were found that report on the OS and PFS of R-BAC in r/r MCL patients following BTKi therapy.

Furthermore, to ascertain the eligibility of cohort III of the ZUMA-2 trial, the EAG identified 19 potential publications. It was noted that most of the information regarding this cohort was disseminated through press releases, except for a published conference abstract that provided a median follow-up of over a year on the ongoing trial.[43] After consulting with the EAG's clinical expert, it was determined that pursuing cohort III of ZUMA-2 would not be advisable, as it may not adequately represent the population under consideration for the treatment of BTKi-naïve patients.

2.4.2 Removal of people with subsequent alloSCT from McCulloch 2020 time-to-event data

Feedback from the EAG's clinical expert was that the time-to-event data from McCulloch 2020[33] was too optimistic compared with expected outcomes for this population. Additionally, the proportion of people receiving subsequent alloSCT was also higher than anticipated.

The EAG identified that McCulloch et al. reported separately PFS outcomes for people who received subsequent alloSCT. The EAG was able to match these to PFS times for the whole population, and remove them, creating a dataset for people who did not receive subsequent alloSCT (Figure 8).

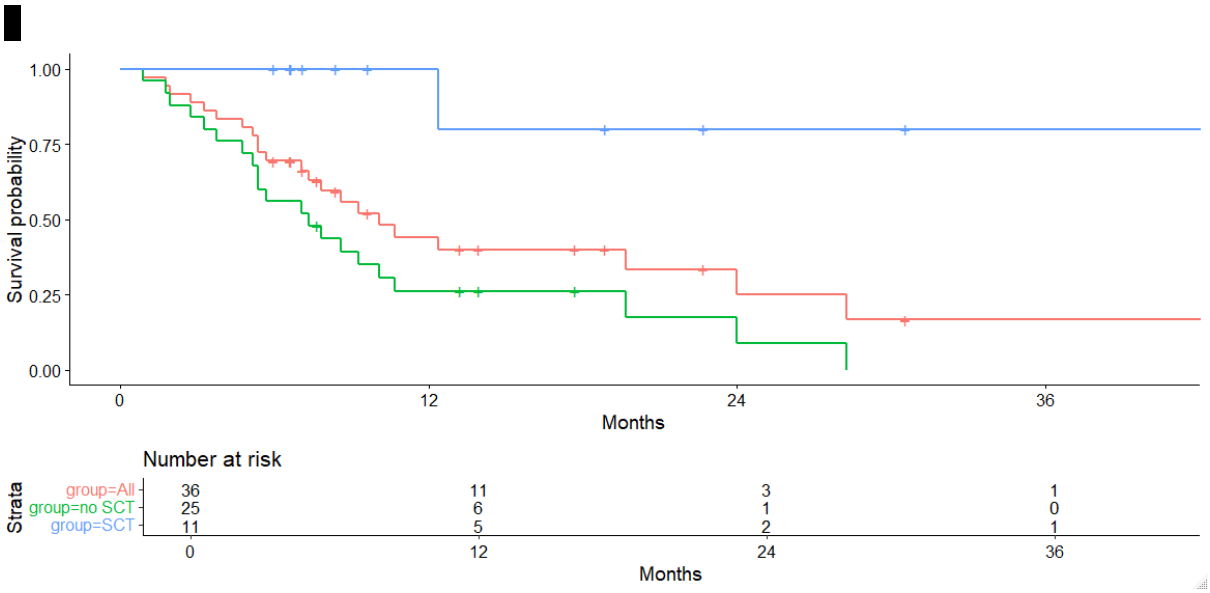


Figure 8: PFS from McCulloch et al. removing people with subsequent alloSCT

OS was not reported for the same subgroup, however the EAG were still able to identify and remove the majority of people who received alloSCT, as their censoring times were identical due to a lack of PFS event. There was one individual who experienced a PFS event and a (separate) OS event for whom the EAG could not identify the OS time with complete certainty. However, the EAG clinical expert stated that survival after disease progression was likely to be short, which narrowed down to two event times. The EAG opted to remove the largest of these to minimise the chance of introducing bias against brexu-cel into the analysis. The impact of the removal of people receiving SCT on OS is shown in Figure 9. These datasets with the effect of alloSCT removed represent the EAGs preferred population for extrapolating PFS and OS for R-BAC.

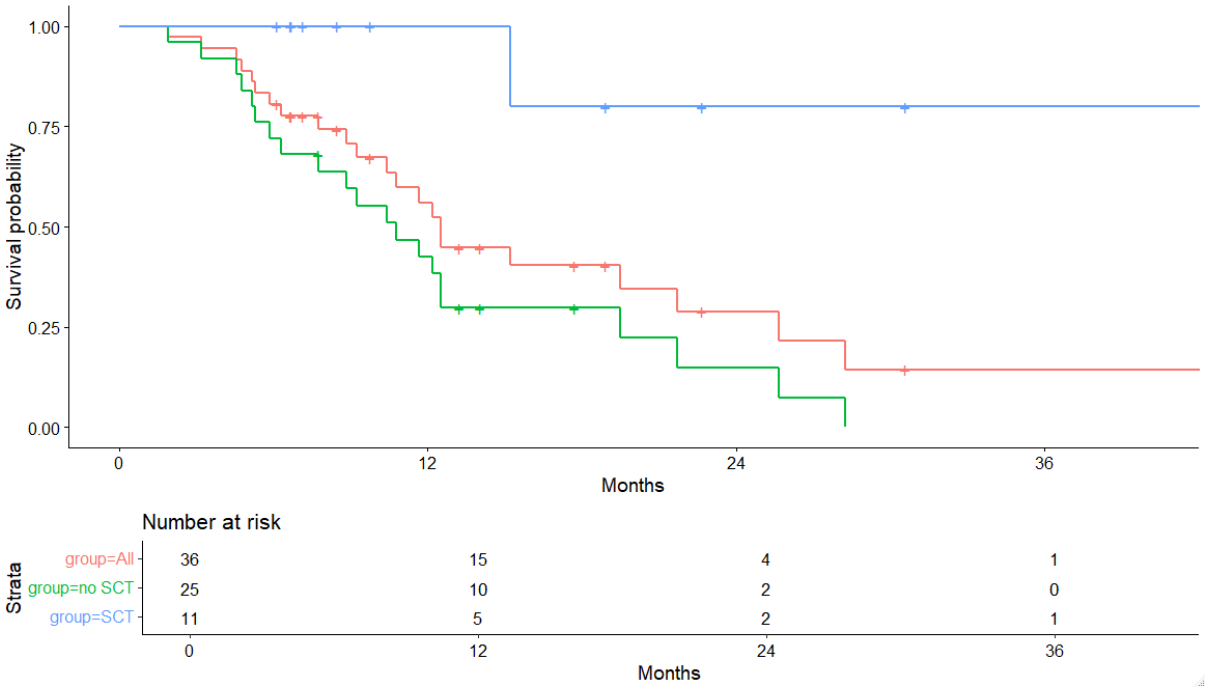


Figure 9: OS from McCulloch et al. removing people with subsequent alloSCT

2.4.3 Exploration of impact of BSH guidelines on SACT Data.

NHS England were able to provide an analysis of the SACT data, based on whether patients were infused before or after the 2022 BSH guideline changes.

The EAG share this plot in Figure 10, and note that no significant difference was found between the survival of the two groups, however this may change with additional follow-up.

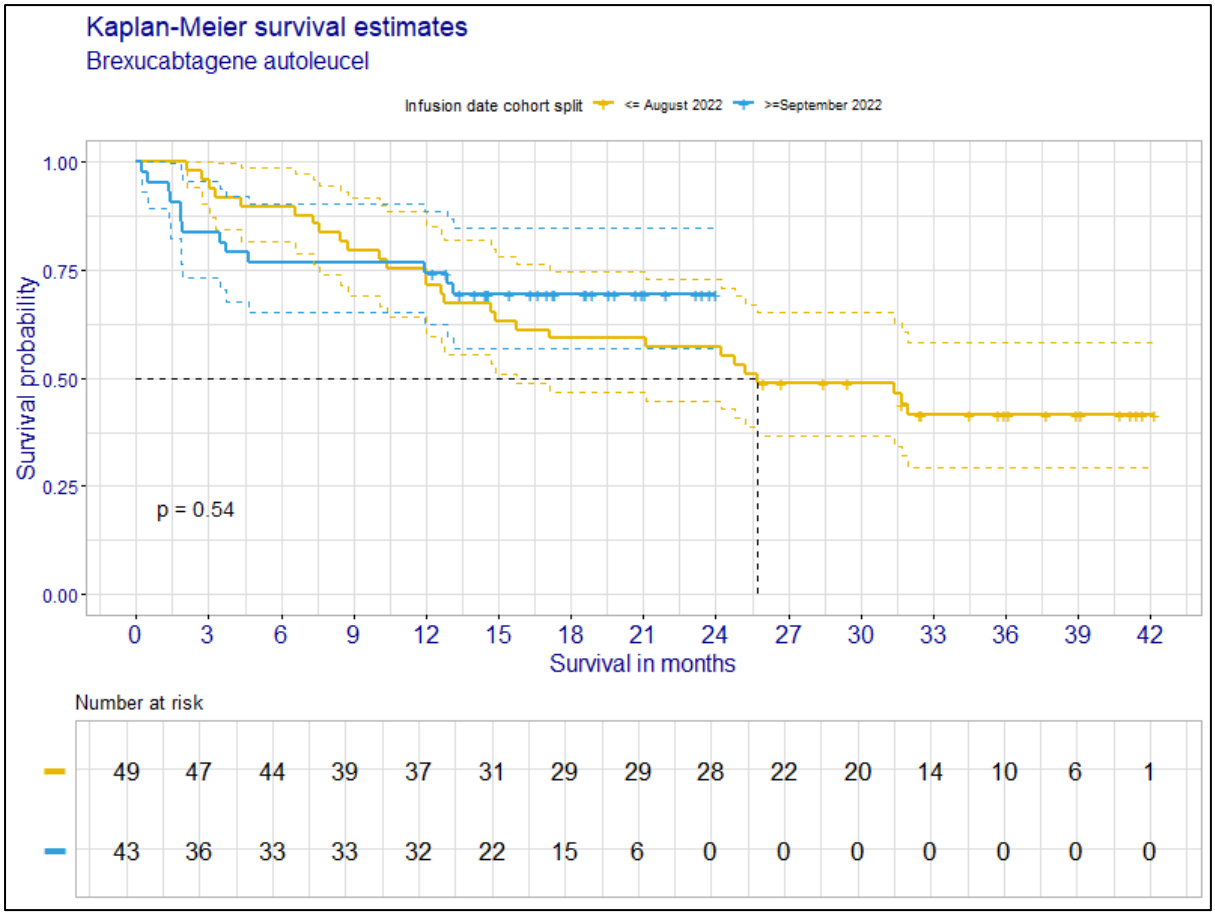


Figure 10: SACT brexu-cel overall survival, by BSH guideline cut-off

2.4.4 Outcomes for post-leukapheresis and pre-infusion period

The EAG preference is to model outcomes for all people who undergo leukapheresis, rather than focus only on those who are infused with brexu-cel. Survival from leukapheresis were not reported for the majority of datasets, including SACT and ZUMA-2.

The EAG requested this information from the company but it was not provided (clarification question B3).

The EAG considers the two distinct populations in turn, those who go on to receive CAR-T infusion, and those who do not.

2.4.4.1 Time from leukapheresis to infusion

To estimate the duration of pre-infusion period for people who were infused, the EAG uses information reported for ZUMA-2, the only source identified by the EAG which reported a mean average, where the mean in the CSR was [redacted] days (SD [redacted]). It is

unclear how representative of NHS care this duration is, though O'Reilly et al. reports a median duration of 36 days,[27] whilst DESCAR-T reports a median of 39 days.[28]

2.4.4.2 Post-leukapheresis survival for people not infused

To estimate the survival of people not infused with CAR-T, the EAG used information reported by the DESCAR-T study, the only source reporting this information identified by the EAG.[28] This study reported overall survival outcomes for people who were not infused with CAR-T, despite going through leukapheresis (Figure 11). Reasons for not receiving an infusion include manufacturing failure, patient decline and subsequent ineligibility, and patient decision, however a detailed breakdown is not provided. The EAG use this data to estimate a mean survival time (area under the curve) of 4.5 months, which it applies for all people who underwent leukapheresis and, in a scenario analysis, also for those approved for leukapheresis. The EAG is unclear how representative this information is for equivalent patients attempting to access CAR-T on the NHS.

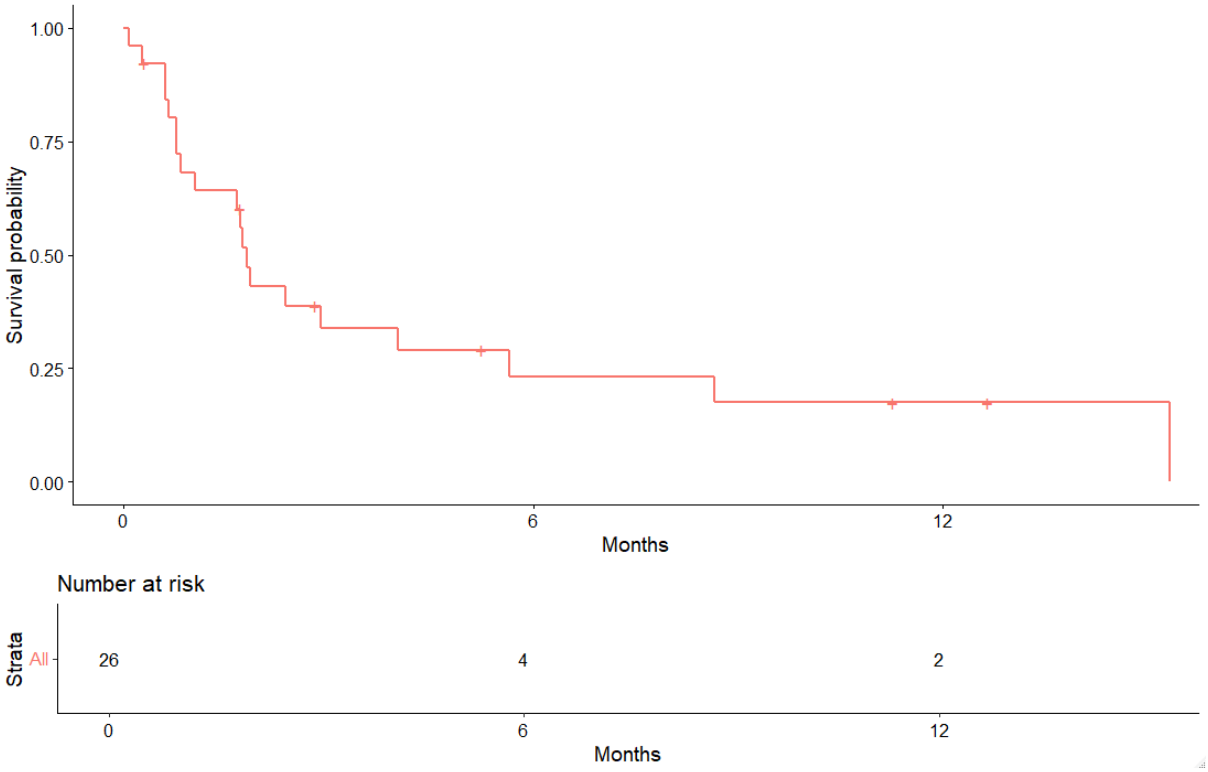


Figure 11: EAG recreated OS data from DESCAR-T for people not infused with brexu-cel

Combining these two approaches, the EAG was able to capture outcomes for the full ITT population. In terms of ratios of non-leukapheresed, leukapheresed and infused populations, the most relevant source providing sufficient information identified by the EAG was the paper by O'Reilly et al.[27] Out of 119 approved applications for brexu-cel, 104 people underwent leukapheresis (87.4%), and 83 were infused (69.7%). This shows high agreement with the SACT data, where 95 people were infused from 135 applications (70.4%).[30]

2.5 *Conclusions of the clinical effectiveness section*

- The EAG is concerned about the generalisability of the ZUMA-2 trial to NHS use and considers the multiple RWE sources to be more representative. Long-term efficacy remains uncertain. Reliance on naïve comparisons means estimates of relative efficacy are highly uncertain.
- For R-BAC, the McCulloch 2020 study is limited by a small sample size, retrospective single-arm design and better than expected outcomes, the latter potentially caused by selection bias towards younger, fitter patients, which may overestimate OS and PFS and lead to inaccurate alloSCT proportions.
- The inadequate assessment of HRQoL, with unaccounted late-occurring safety issues which may impact the HRQoL, and the single-arm design, all introduce potential bias in interpreting HRQoL as measured in the ZUMA trial.
- There is a risk of long-term safety issues, especially regarding secondary malignancies that may require close monitoring.

3 COST EFFECTIVENESS

3.1 *EAG comment on company's review of cost-effectiveness evidence*

3.1.1 Searches

A detailed EAG critique on the cost-effectiveness literature searches by the company can be found in the appendices (section 6.2).

An appropriate range of databases were searched in March 2019 and updated in January 2020 and November 2024 (CS Appendix E, F and G). Conference abstracts and HTA organisations were hand-searched and reference checking was undertaken. As the CRD HTA, NHS EED and ScHARRHUD databases are no longer updated, the EAG recommends that the company search the INAHTA HTA database supported by web search engine to ensure comprehensiveness.

Appropriate databases-specific indexing and free-text terms are used to search for the population of interest, which are combined with appropriate search type filters.

As reported in Section 2.1.1, the search terms and numbers of results are not reported for the non-database searches (Appendix E Original SLR: Other data sources searched). The PRISMA-Flow diagrams for the original and January 2020 update HRQoL searches report that 4 results were identified via searching HTA and grey literature searching (CS Appendix F Figure 8) and 7 (CS Appendix F Figure 9) were retrieved this was in the January 2020 update. Additionally, the PRISMA flow-diagrams for the Cost and healthcare resource identification, measurement and valuation searches the original search reports that 6 additional results (CS Appendix G Figure 11) and 4 for the January 2020 searches (CS Appendix G Figure 12) were retrieved via manually searching HTA and 'grey literature' searches. Not reporting the search terms reduces the transparency and reproducibility of the search methods.

3.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

The EAG reviewed the company's economic evaluation model to assess alignment with NICE standards. The company constructed a de novo cost-effectiveness model

to evaluate the cost-effectiveness of brexu-cel for treating relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of therapy, including a Bruton's tyrosine kinase inhibitor (BTKi). This evaluation was based on the ZUMA-2 clinical trial population. The licensing criteria, and the decision problem are outlined in the submission. The EAG provided a summary of the model structure and critically appraised the clinical evidence (e.g., efficacy, treatment pathway, and mortality) and economic evidence (e.g., drug costs, health state resource use and costs, and utility values). The EAG critiqued the methods and inputs used in the analysis.

3.2.1 NICE reference case checklist

The EAG undertook an evaluation of the company's submission against the NICE reference case. Findings are summarised in the Table 12.

Table 12: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In general, all relevant health effects occurring after treatment have been accounted for in the economic analysis, except those from the pretreatment period.
Perspective on costs	NHS and PSS	Resource use and costs are considered from the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-effectiveness analysis. The company reported pairwise comparisons as well as fully incremental results.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	With a starting age of more than 60 years, the company has used a fixed time horizon of 50 years, which means there are some costs and effects after patients would be more than 100 years old.
Synthesis of evidence on health effects	Based on systematic review	In line with NICE reference case

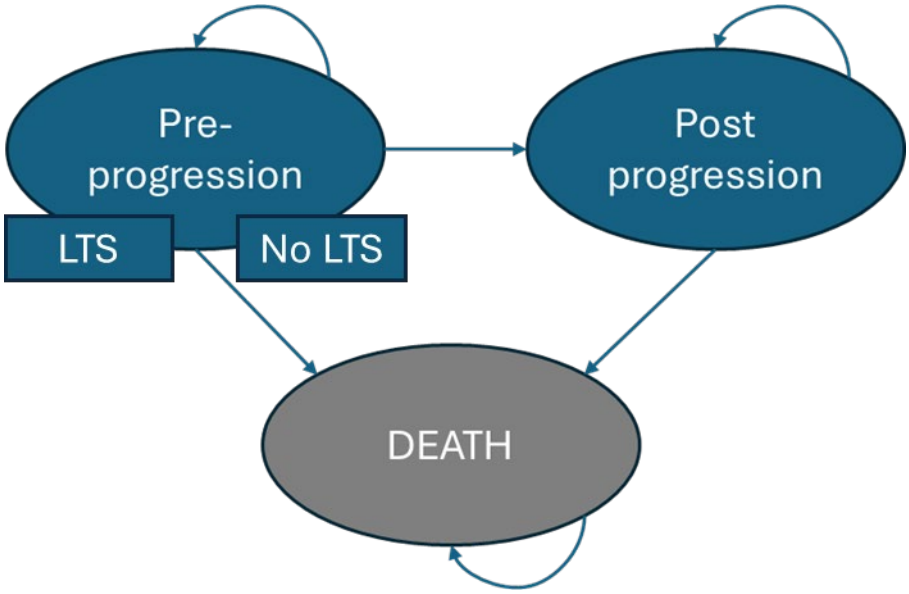
Element of health technology assessment	Reference case	EAG comment on company's submission
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	In line with NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L utility data were collected in the ZUMA-2 clinical trial using EQ-5D-5L tool.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The van Hout et al. algorithm was used to estimate EQ-5D-3L equivalent utility values from the EQ-5D-5L questionnaire data.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company has not incorporated QALY weight into the model.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Some of the cost items, such as the CAR-T tariff and alloSCT cost, need to be updated.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The discount rate is based on 3.5% per annum.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company employs a partitioned survival Markov model for this cost-effectiveness analysis, consistent with the previous technical appraisal (TA677). [44] The model includes three mutually exclusive health states: pre-progression, post-progression, and death, with patients starting in the pre-progression state. This structure reflects the disease pathway, incorporating the transition of patients from pre-progression to post-progression or death (see Figure 12). A key innovation in this model is the differentiation of long-term survivorship (LTS) in the pre-progression state, specifically for brexu-cel patients. This allows the model to account for patients

who remain in pre-progression for extended periods, representing a significant treatment effect seen in the ZUMA-2 trial.

The company applied a 48-month LTS timepoint, based on ZUMA-2 data and real-world evidence, to reflect the reduced probability of disease progression or death after this point. Patients in the LTS group are assumed to follow age-adjusted general population survival curves, adjusted by a standardised mortality ratio (SMR) of 1.09, regardless of whether they are in the pre- or post-progression health state. Pre- and post-progression health states remain distinct beyond the long-term survivor assumption, using general-population and post-progression utilities respectively.



Key: LTS: Long-term survivorship

Figure 12: Model structure schematic (obtained from CS, document B, section B.3.2.2)

EAG comments:

EAG concern 1: Discrepancy in long-term survivorship timepoint: 48-month vs. 60-month plateau

Company's approach: The company applies a 48-month LTS timepoint (cure timepoint) to model long-term survivorship for brexu-cel patients.

EAG's critiques, assumption and justification: The EAG critiques the company's application of a 48-month long-term survivorship (LTS) timepoint, suggesting that there is no evidence to support a plateau in survival curves prior to 60 months, based on Kaplan-Meier (KM) data (Figure 3). While the company justifies its use of

48 months with ZUMA-2 data and emerging real-world evidence, the EAG argues that, between 48 and 88 months, the risk of death remains substantially higher than background mortality. Furthermore, the Mortality Rate Adjustment Factor (MRAF) of 1.09 cannot adequately account for this difference. In the original submission, the company used a 5-year (60-month) LTS timepoint, which the EAG considers more appropriate. Survival data from ZUMA-2 indicate that the risk of progression and death substantially diminishes only after 5 years. However, the EAG believes that even with the 5-year (60-month) LTS timepoint, an alternative MRAF is still necessary to adjust for general population mortality (see concern 2).

EAG Solution:

Base-case analysis: Using the 60-month LTS timepoint
Scenario analysis: 1. Using the company's approach of 48-month LTS timepoint, 2. Using the 36-month LTS timepoint

EAG concern 2: Underestimation of Mortality Rate Adjustment Factor (MRAF)

Company's approach: The company has applied a Mortality Rate Adjustment Factor (MRAF) of 1.09 in their base case, taken from a study of limited relevant due to the patients having diffuse large B-cell lymphoma, and having not received CAR-T therapy.[45]

EAG's critiques, assumption and justification: The EAG critiques the company's use of a Mortality Rate Adjustment Factor (MRAF) of 1.09 in the base case, arguing that it is not justified given the available data. The EAG is happy with the previous ERG critique on company's approach (using the MRAF of 1.09) in the original submission (TA677), "*The ERG considered that the excess mortality risk with DLBCL is not generalisable to people with relapsed or refractory mantle cell lymphoma. It also considered that the excess mortality risk compared with the general population is likely to be higher than predicted by the company. The ERG suggested that it was more appropriate to base the mortality adjustment on data from people with mantle cell lymphoma than with DLBCL."*[44]

In the current submission, the EAG's comparison of ZUMA-2 data over the 60- to 88-month period with general population mortality produces an average MRAF of

[redacted] indicating that the company's selected value underestimates the mortality risk. While acknowledging a downward trend in MRAF over time, the EAG considers an MRAF of 3.00 (SD 0.39) to be the most appropriate value for this evaluation, which was preferred by committee in TA893, (appraisal of brexu-cel for B-ALL).[46]

EAG Solution:

Base-case analysis: using the MRAF of 3.00
Scenario analysis: 1. Company's approach (using the MRAF of 1.09), 2. Using the MRAF of 5.00, 3. No SMR adjustment

3.2.3 Population

The patient population analysed in this submission consists of adults with relapsed or refractory mantle cell lymphoma (r/r MCL) who have received at least two prior lines of therapy, including a Bruton's tyrosine kinase inhibitor (BTKi) based on the ZUMA-2 trial. This aligns with the population assessed in the original submission (TA677).[44]

ZUMA-2 evaluated the safety and efficacy of brexu-cel in patients whose disease progressed following treatment with (i) anthracycline- or bendamustine-containing chemotherapy, (ii) an anti-CD20 antibody, and (iii) a BTKi (ibrutinib and/or acalabrutinib). The mean age of participants in ZUMA-2 was 63.2 years (see Table 13). The company stated that two NHS England consultants confirmed that the ZUMA-2 modified intention-to-treat (mITT) group is representative of the patient population likely to receive brexu-cel in clinical practice.

The company selected the mITT population (n=68) rather than the total enrolled population (n=74) to ensure that the analysis reflects real-world treatment outcomes. The mITT approach includes only patients who received brexu-cel and were evaluable for efficacy and safety assessments. The company stated that this methodology aligns with regulatory standards, which prioritize the evaluation of treatment outcomes among those who complete therapy. Furthermore, the company states selecting the mITT population enhances data integrity by excluding individuals who did not receive the treatment or were not evaluable, thus minimizing bias and improving reliability.

Additionally, the company justifies the use of the mITT population through adherence to the intention-to-treat (ITT) principle, ensuring that patients are analysed based on their initial treatment assignment while excluding those without evaluable data. A subset of 27 patients from the mITT group was also included in the Long-Term Follow-Up (LTFU) study after completing at least 24 months of assessments.

Table 13: Baseline characteristics of patients in ZUMA-2 (Cohort 1) (obtained from CS, document B, section b.2.3.2, table 8 and the model)

Patient characteristics	mITT (n = 68)
Female (%)	16%
Mean age at start (years)	63.2
Mean bodyweight (kg)	82
Mean body surface area (m2)	1.981
mITT, modified intent-to-treat;	

EAG comments :

EAG concern 3: Not using the full patient population

Company's approach: The company has used the mITT population selected as those who received brexu-cel and were evaluable for efficacy and safety assessments.

EAG's critiques, assumption and justification: The company's use of the mITT population for evaluating brexu-cel excludes some patients, such as those who underwent leukapheresis but did not proceed to infusion due to disease progression, manufacturing failure, or post-conditioning ineligibility. By focusing only on patients who received brexu-cel infusion, the company's analysis may not fully reflect treatment barriers, such as disease progression before infusion and manufacturing failure. This exclusion introduces selection bias and may overestimate brexu-cel's efficacy while underestimating real-world treatment challenges. Additionally, economic evaluations based on the mITT population may underestimate costs associated with leukapheresed patients who do not complete treatment.

In clinical practice, the CAR-T-cell process begins with pretreatment steps, with applying for leukapheresis being the key initial stage. All patients initially eligible for CAR-T-cell therapy must undergo leukapheresis. The EAG asserts that the

appropriate evaluation population should include all leukapheresed patients, and possibly also those approved for, but who do not undergo leukapheresis. This approach provides a more accurate assessment of brexu-cel's real-world feasibility and effectiveness.

EAG assumes that the CAR-T-cell process for r/r MCL patients begins at the point of undergoing leukapheresis, but considers the possibility of it beginning at the point of being approved for leukapheresis.

EAG Solution:

Base-case analysis: Using all patients who were approved for leukapheresis.
Scenario analysis:

- Using the company's approach (which involves the mITT population from ZUMA-2 who received brexu-cel), and
- Using ITT Approved population, from SACT (including other available real-world data for extrapolation)
- Using ITT Leukapheresed population, R-BAC OS and PFS from original company's model
- Using ITT information from ZUMA-2, where 68 people are infused out of 74 (i.e. all leukapheresed patients), and
- Using equivalent information from O'Reilly et al. where 83 people are infused out of 104 who underwent leukapheresis.
- Following the EAG approach by using the "Exponential" distribution for overall survival (OS) of brexu-cel. (Rational: Using a 60-month cure rate of [redacted]%, instead of [redacted]% from the Log-normal distribution in the EAG base case and [redacted]% from ZUMA-2, respectively-see section 3.2.6.2.)
- Following the EAG approach by using the "Weibull" distribution for overall survival (OS) of brexu-cel. (Rational: Using a 60-month cure rate of [redacted]%, instead of [redacted]% from the Log-normal distribution in the EAG base case and [redacted]% from ZUMA-2, respectively-see section 3.2.6.2.)

EAG concern 4: Generalizability of ZUMA-2 Trial Data to the UK Patient Population

Company's approach: The company has used the ZUMA-2 trial data to evaluate brexu-cel's clinical effectiveness

EAG's critiques, assumption and justification: The company's use of the ZUMA-2 trial data to evaluate brexu-cel's clinical effectiveness may not fully reflect the real-world patient population in the UK. While ZUMA-2 provided strong evidence of brexu-cel's efficacy in a controlled clinical setting, the trial population had a median age of 65, which is younger than the typical NHS patient population with r/r MCL. According to TA677 Technology Appraisal Guidance,[44] the committee had some concerns about how generalizable the results of the ZUMA-2 study were to the NHS, given that it did not include any patients from the UK. A clinical expert also pointed out that ZUMA-2 patients were 8–10 years younger than the typical NHS patients with r/r MCL. This discrepancy highlights that the ZUMA-2 cohort may not accurately represent the broader patient population in the NHS.

The EAG argues that using the RWE sources for the base case analysis would provide a more accurate reflection of real-world outcomes for brexu-cel. The SACT database collects real-world data from NHS England and includes a diverse patient population that better reflects UK clinical practice, incorporating variations in treatment regimens and patient characteristics. Additionally, the SACT data is more aligned with current treatment guidelines and practices, which have evolved since the introduction of brexu-cel. The other sources report similar outcomes to the SACT dataset, and their pooling considerably boosts the sample size.
The EAG further emphasizes that using RWE data would address the age-related uncertainties raised by the Technology Appraisal Guidance, as it captures a patient population with a broader age range, closer to the actual NHS population. Thus, the EAG assumes that the RWE data are a better source of evidence than the ZUMA-2 trial data, offering a more representative and comprehensive analysis of brexu-cel's effectiveness and cost-effectiveness in real-world UK settings.

EAG Solution:

Base-case analysis: using the RWE data as the main source of data for treatment efficacy

Scenario analysis: Same as the scenarios for concern 3.

3.2.4 Interventions and comparators

The company presents brexu-cel as the intervention, positioning it as a standard of care for eligible relapsed/refractory (r/r) MCL patients post-BTK inhibitor (BTKi) failure. Brexu-cel is an autologous CAR-T therapy, administered as a single infusion following nonmyeloablative conditioning and potentially bridging chemotherapy. The primary comparator in this context is R-BAC, which is an established chemotherapy regimen used when CAR-T therapy is unavailable. R-BAC serves as an alternative treatment for patients who have undergone at least two lines of therapy, including BTKi. The company argues that other potential comparators, such as alloSCT and zanubrutinib, are not relevant. Experts consulted by the company for this re-appraisal of brexu-cel reportedly confirmed R-BAC remained the most relevant comparator, though the company were unable to provide the details of this expert view to the EAG (clarification C1). AlloSCT is rarely used post-BTKi failure, typically reserved for consolidating a response in a small subset of patients, and zanubrutinib is indicated for BTKi-naive patients, not as a third-line therapy. Thus, R-BAC is considered the preferred alternative when CAR-T therapy is not accessible. The company stated that although alloSCT is not expected following brexu-cel, costs were included for a small proportion of patients based on trial data ([redacted]). Conversely, 31% of SoC patients were assumed to undergo alloSCT, following McCulloch (2020).[33]

EAG concern 5: Overestimation of the proportion of patients who can receive alloSCT in the R-BAC arm.

Company's approach: The company assumed, based on McCulloch (2020),[33] that 31% of patients receiving R-BAC treatment can undergo alloSCT. In contrast, this proportion for brexu-cel is only [redacted].

EAG's critiques, assumption and justification: The EAG emphasizes that the proportion of patients eligible for alloSCT in either treatment arm is extremely low. Given the advanced disease stage of r/r MCL patients in the third-line setting, the likelihood of receiving alloSCT is minimal. Historically, only a small subset of young, fit patients with a suitable donor undergoes alloSCT, typically in first remission or after responding to second-line BTK inhibitors. By the third-line setting, most patients

who were eligible would have already received alloSCT earlier in their treatment journey. While rare exceptions exist, alloSCT after brexu-cel or R-BAC remains highly uncommon. The EAG considers that using the same proportion ([redacted]) of patients who can receive alloSCT in both arms better reflects real-world clinical practice and ensures a more appropriate comparison between brexu-cel and R-BAC in terms of both effects and costs.

EAG Solution:

Base-case analysis: Including alloSCT in both arms ([redacted] in brexu-cel and [redacted] in R-BAC)

Scenario analysis: 1. Using the company's approach (including alloSCT in both arms – [redacted] in brexu-cel and 31% in R-BAC), 2. Patients receiving alloSCT, SoC: 15.0%, 3. Patients receiving alloSCT, SoC: 10.0%, 4. 0% in brexu-cel and 31% in R-BAC

3.2.5 Perspective, time horizon and discounting

The company adopts the NHS and Personal Social Services (PSS) perspective in England, evaluating costs and direct health effects on individual patients in accordance with the NICE reference case.

The company states that a 50-year (lifetime) time horizon is implemented to capture all relevant differences in costs and outcomes between the assessed technologies. Given the mean starting age of 63.2 years for the ZUMA-2 mITT cohort, this duration is considered sufficient to encompass the plausible maximum life expectancy by the company, ensuring a comprehensive assessment of long-term benefits.

The model employs a 1-month cycle length (30.44 days), with half-cycle correction (using the midpoint of each cycle) applied to all costs and outcomes beyond the first cycle.

A 3.5% annual discount rate is applied to both costs and QALYs, as per NICE guidelines, reflecting the time preference for health benefits and expenditures.

EAG concern 6: Inappropriate time horizon assumption

Company's approach: The company adopts a fixed 50-year time horizon to account for long-term costs and benefits for patients.

EAG's critiques, assumption and justification: The EAG critiques the company's 50-year time horizon, given the mean patient age of 63.2 years. While the company argues this captures the plausible maximum life expectancy, the EAG believes it

may overestimate survival for some patients. A more appropriate approach would be 100 years minus the starting age, a common practice in health economic models. EAG recommends ensuring the horizon aligns with expected maximum survival, rather than a fixed 50-year limit, to better reflect the long-term impact of brexu-cel on patient outcomes and cost-effectiveness.

EAG Solution:

Base-case analysis: Using the 100 years minus the starting age as a time horizon

Scenario analysis: 1- Using the company's approach (fixed 50-year time horizon), 2- Using the fixed 20 years' time horizon.

EAG concern 7: Inappropriate application of half-cycle correction method

Company's approach: The company applies a half-cycle correction using cycle midpoints (e.g., 15.22 days) for costs and outcomes in a 1-month cycle model.

EAG's critiques, assumption and justification: The EAG critiques the company's use of midpoint-based half-cycle correction (using the midpoint of each cycle) as this is not the conventional method for applying this correction. The more appropriate approach is to use the average health state occupancy across all relevant health states, including Pre-progression, Post-progression, and Death. This method more accurately reflects the distribution of both costs and health outcomes over time, ensuring that they are allocated proportionately based on actual time spent in each health state, rather than assuming a uniform distribution across the cycle.

EAG Solution:

Base-case analysis: Use of average health state occupancy for half-cycle correction

Scenario analysis: Using the company's approach (using cycle midpoints)

3.2.6 Treatment effectiveness and extrapolation

The company's survival modelling uses relative survival models, where survival is estimated relative to background mortality. Background mortality is then re-applied when the survival extrapolations are implemented in the economic model. Note that models which explicitly assume a cure (such as mixture cure models) were not used by the company. Instead, the company assumes that people who remain alive after 4 years in the brexu-cel arm are considered cured and apply a mortality rate linked to background mortality. The company does not make this assumption for the R-BAC

arm. In summary, the EAG considers the company's choice of data and extrapolations to be optimistic and likely overestimate the benefit of brexu-cel in the target population.

3.2.6.1 Progression free survival

Brexu-cel PFS – Company

For progression-free survival, the company extrapolate using mITT data from ZUMA-2 (n=68). The company fitted a standard set of parametric models to the data and compared the visual fit, information criterion and predicted PFS at key milestones. The company select the log-normal model based on having the lowest AIC and BIC, and a reasonable visual fit. Due to the high similarity of models to the early trial follow-up and the assumption of a cure for people who survive beyond 48 months, the choice of PFS extrapolation is not a driver of the model.

Brexu-cel PFS – EAG

The EAG prefers to extrapolate using all information for brexu-cel. The EAG combines the three RWE sources for brexu-cel (O'Reilly, DESCAR-T, US Consortium) with the ZUMA-2 follow-up.[27-29] The EAG fitted the same set of standard parametric models to this data, but included a covariate to distinguish whether each observation has come from RWE or trial data. This allows the extrapolations to fit to the less mature RWE whilst being informed by the long-term shape of the ZUMA-2 PFS data. The EAG then extrapolated using parameters relevant to the RWE data. Based on goodness-of-fit criteria (Table 14), and the combination with the EAG's preferred OS model (i.e. the life-years spent in the resulting post-progression health state), the EAG selected the log-normal model.

Table 14: Goodness of fit criteria for EAG parametric models for brexu-cel PFS

	AIC	BIC	60 month cure rate from EAG models	48 month cure rate from company models
Exponential	1776.9	1785.1	[redacted]	[redacted]
Weibull	1766.4	1778.7	[redacted]	[redacted]
Log-normal	**1743.4**	**1755.8**	[redacted]	[redacted]
Log-logistic	1752.9	1765.3	[redacted]	[redacted]

Gompertz	1757.7	1770.0	[redacted]	[redacted]
Generalised gamma	1742.8	1759.2	[redacted]	[redacted]

Figure 13: EAG preferred extrapolation for brexu-cel PFS (log-normal)

R-BAC PFS – Company

To model progression-free survival of people receiving R-BAC, the company extrapolate using data from McCulloch 2020.[33] The company fitted the same range of standard parametric models and selected their preferred model (log-normal) based on all models having a similar visual fit to the Kaplan-Meier estimator, with log-normal having a slightly superior AIC. The EAG notes that the difference in AIC between the parametric models was small, with the exponential, generalised gamma and log-logistic models having a difference of less than 2 units.

R-BAC PFS – EAG

As mentioned in section 2.4.2, the EAG prefers to remove the people who received subsequent alloSCT from McCulloch 2020[33] prior to extrapolation, creating a dataset more closely aligned with real-world patient population. Aside from this difference in population, the EAG otherwise uses the same approach employed by the company

to obtain a preferred extrapolation. The EAG selected the log-normal model as it is among the best fitting models, and is consistent with the EAG selection for brexu-cel PFS.

Table 15: Goodness of fit criteria for EAG parametric models for R-BAC PFS

	AIC	BIC
Exponential	143.8	145.0
Weibull	144.1	146.5
Log-normal	**142.9**	**145.3**
Log-logistic	143.3	145.7
Gompertz	145.1	147.6
Generalised gamma	144.8	148.4

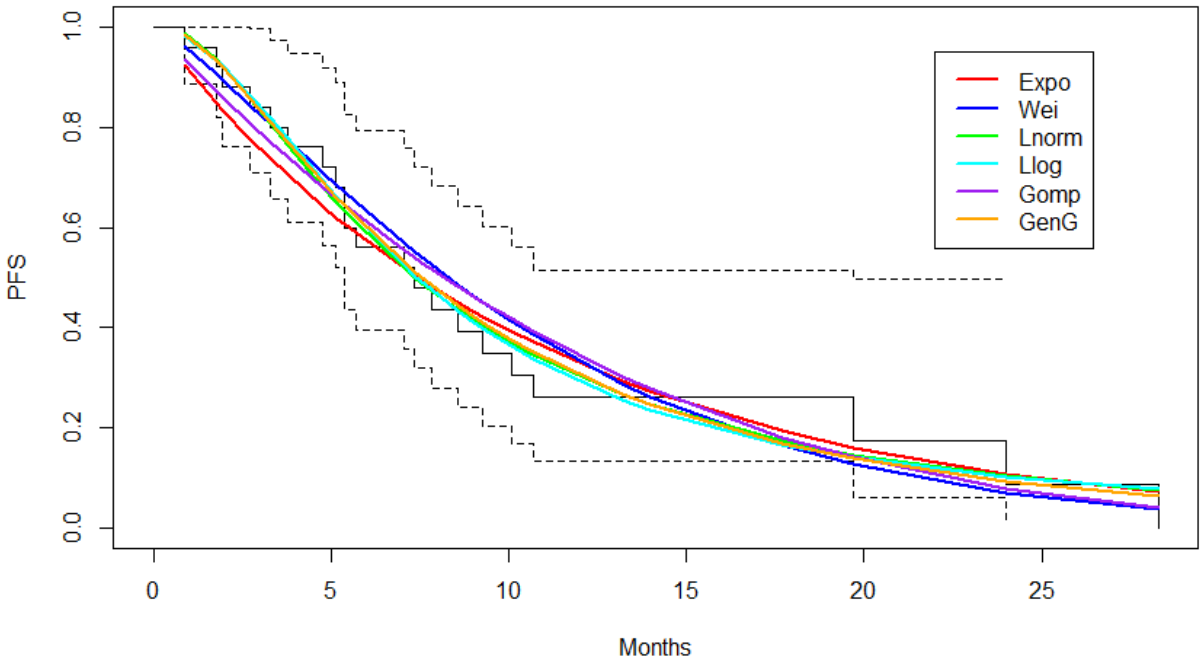


Figure 14: Visual fit of parametric models fitted to EAG preferred R-BAC PFS data

3.2.6.2 Overall Survival

Brexu-cel OS - Company

For the overall survival of people receiving brexu-cel, the company extrapolate using mITT data from ZUMA-2 (n=68). All candidate models showed a high level of

agreement at 48 months and had largely similar AIC and BIC. The company opt for the log-normal extrapolation but note that the exponential distribution could also have been selected. Again, the choice of model is not too influential due to the assumption of cure from 48 months in the company base case.

Brexu-cel OS - EAG

For brexu-cel OS, the EAG prefers to utilise all the available information for brexu-cel. The EAG considers that the RWE sources are likely to give the most accurate estimate for real-world use of brexu-cel, but includes the ZUMA-2 data to inform the long-term efficacy. Again, the EAG pools the RWE sources, whilst using a covariate to distinguish between RWE and trial sources.[28-30] This allows the RWE to be extrapolated but to incorporate the longer follow-up of ZUMA-2 which influences the shape of the extrapolation. The EAG selects a log-normal extrapolation based on the lowest goodness of fit statistics, given the high uncertainty about the long-term efficacy of brexu-cel in the real-world, which has a 60 month cure rate of [redacted]%.

Given that the ongoing response rate in ZUMA-2 is [redacted]/68 ([redacted]), it remains possible that the EAGs preferred extrapolation for brexu-cel combined with a 60 month cure assumption overestimates optimistic, hence the EAG explores the impact of using exponential and Weibull extrapolations. The smaller size of the post-progression health state at 60 months associated with these two choices of OS distribution (i.e. the difference between PFS and OS) may also support their use, as a sustained period of post-progression survival may not be clinically valid.

Table 16: Goodness of fit criteria for EAG parametric models for brexu-cel OS

	AIC	BIC	60-month cure rate from EAG models (diff vs preferred PFS cure)	48-month cure rate from company models (diff vs preferred PFS cure)
Exponential	1685.2	1678.8	[redacted]	[redacted]
Weibull	1684.6	1682.3	[redacted]	[redacted]
Log-normal	**1680.4**	**1677.2**	[redacted]	[redacted]
Log-logistic	1682.1	1679.5	[redacted]	[redacted]

Gompertz	1683.6	1680.9	[redacted]	[redacted]
Generalised gamma	1681.7	1683.0	[redacted]	[redacted]

Figure 15: EAG preferred extrapolation for brexu-cel OS (log-normal)

R-BAC OS – Company

The company extrapolates OS data from McCulloch et al. (2020) in the same approach. [33] The log-normal model is selected based on having the lowest AIC.

R-BAC OS – EAG

The EAG employs an identical approach to its preference for PFS of R-BAC: using the McCulloch dataset[33] but excluding people who received subsequent alloSCT. The EAG fitted a range of parametric models and again opted for the log-normal model due to a combination of low goodness-of-fit scores, visual fit and long-term plausibility. The EAG considers that the decreasing hazard rate associated with the log-normal model when extrapolated into the future is consistent with the possibility of a small number of people receiving successful alloSCT.

Table 17: Goodness of fit criteria for EAG parametric models for R-BAC OS

	AIC	BIC
Exponential	152.9	154.1
Weibull	147.8	150.3
Log-normal	**147.4**	**149.9**
Log-logistic	148.2	150.6
Gompertz	149.9	152.4
Generalised gamma	149.1	152.7

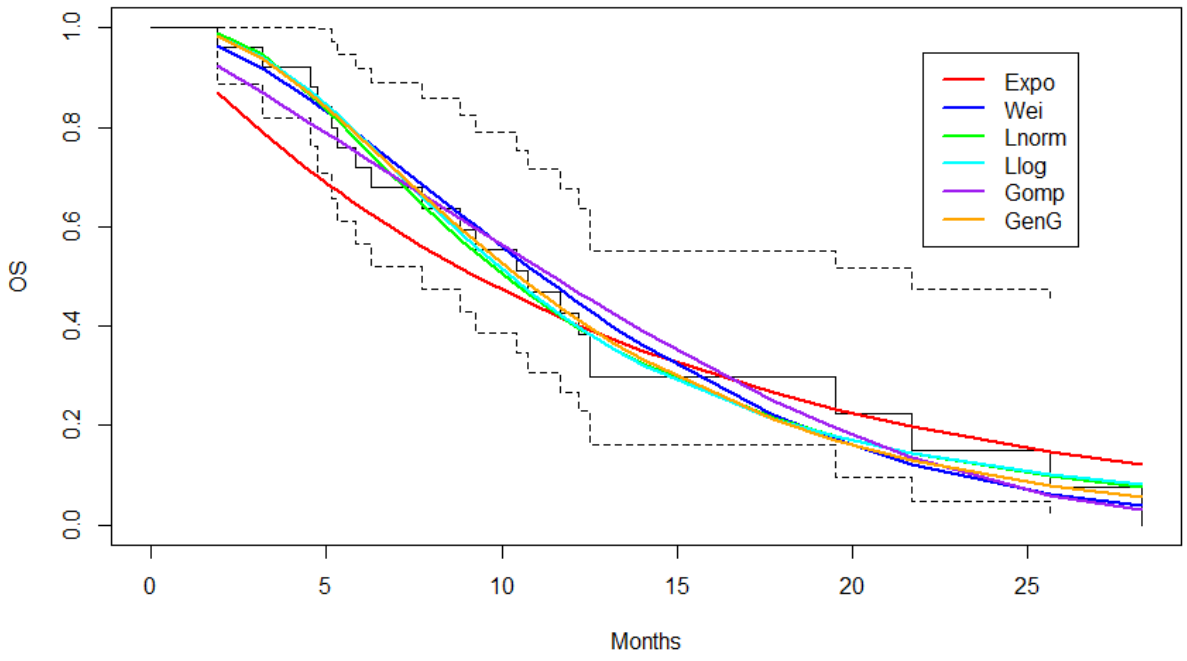


Figure 16: Visual fit of parametric models fitted to EAG preferred R-BAC OS data

3.2.7 Health-related quality of life

The company stated that the approach to health-related quality of life (HRQoL) in this evaluation aligns with NICE's reference case, prioritizing patient-based utilities. For pre-progression, the utility estimate of [redacted] was derived from EQ-5D-5L data in the ZUMA-2 trial, using regression analysis and the van Hout

algorithm[47] to convert the data to EQ-5D-3L utility values. The post-progression utility of 0.724 was based on an estimate from TA502,[48] given the limited post-progression data from ZUMA-2. The company emphasizes that the HRQoL data from ZUMA-2 showed a [redacted] in quality of life during the acute treatment phase, which [redacted] by Month 3, with overall health [redacted] by Month 6 (Table 18).

Table 18: ZUMA-2 EQ-5D-3L-equivalent utility data summary over scheduled data collection points

	Screening	Week 4	Month 3	Month 6
N observations	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
1st – 3rd quartile	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]

Key: EQ-5D-3L, EuroQol 5 Dimension 3 Level; SD, standard deviation
Notes: Estimates to 3 decimal places. n = 6 further observations from n = 2 patients who were retreated with brexu-cel also collected.

For long-term survivors (LTS), the company used general population utility values. The approach to capturing utility for LTS patients included age and gender adjustments based on the Health Survey for England data, yielding a utility value of [redacted] for patients aged around 67 years. The company stated that this estimate aligns with the approach used in NICE appraisals for other therapies, such as TA502[49], which also utilized general population utility values for long-term survivors. The company also recognizes the impact of adverse events on HRQoL, incorporating disutility values for grade 3 and 4 adverse events into the model. However, a conservative approach was applied to the standard of care (SoC) arm, assuming no adverse event-related disutilities (see column of 'Incidence from Company submission' in Table 19).

EAG concern 8: Poorly Justified Assumptions in Pre/Post-Progression, and LTS HRQoL Estimates

Company's approach: The company estimates HRQoL using ZUMA-2 patient-reported data, deriving pre-progression ([redacted]), post-progression (0.724, from

TA502), and long-term survivor ([redacted]) utilities. The company assumes LTS HRQoL matches the general population, applying a disutility for AEs, and argue that incorporating time-dependent utilities would not impact cost-effectiveness results.

EAG's critiques, assumption and justification: The EAG raises several concerns regarding the company's methodology for incorporating health-related quality of life (HRQoL) data—including pre-progression, long-term survivors (LTS +4y), and post-progression—into the model. Below are key critiques along with additional considerations:

1. **Pre-Progression Utility ([redacted]):** The EAG acknowledges that a utility value of [redacted] and may be justifiable if adverse event (AE) disutilities are excluded. However, the EAG believes that the pre-progression utility should not exceed the general population utility at the baseline age.

2. **Post-Progression Utility (0.724):** The EAG challenges the company's approach, arguing that deriving post-progression utility from the difference between TA502 utilities lacks methodological robustness. The EAG proposes either calculating post-progression utility proportionally (e.g., (0.824×0.68)/0.78=0.715 or directly adopting the TA502 post-progression value of 0.68, which EAG considers more appropriate. Both TA502 and the current submission highlight the limited availability of post-progression data.

3. **Long-Term Survivors (LTS):** The EAG finds the assumption regarding LTS utility overly optimistic, citing a higher mortality risk indicating that LTS may not fully regain the HRQoL of the general population. EAG argues that the increased mortality risk suggests persistent health complications, necessitating a utility value lower than that of the general population. The ERG and clinical experts in the original submission also noted that long-term survivors may experience slightly higher mortality and reduced HRQoL due to the risks associated with CAR-T therapy and prior treatments.

EAG Solution:

Base-case analysis:

- Pre-Progression: Capped at general population utility (decrement by AEs impacts)
- Post-Progression: Direct TA502 value (0.68)
- LTS: Capped at general population utility

Scenario analysis:

Scenario 1:

- Pre-Progression: From TA502 value (0.78)
- Post-Progression: Direct from TA502 value (0.68)
- LTS: Capped at general population utility

Scenario 2 (company's approach)

- Pre-Progression: From ZUMA-2 value ([redacted])
- Post-Progression: 0.724
- LTS: [redacted]

Scenario 3

- Pre-Progression: Capped at general population utility (decrement by AEs impacts)
- Post-Progression; Direct TA502 value (0.68)
- LTS: General population utility multiplied by 0.90

EAG concern 9: Underestimation of Adverse Events (events and incidences)

Company's approach: The company uses ZUMA-2 data for information on brexu-cel adverse events (AEs), including Grade 3 and 4 AEs which occurred in ≥5% of patients ('Incidence' column; Table 9; Company submission).

EAG's critiques, assumption and justification: The EAG critiques the company's approach to adverse events (AEs), highlighting discrepancies between the company's submission ('Incidence' column; Table 9; Company submission) and the CSR cohort 1 incidence rates (Table 19). For example, incidence rates for neutropenia vary substantially ([redacted]) as also do those for thrombocytopenia ([redacted]). Additionally, the EAG highlights the exclusion of certain AEs, such as infections (excluding pneumonia and sepsis) ([redacted]),

neurological events ([redacted]), and hyperglycaemia ([redacted]). The EAG suggests that the company's reporting of AEs may not fully reflect the burden of adverse events for patients treated with brexu-cel, potentially influencing the cost-effectiveness outcomes.

Table 19: Disutility and duration of adverse event

Adverse event grade 3 and above except CRS with any grades.	Incidence from CSR cohort*	Incidence from Company submission**	Disutility**	Duration (days)**
Cytokine release syndrome (CRS)	[redacted]	[redacted]	0.76	11.0
White blood cell count decreased	[redacted]	[redacted]	0.15	40.0
Anaemia	[redacted]	[redacted]	0.12	14.0
Neutrophil count decreased	[redacted]	[redacted]	0.15	17.0
Hypotension	[redacted]	[redacted]	0.15	5.0
Hypoxia	[redacted]	[redacted]	0.11	2.0
Hypophosphataemia	[redacted]	[redacted]	0.15	16.0
Encephalopathy	[redacted]	[redacted]	0.15	12.0
Platelet Count decreased	[redacted]	[redacted]	0.11	50.0
Neutropenia	[redacted]	[redacted]	0.09	47.0
Pyrexia	[redacted]	[redacted]	0.11	2.0
Confusional state	[redacted]	[redacted]	0.15	7.0
Aspartate aminotransferase increased	[redacted]	[redacted]	0.15	7.0
Alanine aminotransferase increased	[redacted]	[redacted]	0.15	7.0
Hypertension	[redacted]	[redacted]	0.15	5.0
Pneumonia	[redacted]	[redacted]	0.15	7.0
Hyponatraemia	[redacted]	[redacted]	0.15	7.0
Thrombocytopenia	[redacted]	[redacted]	0.11	63.0
Leukopenia	[redacted]	[redacted]	0.15	21.0
Febrile Neutropenia	[redacted]	[redacted]	0.09	47.0
Acute Kidney Injury	[redacted]	[redacted]	0.15	7.0
Lymphocyte count decreased	[redacted]	[redacted]	0.15	64.0
Sepsis	[redacted]	[redacted]	0.15	7.0
Lymphopenia	[redacted]	[redacted]	0.15	21.0
Hypocalcaemia	[redacted]	[redacted]	0.15	7.0

Hypogammaglobulinaemia	[redacted]	[redacted]	0.00	11.0
Hypokalaemia	[redacted]	[redacted]	0.15	7.0
Respiratory Failure	[redacted]	[redacted]	0.15	7.0
Infection (Pneumonia and Sepsis excluded)***	[redacted]	[redacted]	0.22	15.1
Neurological event (including ICANS) *** #	[redacted]	[redacted]	0.22	5.9
Diarrhoea***	[redacted]	[redacted]	0.05	7.0
Hyperglycaemia***	[redacted]	[redacted]	0.06	7.5

*Derived from clinical release syndrome (CRS), Table 14.3.2.1.1a, Table T14.3.3.1.1a, and the company's response to the EAG clarification question.
**Derived from CS, document B, section B.3.4.
***The duration and disutility values for these AEs are taken from TA893.
At the factual accuracy check, the company stated that ICANS events were the combined total of Encephalopathy and Confusional state events.
For items marked as "Not reported" in this table, the company did not provide clear information in the submission, and the EAG identified these items through other sources. However, the EAG still lacked sufficient clarity on their details. As a result, the associated QALY losses were not included in the EAG base case analysis. The related cost estimates, however, were incorporated into the scenario analysis titled "Estimating the CAR-T tariff cost based on different cost items.

EAG Solution:

Base-case analysis: Using the adverse events and their incidence rates from the CSR cohort 1 document.

Scenario analysis: Using the adverse events and their incidence rates from the company submission.

3.2.8 Resources and costs

The company stated that for the identification of cost and resource use in the literature, a systematic review of cost and healthcare resource utilization data specific to r/r MCL was conducted, with updates to previous searches. However, the company noted that the studies identified were deemed inapplicable to the present evaluation, as they were conducted in the USA. Consequently, the assumptions regarding healthcare resource utilization were aligned with those from the original submission (TA677).

3.2.8.1 Intervention and Comparators' Costs and Resource Use

The costs associated with brexu-cel include drug acquisition, bridging therapy, conditioning chemotherapy, and a CAR-T tariff that encapsulates leukapheresis,

infusion, monitoring, hospitalization, and management of emergent adverse events within the first 100 days post-infusion. Given that brexu-cel is administered as a one-time infusion, all related costs are assumed to be incurred at the initiation of the treatment cycle, ensuring alignment with the model structure.
Bridging therapy costs were derived from the ZUMA-2 trial, where 36.8% of patients required R-BAC before infusion. Conditioning chemotherapy was administered to all patients in the mITT population, utilizing cyclophosphamide and fludarabine. Costs for these items were obtained from the electronic Market Information Tool (eMIT) and incorporated into the model, assuming whole-vial usage without sharing to account for potential wastage (Table 20).

Table 20: Cost and average number of vials required per administration of conditioning chemotherapies (Obtained from CS, document B, section B.3.5.2)

Conditioning chemotherapy	Dose needed	Vial size (mg)	Cost per vial*	Mean number of vials per patient per day
Fludarabine	30 mg/m^2/day	50 mg	£105.93	1.91
Cyclophosphamide	500 mg/m^2/day	500 mg	£11.18	0.47
		1,000 mg	£13.11	1.00
Key: eMIT, electronic Market Information Tool * eMIT national database, 23 October 2024				

The acquisition cost of brexu-cel was established as a single payment of £[redacted], reflecting a negotiated discount from the list price. Additionally, in line with TA872, a lump-sum CAR-T tariff of £41,101 was included to cover the primary hospitalization and associated management of CAR-T-related toxicities. However, the company contests the applicability of this tariff within the context of a NICE health technology appraisal, arguing that a bottom-up approach would provide a more transparent and evidence-based cost estimate. Furthermore, the company highlights that NHS efficiencies have likely reduced CAR-T management costs over time, in line with the NHS Long Term Plan objectives. The company does not include any costs relating to ICU for brexu-cel.

Standard of Care (SoC) Costs and Resource Use

The SoC comparator assumes all patients receive R-BAC, consistent with previous appraisals. Drug acquisition costs were derived from eMIT and BNF, with cost-

minimization strategies such as vial optimization considered. The average number of cycles per patient was estimated at four, following McCulloch (2020),[33] with administration costs incorporated based on NHS reference costs. The total per-cycle SoC costs, including both drug acquisition and administration, were calculated to reflect real-world practice (Table 21 and Table 22).

Table 21: Costs and Dose needed of SoC therapies (Obtained from CS, document B, section B.3.5.2)

SOC drug	Dose needed (mg/m²)	Dose per vial (mg)	Units per package	Cost per package	Cost per mg
Rituximab[1]	375	100	2	£314.33	£1.57
		500	1	£785.84	£1.57
Bendamustine[2]	70	25	5	£40.86	£0.33
		100	1	£91.99	£0.92
		100	5	£127.14	£0.25
Cytarabine[2]	500	500	5	£30.79	£0.01
		1000	1	£7.76	£0.01
		2000	1	£14.81	£0.01
		100	5	£13.85	£0.03
Sources: [1] eMIT: Drugs and pharmaceutical electronic market information tool (eMIT). Department of Health and Social Care (2024). [2] BNF: British National Formulary (BNF). Joint Formulary Committee (2024). Accessed November 1st 2024 at https://bnf.nice.org.uk/					

Table 22: SoC regimen drug acquisition costs per treatment cycle (Obtained from CS, document B, section B.3.5.2)

Individual drugs schedule		Day of chemotherapy cycle			Total drug acquisition/ administration cost per treatment cycle	Cycle frequency
		Day 1	Day 2	Day 3		
Acquisition costs per treatment cycle	Rituximab, Day 1	£1,246.14	£0.00	£0.00	£1,362.17	Every 4 weeks (4 treatment cycles assumed)
	Bendamustine, Days 1-2	£42.06	£42.06	£0.00		
	Cytarabine, Days 1-3	£10.64	£10.64	£10.64		
Administration costing per treatment cycle	Rituximab, Day 1	£394.17	£0.00	£0.00	£1,182.50	
	Bendamustine, Days 1-2	£0.00	£394.17	£0.00		
	Cytarabine, Days 1-3	£0.00	£0.00	£394.17		

EAG concern 10: Underestimation of CAR-T Tariff plus ICU costs

Company's approach: The company has used a £41,101 tariff for CAR-T drug administration (including ICU costs).

EAG's critiques, assumption and justification: The EAG critiques the company's adoption of a £41,101 tariff for CAR-T drug administration. The EAG asserts that a more robust approach, informed by prior Appraisal Committee (AC) experience, involves using the tariff cost of £58,964 for CAR-T infusion and monitoring, supplemented by ICU-related expenses.[50]

Furthermore, while the company's concerns about insufficient transparency from NHS England are valid, they do not justify retaining an outdated figure. The EAG highlights that, in the final appraisal document of TA1048[50], point 3.18 states that "NHS England confirmed that costs associated with ICU admission are not included in the CAR-T or stem cell transplant tariffs". The company stated that, according to ZUMA-2, 23% of patients require ICU care. However, another study conducted in the UK with real-world data, (O'Reilly et al. (2024)) reported that 27% of patients required ICU admission.[27]

The EAG believes that the company's approach underestimates costs associated with brexu-cel.

EAG Solution:
Base-case analysis: Using the tariff costs for CAR-T infusion and monitoring, valued at £58,964 + ICU costs (proportion of 27%)
Scenario analysis: 1. Using the tariff costs for CAR-T infusion and monitoring, valued at £41,101.
2. Estimating the CAR-T tariff cost based on different cost items (with 27% proportion for ICU)

3.2.8.2 Health-State Costs and Resource Utilization

Resource utilization was stratified by disease progression status, with costs applied accordingly. Given the absence of UK-specific data, resource use estimates were derived from NICE TA502,[48] which involved a clinician survey of medical interventions required for MCL patients. Health-state costs incorporated routine clinical monitoring, imaging, hospital visits, and transfusions, with differential costs

applied for long-term survivors to reflect lower ongoing healthcare utilization beyond 48 months (see Table 23).

Table 23: Frequency of resource use by health state as reported in TA502 and applied in the model (Obtained from CS, document B, section B.3.5.3)

Resource type	Frequency / model cycle (pre-progression, up to LTS timepoint)	Frequency / model cycle (post-progression)	Unit cost*
Full blood count	0.39	0.78	£3.10
X ray	0.06	0.06	£43.13
Blood glucose	0.02	0.00	£1.53
Lactate dehydrogenase	0.26	0.44	£1.53
Lymphocyte counts	0.39	0.78	£3.10
Bone Marrow Exam	0.06	0.00	£451.84
Office visit	0.39	0.78	£182.39
Inpatient stay	0.03	0.17	£3,106.70
Biopsy	0.04	0.00	£6,741.96
Blood transfusion	0.07	0.33	£398.79
Platelet infusion	0.00	0.17	£398.79
CT-Scan	0.00	0.00	£113.27
PET Scan	0.00	0.00	£613.44

*The company stated that the most recent NHS reference costs (2023–2024) were used to derive costs for each of the resource use components
Note: For pre-progression beyond LTS timepoint, only office visit twice a year is assumed.

3.2.8.3 Adverse Event Costs

The company included adverse event (AE) costs within the CAR-T tariff, except for hypogammaglobulinemia, which necessitates long-term intravenous immunoglobulin (IVIg) therapy. The company stated that the cost estimates were based on NICE TA559[51] and validated by clinical experts. The monthly cost of IVIg treatment was estimated at £45.22, considering dosing regimens and treatment duration assumptions. The company stated that the safety profile of brexu-cel was derived from the ZUMA-2 trial, with real-world UK evidence suggesting lower rates of severe cytokine release syndrome (CRS) and neurological toxicities than those reported in the trial.

Table 24: IVIg dosing parameters (Obtained from CS, document B, section B.3.5.4)

IVIg therapy*	Dose (g/kg)	Frequency	Duration	Source
Kiovig	0.5	Every 4 weeks	12 months	TA559, Hettle et al., Clinical expert opinion.

Key: IVIg, intravenous immunoglobulin
*The percentage of patients experiencing hypogammaglobulinaemia with a grade ≥3 in ZUMA-2 is [redacted]

EAG concern 11: Underestimating IVIg Therapy Needs

Company's approach: The company adopts a [redacted] incidence rate for grade ≥3 hypogammaglobulinaemia and assumes a 12-month IVIg treatment duration.

EAG's critiques, assumption and justification: The EAG critiques the company's approach to adopting a [redacted] incidence rate for grade ≥3 hypogammaglobulinaemia, as reported in the ZUMA-2 trial, asserting that this estimate likely underrepresents the proportion of patients requiring IVIg therapy. Consequently, this assumption may distort the cost-effectiveness analysis. The reported incidence rate serves as the basis for a weighted average monthly IVIg cost of £45.22, which is notably lower than alternative estimates. For instance, Wang et al. (2020)[52] and the TA677 (original submission) report indicate that 32% of patients received IVIg, while Wang et al. (2023)[35] report a figure of 38%. Clinical experts consulted by CADTH estimate that 30–40% of patients require IVIg therapy for a duration of one to two years.[41] The EAG argues that using the [redacted] incidence rate to estimate the need for IVIg therapy may potentially misrepresent real-world treatment needs.

Additionally, concerns arise regarding the assumed 12-month IVIg treatment duration, which aligns with TA559[51] and has been endorsed by NHS consultants yet is questioned by the EAG due to its uncertainty. Drawing on critiques from TA677, where the Evidence Review Group (ERG) supported a three-year duration—subsequently accepted in TA567[53]—the EAG underscores the potential underestimation of long-term costs associated with the [redacted] incidence cohort. This discrepancy suggests that the company's approach may not comprehensively reflect clinical practice or align with previous health technology assessments. The EAG assumes that 38% of patients undergoing brexu-cel treatment need to receive IVIg therapy for a period of one year. This remains an area of uncertainty, as the EAG is unable to rule out the possibility that other causes of requiring IVIg (i.e. aside from hypogammaglobulinaemia) may be accounted for in the CAR-T tariff.

EAG Solution:

Base-case analysis: Using 38% for patients requiring IVIg therapy for a period of one year.

Scenario analysis:

- Scenario 1: Using [redacted]% for patients requiring IVIg therapy for a period of one year.
- Scenario 2: Using 38% for patients requiring IVIg therapy for two years.
- Scenario 3: Using 10% for patients requiring IVIg therapy for two years.

3.2.8.4 Allogeneic Stem Cell Transplantation (AlloSCT) Costs

The unit cost of alloSCT (£47,508.32) was sourced from NHS reference costs and applied at the start of the model to avoid temporal complexity. Two experts consulted previously by the company in the original appraisal estimated subsequent alloSCT proportions following R-BAC to be below 30% and below 15%. The EAG's clinical expert provided similar input, and commented that the assumption of equal proportions of subsequent alloSCT across groups was reasonable.
The EAG's clinical expert described how a potential loss of access to brexu-cel would increase earlier usage of alloSCT on the NHS, however the EAG has not been able to explore the potential impact of this.

Table 25: Cost of alloSCT (Obtained from CS, document B, section B.3.5.5)

Currency code	Currency description	Unit cost
SA39A	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 19 years and over	£47,508.32

EAG concern 12: Underestimating alloSCT Costs

Company's approach: Initially, the company applied £47,508.32 for alloSCT costs; in clarification, revised to £106,393.02, adding £1,927.09 for harvesting and £56,957.61 for follow-up, aligning with TA893[54] methodology.

EAG's critiques, assumption and justification: The EAG critiques the company's approach to alloSCT costs, noting that the use of only the SA39A code underestimates the full cost by excluding stem cell harvesting and follow-up. While the company has updated the costs (in response to EAG clarification question) to include these components, the revised costs still appear lower than those in TA893.

The EAG suggests that a more comprehensive approach is necessary to reflect the true cost of alloSCT. Subsequent alloSCT costs used in TA893 can be a more appropriate source.

Table 26: Cost of alloSCT (EAG inputs, taken from TA893 Company Submission)

Component	Cost
Stem cell harvesting	£4,699.80
AlloSCT procedure	£66,744.65
Follow-up, up to 24 months post alloSCT	£46,307.00

EAG Solution:

Base-case analysis: Following the approach in TA893 (£117,751.45)

Scenario analysis: The company's approach

3.2.8.5 End-of-Life Care Costs

Palliative care costs were included for patients at the end-of-life stage, assuming a median duration of 37 days, consistent with Bennett et al. (2016).[55] Costs were derived from NHS reference costs, incorporating specialist palliative care services (see Table 26).

Table 27: End-of-life care costs (Obtained from CS, document B, section B.3.5.6)

Currency code	Currency description	Activity	Unit cost
N21AF	Specialist Nursing, Palliative/Respite Care, Adult, Face to face	473,262	£142
N21AN	Specialist Nursing, Palliative/Respite Care, Adult, Non face to face	438,954	£76

3.2.9 Severity

The company recognizes that brexu-cel was originally assessed under the end-of-life (EOL) criteria, as outlined in TA677. However, NICE's January 2022 update replaced these criteria with the severity modifier. The company considers the ongoing review an extension of the initial appraisal rather than a new assessment and maintains that applying the severity modifier retrospectively would contradict the established Cancer Drugs Fund exit process, raising concerns about procedural fairness.

The company was invited to submit a case for the application of a severity modifier during the clarification stage by NICE and the EAG, however it declined this opportunity. Hence the EAG does not critique or explore this potential on behalf of the company.

4 COST EFFECTIVENESS RESULTS

4.1 *Company's cost effectiveness results*

Table 28 presents base case outputs, incorporating a discounted brexu-cel price of £[redacted]. Time-preference discounting applies to costs and QALYs but not life years. Brexu-cel is expected to provide [redacted] additional life years and [redacted] discounted QALYs versus R-BAC, at an extra cost of £[redacted]. The company stated that the resulting ICER (£54,366/QALY) is near the WTP threshold and lower than TA677's ICER (£58,302).

In their clarification responses, the company provided a new base case, which made minor changes to the model inputs. However, given that this was provided with limited exploration of uncertainty (i.e. no scenario analyses), the EAG presents output from both models where possible, with post-clarification results labelled as "new". The changes related to the inclusion of pre-infusion costs for those not infused (response B2), updated uncertainty around utility values (response B5), and updated alloSCT costs (response B14).

Table 28: Base-case deterministic cost-effectiveness results (obtain from CS, section B.3.10)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
R-BAC	[redacted]	[redacted]	[redacted]	-	-	-	-
brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,366
R-BAC (new)	[redacted]	[redacted]	[redacted]	-	-	-	-
brexu-cel (new)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,270

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

4.2 *Company's sensitivity analyses*

4.2.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) results for the base case are summarized in Table 29, Figure 18 and [redacted]. These results are derived from 1,000 random draws from distributions of uncertain input parameters. The PSA findings indicate that brexu-cel consistently provides a QALY benefit over the standard of care (SoC) at a positive incremental cost. Compared to deterministic results, PSA yields a slightly higher mean ICER. Figure 18 shows a [redacted] of cost-effectiveness at a £50,000 WTP threshold.

Table 29: Mean PSA base case results (obtain from CS, section B.3.11.1)

Technologies	Mean costs	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline
R-BAC	[redacted]	[redacted]	[redacted]	[redacted]	
brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	£56,888
R-BAC (new)	[redacted]	[redacted]			
brexu-cel (new)	[redacted]	[redacted]	[redacted]	[redacted]	£52,663

Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SoC, standard of care.

[redacted]

17
(obtain from CS, section B.3.11.1)

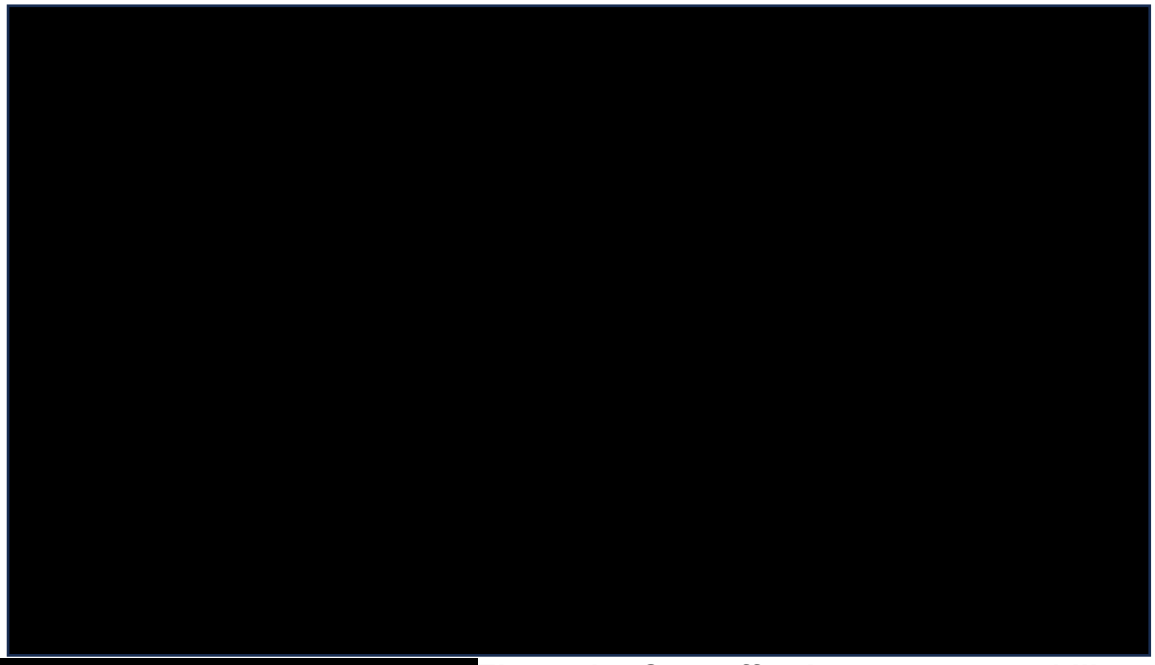
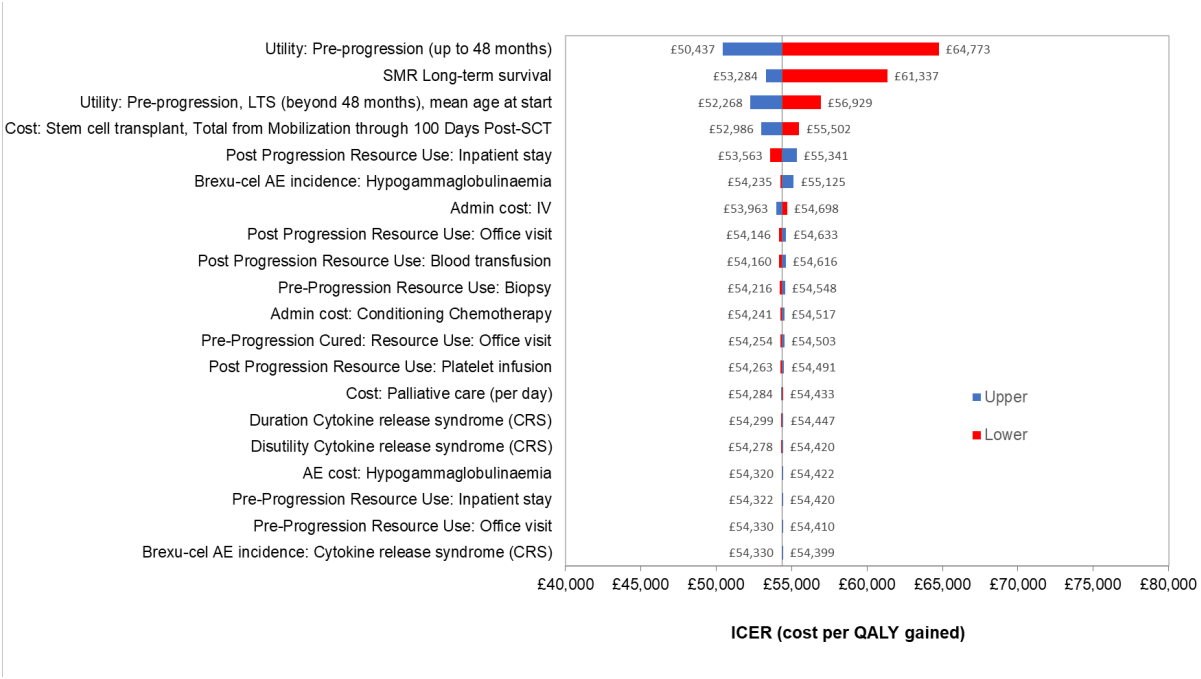


Figure 18: Cost-effectiveness acceptability curve, from base case probabilistic results (obtain from CS, section B.3.11.1)

Deterministic sensitivity analysis Figure 19 presents a tornado diagram illustrating the 20 parameters with the greatest impact on the ICER relative to SoC in one-way sensitivity analyses (OWSA). In this analysis, all parameters with univariate uncertainty distributions were varied to their upper and lower confidence interval limits. The ICER was most sensitive to uncertainty in the pre-progression utility estimate derived from ZUMA-2 EQ-5D data and the assumption regarding the SMR long-term survival.



Key: EOL, end of life; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin, OWSA, one-way sensitivity analysis; SCT, stem cell transplant; SoC, standard of care.

Figure 19: Tornado diagram showing OWSA results (obtain from CS, section B.3.11.2)

4.2.2 Scenario analysis

The scenario analyses assess the sensitivity of cost-effectiveness outcomes to methodological, parameter, and structural uncertainties within the cost-effectiveness analysis. Table 30 outlines the scenarios tested, their underlying rationale, and the corresponding ICER for each. The most influential scenarios involve variations in discount rate assumptions, model time horizon, and the incorporation of the SACT-reported median age.

Table 30: Scenario analyses impact summary (obtain from CS, section B.3.11.3)

Base case equivalent	Scenario detail	Brief rationale	ICER	IMPACT
Base case			54,366	-
Time horizon: 50 years	Time horizon: 20 years	Alternative time horizons	60,419	+11%
	Time horizon: 30 years		54,696	+1%
	Time horizon: 40 years		54,368	0%
Discount rate 3.5%	Annual discount rate for costs 1.5%; QALYs 1.5%	Alternative discount rates	45,155	-17%
	Annual discount rate for costs 6.0%; QALYs 6.0%		67,056	+23%
Long-term survivor for brexu-cel at: 48 months	LTS for brexu-cel patients at 36 months	Alternative LTS assumptions	43,946	-19%
	LTS for brexu-cel patients at 60 months		60,309	+11%
SMR of 1.09 applied to general population survival data for LTS	No SMR adjustment (general population survival)	Alternative LTS assumptions	53,284	-2%
Proportion of patients receiving subsequent alloSCT, SoC: 31%	Patients receiving alloSCT, SoC: 15.0%	Alternative SoC subsequent alloSCT assumptions	56,200	+3%
	Patients receiving alloSCT, SoC: 40.0%		53,335	-2%
Proportion of patients receiving alloSCT, brexu-cel: 2.9%	Patients receiving alloSCT, brexu-cel: 0%	Alternative assumption	54,034	-1%
Mean age: 63.2 years	SACT-based age: 67.5 years (pre-progression utility also age-adjusted)	Consideration of RWE	£63,631	+17%

Key: alloSCT, allogeneic stem cell transplant; ICER, incremental cost-effectiveness ratio; LTS, long term survival; QALY, quality-adjusted life year; SACT, Systematic Anti-Cancer Therapy; SMR, standardised mortality ratio; SoC, standard of care.

4.3 *Model validation and face validity check*

The company conducted a cost-effectiveness analysis estimating a mean life expectancy of [redacted] for post-ibrutinib MCL patients receiving brexu-cel, compared to [redacted] without treatment. However, due to limited data maturity, validating absolute and relative survival estimates remains challenging.

To address this, the company utilized real-world data from the Systemic Anti-Cancer Therapy (SACT) dataset (January 2021–September 2023), which included 92 brexu-cel-treated patients, with complete survival data for 69. Model-estimated overall survival (OS) exceeded SACT data but remained within confidence intervals. Potential discrepancies may stem from early treatment delays and evolving clinical guidelines optimizing CAR-T-cell therapy outcomes (see Table 31).

Table 31: Comparison of estimated overall survival to validation data-set (obtain from CS, section B.3.14.1)

Time period	OS (%), SACT data	OS (%), Model estimation
6 month	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
Source: National Disease Registration Service (NDRS), 2024, Brexucabtagene autoleucel (was KTE-X19) for treating relapsed or refractory mantle cell lymphoma – data review		

The company stated that the original cost-effectiveness model underwent independent review in April 2020, with subsequent updates assessed by NHS clinicians and a health economist. Quality assurance involved external validation, error-checking, and adherence to peer-reviewed modelling checklists to ensure methodological robustness.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 *EAG's changes made to the company's base-case model*

Table 32 presents the company data/approach used in the company's base case for certain parameters, along with new values/approaches derived from the EAG concerns outlined in section 3.2. For further details and justifications, please refer to the associated sections listed in the last column of Table 32. The table includes the EAG's preferred assumptions, which will be used in the forthcoming sections.

Table 32: EAG's changes made to the company's base-case model*

Area of change	Company's Value/approach	EAG's value/approach	Reference to related section(s)
Population approach and extrapolation	Intervention: Using the mITT from ZUMA-2 Comparator: R-BAC based on McCulloch (2020)	Intervention: Using the ITT population (leukapheresed patients) from real world sources. Comparator: Comparator: R-BAC based on McCulloch (2020) with using the updated extrapolation with excluding the alloSCT effects	Sections 2.2.3, 2.2.4, 2.2.5, 3.2.3 and 3.2.6
Time horizon	Using the company's approach (fixed 50-year time horizon)	Using the 100 years minus the starting age as a time horizon	Section 3.2.5
Half-cycle correction	Using cycle midpoints	Use of average health state occupancy for half-cycle correction	Section 3.2.5
Cure time point	Using the 48-month LTS timepoint.	Using the 60-month LTS timepoint	Section 3.2.2 and section 3.2.6
Proportion receiving alloSCT and associated costs	Including alloSCT in both arms ([redacted]% in brexu-cel and 31% in R-BAC) with updated costs	Including alloSCT in both arms ([redacted]% in brexu-cel and [redacted]% in R-BAC) with updated costs	Section 3.2.8.4
Mortality Rate Adjustment Factor (MRAF)	Using the MRAF of 1.09	Using the MRAF of 3.00	Section 3.2.2
IVIg Therapy Needs	Using [redacted]% for patients requiring IVIg therapy for a period of one year	Using 38% for patients requiring IVIg therapy for a period of one year	Section 3.2.8.3
Adverse events source	Incidence rates that are reported in the main submission	Using the most updated incidence rates	Sections 2.2.8, and 3.2.7

Area of change	Company's Value/approach	EAG's value/approach	Reference to related section(s)
CAR-T tariff costs	Using the tariff costs for CAR-T infusion and monitoring, valued at £41,101	Using the tariff costs for CAR-T infusion and monitoring, valued at £58,964 + ICU costs (with the probability of 27% for requiring ICU)	Section 3.2.8.1
Pre/Post-Progression, and LTS HRQoL Estimates	Pre-Progression; ZUMA-2 value ([redacted]), Post-Progression: [redacted], LTS: GPU	Pre-Progression; GPU, Post-Progression: Direct TA502 value (0.68), LTS: GPU	Section 3.2.7
mITT: Modified intention to treat; ITT: Intention to treat; OS: Overall survival; EFS: Event-free survival; GPU: general population utility; ICU: intensive care unit; IVIg: Intravenous immunoglobulin; MRAF: mortality rate adjustment factor; EAG: external assessment group; LTS: long term survivorship; HRQoL: health related quality of life; *Appendix 6.5 provides technical details regarding the changes made to the company's model (related to the base case and some of scenario analyses).			

5.2 *Impact of EAG changes on the company's base-case results*

Table 33 illustrates the results of the EAG exploratory analysis comparing brexu-cel with the comparator, focusing on the ICER relative to the company's base case (£54,366/QALY). The EAG's preferred assumptions notably influence the ICER, with the greatest impact observed when adjusting the mortality rate adjustment factor (MRAF) to 3.00, increasing the ICER by 33.32% to £72,483/QALY, driven by a substantial reduction in incremental QALYs [redacted]. Likewise, using the ITT population (leukapheresed patients) from real world databases raises the ICER by 25.73% to £68,352/QALY, reflecting a lower QALY gain [redacted] Other assumptions, such as CAR-T tariff costs (+13.71%) and the 60-month cure time point (+10.93%), also considerably affect the ICER, underscoring the sensitivity of cost-effectiveness estimates to these parameters.

Note that the EAG uses the company base-case prior to the clarification stage as the starting point for its changes. From the clarification responses, it was unclear whether the company fully supported their revisions, e.g. response B2: "this appraisal is the conclusion of this original submission therefore there is no change to this." The choice of starting model has minimal impact on the EAG base-case, given that the EAG pursues alternative approaches and assumptions relating to the modelling of non-infused patients, utility values and alloSCT costs.

Table 33: Results of EAG's exploratory analysis for the comparison between brexu-cel and comparator

Change row	EAG preferred assumption		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Impact on ICER
	Company's base case		[redacted]	[redacted]	**£54,366**	-
1	Population approach	Using the ITT population (leukapheresed patients) from real world databases, and removing alloSCT effects from R-BAC source	[redacted]	[redacted]	£68,352	+25.73%
2	Time horizon	Using the 100 years minus the starting age as a time horizon	[redacted]	[redacted]	£54,378	+0.02%
3	Half-cycle correction	Use of average health state occupancy for half-cycle correction	[redacted]	[redacted]	£54,428	+0.11%
4	Cure time point	Using the 60-month LTS timepoint	[redacted]	[redacted]	£60,309	+10.93%
5	Proportion receiving alloSCT and associated costs	Including alloSCT in both arms ([redacted]% in brexu-cel and [redacted]% in R-BAC) with updated costs	[redacted]	[redacted]	£57,586	+5.92%
6	Mortality Rate Adjustment Factor (MRAF)	Using the MRAF of 3.00	[redacted]	[redacted]	£72,483	+33.32%
7	IVIg Therapy Needs	Using 38% for patients requiring IVIg therapy for a period of one years	[redacted]	[redacted]	£57,618	+5.98%
8	Adverse events (AEs) source	Using the most updated incidence rates of AEs	[redacted]	[redacted]	£54,818	+0.83%
9	CAR- T tariff costs	Using the tariff costs for CAR-T infusion and monitoring, valued at £58,964 + ICU costs (with 27% for ICU)	[redacted]	[redacted]	£61,819	+13.71%
10	Pre/Post-Progression, and LTS HRQoL Estimates	Pre-Progression; GPU, Post-Progression: Direct TA502 value (0.68), LTS: GPU	[redacted]	[redacted]	£56,114	+3.21%
Changes 1 through 10 (EAG base case)			[redacted]	[redacted]	£127,961	+135.37%

ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group; ITT: Intention to treat; GPU: general population utility; ICU: intensive care unit; IVIg: Intravenous immunoglobulin; MRAF: mortality rate adjustment factor; EAG: external assessment group; LTS: long term survivorship; HRQoL: health related quality of life;

5.3 *Results of EAG base case analysis*

5.3.1 EAG cost-effectiveness results

The EAG's base-case analysis compares brexu-cel versus standard of care (SoC), using the PAS agreement in place for brexu-cel and list, eMIT, or PAS prices for the comparators (see appendix 6.6 for list of analyses applying confidential prices when in place for comparator and the source of prices) (results presented in a separate confidential appendix document). In appendix 6.5 we provide details of the changes made in the spreadsheets used to amend the company's economic model, which formed the basis of the EAG model. This section covers the results:

- EAG's deterministic and probabilistic base-case results
- EAG's probabilistic sensitivity analysis (PSA) results (scatter plot and CEAC)
- EAG's one-way sensitivity analysis results
- EAG's scenario analysis results

5.3.1.1 EAG's deterministic and probabilistic base-case results

Table 34 and Table 35 summarizes the deterministic and probabilistic cost-effectiveness outcomes of brexu-cel compared to standard of care (SoC), as assessed by the EAG, based on the EAG preferred assumptions, with the patient access scheme (PAS) discount incorporated(only for brexu-cel). The deterministic ICER is calculated at £127,961 per QALY, while the probabilistic ICER is £131,099 per QALY, reflecting a degree of uncertainty, particularly regarding treatment effectiveness. Furthermore, the presence of negative incremental net health benefits at willingness-to-pay thresholds of £20,000 and £30,000 highlights the cost-effectiveness concerns under the EAG's preferred assumptions. Overall, these findings suggest that the EAG's methodological choices substantially influence the economic evaluation of brexu-cel, highlighting critical differences from the company's base-case.

Table 34: EAG Deterministic results considering PAS discount for brexu-cel

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£127,961	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay

Table 35: EAG Probabilistic results considering PAS discount for brexu-cel

Technologies	Total costs	Total QALY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	£131,099	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay

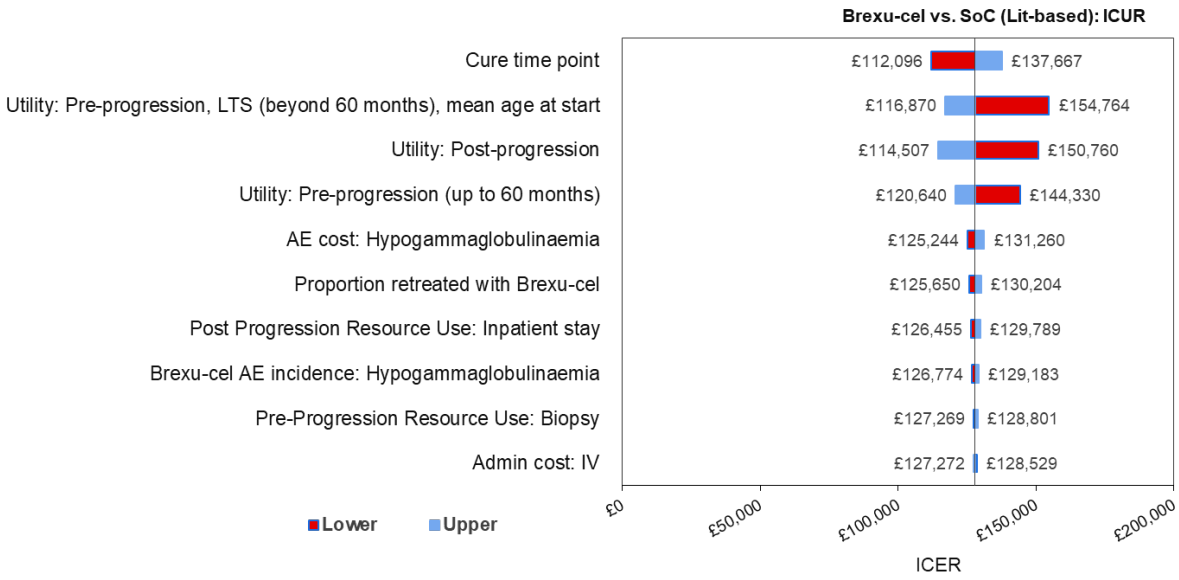
5.3.1.2 EAG's probabilistic sensitivity analysis (PSA) results (scatter plot and CEAC)

Figure 20: EAG scatterplot of brexu-cel vs. comparator

Figure 21: EAG CEAC of brexu-cel vs. comparator

5.3.1.3 EAG's one-way sensitivity analysis results

Figure 22 illustrates the results of the one-way sensitivity analysis (OWSA) conducted by the EAG, which examines the influence of key input parameters on the incremental cost-effectiveness ratio (ICER) for the intervention compared to standard of care (SoC). The analysis identifies the utility value during the pre-progression phase beyond 60 months (associated with the long-term survivorship (LTS) period) and the utility value during the post-progression phase as the most influential factors, demonstrating that changes in these parameters substantially impact the cost-effectiveness results. At the next level of influence, the cure time point and the utility value of the pre-progression phase up to 60 months also significantly affect the ICER under the EAG's preferred assumptions.



Key: EOL, end of life; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin, OWSA, one-way sensitivity analysis; SCT, stem cell transplant; SoC, standard of care.

Figure 22: EAG tornado diagram showing OWSA results

5.3.1.4 EAG's scenario analysis results

Table 36 presents the EAG's scenario analysis, which explores the cost-effectiveness of brexu-cel relative to standard of care under a range of alternative assumptions. In the EAG's base-case analysis, the intervention incurs incremental costs of £[redacted] and yields [redacted] incremental quality-adjusted life years (QALYs), resulting in an incremental cost-effectiveness ratio (ICER) of £127,961 per QALY. The findings demonstrate substantial variability in cost-effectiveness outcomes depending on the scenario applied. The most pronounced reduction in ICER is observed when the standardized mortality ratio (SMR) adjustment is excluded, leading to a 22.58% decrease in ICER to £99,067, attributed to an increase in incremental QALYs to [redacted]. Similarly, applying a mortality rate adjustment factor (MRAF) of 1.09 results in a 21.2% reduction in ICER to £100,829, with QALYs [redacted]. Conversely, the scenario using the intention-to-treat (ITT) leukapheresed population, incorporating overall survival and progression-free survival data from the R-BAC regimen, produces the largest ICER increase (34.74%) raising the ICER to £172,410 due to a decrease in QALYs to [redacted] Similar ICER increases are seen when alternative, and potentially more plausible OS extrapolations for brexu-cel are used. Incremental cost estimates [redacted] across scenarios, ranging from a peak of [redacted] These results highlight the [redacted] of cost-effectiveness estimates to assumptions related to [redacted].

Table 36: EAG's Scenario analysis results

Irst lineScenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Impact
EAG Base case		[redacted]	[redacted]	£127,961	-
Population approach*	Using the mITT from ZUMA-2 (company's approach)	[redacted]	[redacted]	£103,034	-19.48%
	Using ITT Approved population, from SACT (including other available real-world data)	[redacted]	[redacted]	£135,584	+5.96%
	Using ITT Leukapheresed population, R-BAC OS and PFS from original company's model	[redacted]	[redacted]	£172,410	+34.74%
	Using the ITT Leukapheresed population, from ZUMA-2 trial	[redacted]	[redacted]	£111,113	-13.17%
	Using ITT Leukapheresed population, from O'Reilly et al. (2024)[27]	[redacted]	[redacted]	£137,883	+7.75%
	Following the EAG approach by using the "Exponential" distribution for overall survival of brexu-cel.	[redacted]	[redacted]	£167,627	+31%
	Following the EAG approach by using the "Weibull" distribution for overall survival of brexu-cel.	[redacted]	[redacted]	£151,702	+18.55%
Time horizon	Time horizon: 50 years (company's approach)	[redacted]	[redacted]	£127,961	- ~0%
	Time horizon: 20 years	[redacted]	[redacted]	£129,205	+0.97%
Half-cycle correction	Using cycle midpoints (company's approach)	[redacted]	[redacted]	£129,405	+1.13%
	Using the 48-month LTS timepoint	[redacted]	[redacted]	£120,055	-6.18%

Irst lineScenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Impact
EAG Base case		[redacted]	[redacted]	£127,961	-
Cure time point	(company's approach)				
	Using the 36-month LTS timepoint	[redacted]	[redacted]	£109,014	-14.81%
	Using the 72-month LTS timepoint	[redacted]	[redacted]	£133,476	+4.31%
Proportion receiving alloSCT and associated costs	[redacted]% in brexu-cel and 31% in R-BAC (company's approach) ***	[redacted]	[redacted]	£120,630	-5.73%
	[redacted]% in brexu-cel and 15% in R-BAC) with updated costs	[redacted]	[redacted]	£120,137	-6.11%
	[redacted]% in brexu-cel and 10% in R-BAC) with updated costs	[redacted]	[redacted]	£123,370	-3.59%
	0% in brexu-cel and 31% in R-BAC) with updated costs	[redacted]	[redacted]	£107,915	-15.67%
Mortality Rate Adjustment Factor (MRAF)	Using the MRAF of 1.09 (company's approach)	[redacted]	[redacted]	£100,829	-21.2%
	Using the MRAF of 5.00	[redacted]	[redacted]	£146,641	+14.6%
	No SMR adjustment	[redacted]	[redacted]	£99,067	-22.58%
IVIg Therapy Needs	Using [redacted]% for patients requiring IVIg therapy for a period of one year (company's approach)	[redacted]	[redacted]	£120,118	-6.13%
	Using 10% for patients requiring IVIg therapy for two years	[redacted]	[redacted]	£123,965	-3.12%
	Using 38% for patients requiring IVIg therapy for two years	[redacted]	[redacted]	£135,662	+6.02%
Adverse events source**	Incidence rates that are reported in the main submission (company's approach)	[redacted]	[redacted]	£125,628	-1.82%
	Using the tariff costs for CAR-T infusion	[redacted]	[redacted]	£114,416	-10.59%

Irst lineScenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Impact
EAG Base case		[redacted]	[redacted]	£127,961	-
CAR-T tariff costs	and monitoring, valued at £41,101 (company's approach)				
	Estimating the CAR-T tariff cost based on different cost items (£61,585)****	[redacted]	[redacted]	£129,110	+0.90%
Pre/Post-Progression, and LTS HRQoL Estimates	Pre-Progression: ZUMA-2 value ([redacted]), post-progression: 0.724, LTS: GPU (company's approach)	[redacted]	[redacted]	£122,794	-4.04%
	Pre-Progression: ZUMA-2 value ([redacted]), post-progression: 0.724, LTS: GPU*0.90	[redacted]	[redacted]	£132,782	+3.77%
	Pre-Progression; TA502 value (0.78), Post-Progression: Direct TA502 value (0.68), LTS: GPU	[redacted]	[redacted]	£127,748	-0.17%

mITT: Modified intention to treat; ITT: Intention to treat; OS: Overall survival; EFS: Event-free survival; GPU: general population utility; ICU: intensive care unit; IVIg: Intravenous immunoglobulin; MRAF: mortality rate adjustment factor; EAG: external assessment group; LTS: long term survivorship; HRQoL: health related quality of life;
* Baseline characteristics and other related data from each source are presented in the appendix 6.5.
**The new values are presented in the appendix 6.5.
***The company's value of cost of alloSCT in the original company submission was £47,508.32.
****This includes the company's value for leukapheresis, the costs associated with brexu-cel infusion and subsequent monitoring (including hospitalization, assuming a 27% ICU admission rate), as well as the costs of emergent adverse events—estimated based on EAG's preferred proportions of adverse events and one year of IVIG treatment for 38% of patients.

5.4 *EAG's model validation*

The EAG undertook a structured internal validation process to ensure the accuracy, consistency, and robustness of the revised economic model. All modifications

introduced to the model were subject to team-wide review and discussion. The final validation procedure included several key steps:

- Detailed cell-by-cell examination of model formulae to verify correctness.
- Logical consistency testing to confirm the integrity of model calculations.
- Input validation to detect and address discrepancies.
- Implementation and functional testing of all model adjustments.

In parallel, expert validation was conducted to assess the clinical and technical appropriateness of the model's assumptions and inputs. This process involved consultation with the EAG's clinical advisor, ensuring alignment with real-world clinical practice and plausibility of assumptions. Areas addressed during expert review included:

- Incorporation of costs related to allogeneic stem cell transplantation (alloSCT) in the R-BAC treatment arm.
- Assumptions concerning the incidence and management of adverse events.
- The use and calibration of the Mortality Rate Adjustment Factor (MRAF).
- Application of an intention-to-treat (ITT) population, based on leukapheresed patient data from real-world sources.
- Estimation of the proportion of patients requiring intravenous immunoglobulin (IVIg) and duration of such treatment.
- Validation and selection of survival curves used in the model.

To ensure consistency with established methodological standards, the EAG also reviewed previous NICE technology appraisals, particularly the original submission (TA677), ensuring that model revisions were consistent with precedent and aligned with NICE methodological guidance.

Collectively, these validation activities ensured that the EAG's amendments to the company's economic model were methodologically sound, clinically appropriate, and in line with NICE standards for economic evaluation.

5.5 *Conclusions of the cost effectiveness section*

The EAG undertook a detailed assessment of the cost-effectiveness of brexu-cel in comparison to standard of care (SoC). This evaluation identified methodological limitations in the company's submission that affected the credibility of ICER. Key concerns included a lack of consideration of people who underwent leukapheresis but were not infused with brexu-cel. Incorporating these patients through an ITT population approach and using real-world evidence to inform the efficacy of brexu-cel increased the ICER by 25.73% to £68,352 per QALY, largely due to a [redacted].

Additionally, the company relied on outdated CAR-T tariff costs and excluded the intensive care unit (ICU) stays costs. Adjusting for this concern increased the ICER by 13.71% to £61,819, with incremental costs rising to [redacted]. The use of an elevated mortality rate adjustment factor (MRAF) of 3.00 further affected the [redacted], producing an ICER of £72,483 and QALYs of [redacted]. Utility values used by the company, also [redacted] QALY estimates; correcting this assumption resulted in a modest increase in the ICER to £56,114. Other concerns include the underestimation of IVIg usage, higher than expected utility values.

In the EAG's deterministic base-case, which reflects all preferred assumptions and includes the patient access scheme (PAS) discount, brexu-cel was associated with an ICER of £127,961 per QALY, based on incremental costs of £[redacted] and [redacted] QALYs gained. The corresponding probabilistic analysis yielded a [redacted] ICER of £131,099 per QALY, suggesting some uncertainty around the estimates. Scenario analyses revealed that results were sensitive to assumptions around mortality and patient population. For example, excluding the standardised mortality ratio (SMR) adjustment reduced the ICER to £99,067, while using the ITT population with R-BAC survival data increased the ICER to £172,410.

6 Appendices

6.1 *Detailed critique on the Company's Clinical Searches*

Reasonably comprehensive searches in four relevant bibliographic databases were undertaken in February 2019, which were updated and re-ran in January 2020 and November 2024. The EAG has some concerns over the reporting of the database

and non-database searches. The search strategy section reports that the original and update database searches were carried out on Medline In-Process via PubMed and Medline and Embase via Embase.com; however, the tables report that PubMed was searched (CS Appendix 1.1 Tables 1, 4, 5, 8, 9, and 12) and that Embase was searched via Embase.com (CS Appendix 1.1 Tables 2, 4 6, 8, 10, 12). The Summary of Search Results tables lists PubMed, Embase and the Cochrane Library only and the results for Medline via Embase.com are not listed. The company confirmed in the clarification questions that the searches included only the searches reported in Tables 8, 50, 68 and 93. Medline and Medline-in-Process are included in PubMed but the EAG would recommend searching Medline and Medline-in-Process via a database such as Embase.com or Ovid as they include additional controls to give the searcher increased control over the search. It would also allow the searcher to search within the Keyword field, which would increase the sensitivity of the search.

Medline is indexed within PubMed and contains additional content and in-process records. Suitable terms, including database-specific thesaurus headings and free-text terms, were combined appropriately to identify studies relating to the population of interest (r/r MCL) and study types only. The search terms for the population were not combined with any search terms for the intervention of interest, which increases the sensitivity of the searches. Search terms for the concepts related to refractory disease are limited. Additional search terms could include (but not limited to) terms related to drug resistance, salvage therapy or treatment failure. The Embase free text searches were not searched in fields beyond the Title or Abstract fields. Searching in the 'Keywords/identifiers (KW) would increase the comprehensiveness of the search (CS Appendix B.1.1. Identification and selection of relevant studies - Table 2: Embase search terms (14 February 2019), Table 6 Embase search strategy (10 January 2020 and Table 10 Table 10: Embase search strategy (11 November 2024)).

Non-database searches, including conference abstracts, clinical trial registries, hand-searching of relevant HTA organisations, and reference checking is reported to have been carried out in February 2019 and January 2020 only (CS Appendix 1.1). The search terms applied, and numbers of results are not reported, which reduces the transparency of the searches. The EAG has some concerns over the reporting of non-database searches. The company confirmed in the clarification questions that

non-database searching, (referred to as ‘other data sources searched’) was not carried out in the November 2024 update. They clarified that ‘pragmatic searches’ were carried out for studies relating to the intervention of interest published after 2020, which yielded no additional studies for inclusion (CS clarification questions). The PRISMA flow diagram of the 2024 SLR Update reports that two studies were identified ‘through other methods’ (CS Appendix 1.1 Figure 3: PRISMA flow diagram (Updated SLR 2024). Not reporting the search terms or numbers of results reduces the transparency and reproducibility of the systematic literature review. Only conference proceedings from 2018 onwards were searched and it is not reported how these were searched, i.e. via the conference websites or via a database that indexes conference abstracts such as Embase. A search of older conference proceedings may have identified further trials that were never published, to counter publication bias.

The updated SLR search carried out in November 2024 is in line with the previous SLR search strategy. However, the search was only run for records between 2020 to 2024. The EAG believe that the update search should not have been limited to this date, given the addition of patients that have received at least two previous lines of therapy, including a BTK inhibitor to the existing population; therefore, the search may have excluded potentially relevant studies published prior to 2020. The searches were limited to studies published in English, which could introduce language bias.

6.2 *Detailed critique on the Company’s Cost Searches*

Searches to identify Cost-effectiveness, Health-related quality of life (HRQoL) and Cost and healthcare resource identification, measurement and valuation studies were carried out separately in March 2019 and updated in January 2020 and November 2024 (CS Appendix E, F and G). An appropriate range of databases were searched including Medline, Embase, the Cochrane Library, EconLit, EconPapers, the CEA Registry and the CRD Databases. Five conference abstracts were searched and HTA organisations were hand-searched for relevant publications. Reference checking of systematic reviews and meta-analyses was undertaken. As the CRD HTA, NHS EED and ScHARRHUD databases are no longer updated, the

EAG recommends also searching the INAHTA HTA database and using a web search engine such as Google to ensure comprehensiveness.

Appropriate databases-specific indexing and free-text terms are used to search for the population of interest, which are combined with appropriate search filters to limit to publication types. The EAG note that search terms for disease stage, i.e. relapsed, refractory or recurrent disease are not applied for the searches for cost-effectiveness, HRQoL or cost and healthcare resource identification, measurement and valuation studies as per the clinical effectiveness searches, which increases the sensitivity of the searches and intervention, or comparator(s) search terms of interest are also omitted.

The EAG has concerns about the reporting the database searching. The Search Strategy section of Appendix G reports that Medline was searched via Embase.com and Medline-in-Process being searched via PubMed. The search tables 47-50, 64-68 and 90-91 and 93 report that the databases searched were PubMed and Embase via Embase.com. The company confirmed that the searches carried out were the ones reported in Tables 8, 50, 68 and 93 of the appendices. Although Medline and Medline-In-Process are indexed within PubMed; the EAG would recommend searching Medline and Medline-In-Process via Embase.com or Ovid as an alternative or in addition to PubMed, as it offers additional advanced search functionality allowing for more precise control over complex searches. It would also have ensured that the keyword field could have been searched, which would have increased the sensitivity of the searches.[56] The EconLit searches do not report which search fields were searched (CS Appendix E Tables 36, 43, Appendix F 60, 67, Appendix G 78 and 86). The update searches are reproduced accurately, and the searches are limited to the date of that the original searches were ran. Searches limits are applied to limit the studies to studies published in English language, which could risk language bias.

As reported in section 2.1, the search terms and numbers of results are not reported for the non-database searches (Appendix E Original SLR: Other data sources searched). The PRISMA-Flow diagrams for the original and January 2020 update HRQoL searches report that 4 results were identified via searching HTA and grey literature searching (CS Appendix F Figure 8) and 7 (CS Appendix Figure 9) were

retrieved this was in the January 2020 update. Additionally, the PRISMA flow-diagrams for the Cost and healthcare resource identification, measurement and valuation searches the original search reports that 6 additional results (CS Appendix G Figure 11) and 4 for the January 2020 searches (CS Appendix G Figure 12) were retrieved via manually searching HTA and 'grey literature' searches. Not reporting the search terms reduces the transparency and reproducibility of the search methods.

6.3 *EAG Risk of Bias Assessment of ZUMA-2*

The EAG used Down and Black critical appraisal tool to assess the (ZUMA-2) trial.

Description of criteria	Company Response	EAG Response
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes CS, document B, section B.2.4.1
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes All main outcomes are defined
Are the characteristics of the patients included in the study clearly described?	Yes	Yes CS, document B, section B.2.3.2
Are the interventions of interest clearly described?	Yes	Yes CS, document B, section B.2.3.1, Table 7
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A	No, the company does not state potential confounders. While subgroup analysis was performed based on baseline characteristic (see CS appendix C, Table 24), controlling and adjustment for confounders should have been performed.
Are the main findings of the study clearly described?	Yes	Yes CS, document B, section B.2.6.1
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes A 95% confidence interval has been provided for studies with statistical analyses
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes, CS document B, section B.2.11
Have the characteristics of patients lost to follow-up been described?	No	No Missing data, loss to follow-up at different time points has not been reported
Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the	Yes	Not all actual values are reported. CSS document B, section B.2.6

probability is less than 0.001?		
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	UTD	The CS does not report any information in this regard. While the company has an eligibility criterion, it has strict organ function requirement, the ECOG PS of 0 and 1 mostly relates to young and fit patients, does not include patients with controlled virus, therefore, does not reflect real-world clinical setting and reflects that the population were patients likely to respond favourably to brexu-cel
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	UTD	The EAG is unable to determine if the treatment centres where representative of the UK, NHS practice as no information is provided
Was an attempt made to blind study subjects to the intervention they have received?	No	No As no comparators were used, all subjects, staff and investigators were unblinded. However, the EAG clinical expert advice states that other comparators such as R-BAC could have been used.
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	No The investigators were not blinded
If any of the results of the study were based on “data dredging”, was this made clear?	Yes	No The EAG identified no data dredging
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
Was compliance with the intervention/s reliable?	Yes	Unable to ascertain as no information has been reported
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes All main outcome measures were defined and accurate
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	Probably no Patients were included from 32 locations (24 sites in the US, 3 sites in France, 3 sites in the Netherlands, 2 sites in Germany based on specific eligibility criteria. The EAG notes that it appears patients were selectively picked by the company rather than being broadly recruited. ZUMA-2 trial was an open label uncontrolled single arm study.
Were study subjects in different	N/A	Information about the timing of

intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?		recruitment is not provided. However, due to the study design it is likely that patients were selected based on their fitness and baseline characteristics at various time points
Were study subjects randomised to intervention groups?	N/A	ZUMA-2 was a single arm non RCT open label study design
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A	No The company has not reported any information about the recruitment process and its validity. All patients, assessors, analysers and investigators were unblinded.
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No	No No adjustments were conducted for the confounders
Were losses of patients to follow-up taken into account?	Yes	No The EAG is unable to ascertain these criteria
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes	The company has considered at least 60 infused patients to be powered enough. However, in line with the previous TA677 EAG assessment, the EAG agrees with the concerns due to limited sample size and its effect on survival

6.4 *EAG ROBIS Assessment of Company's Systematic Literature Review*

EAG modified ROBIS evaluation of the company's SLR

ROBIS domain, and signalling questions	**EAG's rating**	**Reasoning**
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	No	The EAG is not aware of any pre-published protocol for the CS SLR. The SLR was updated in November 2024, which was aligned with the NICE final scope's intended population. The updated eligibility criteria are provided in CS Appendix Table 16. However, a publication year filter is applied to the updated SLR studies from 2020 – 2024, which is not stated or

		justified in the eligibility criteria. This approach may have led to the exclusion of relevant studies. The company also provides a Prisma flow diagram in CS Appendix B, Figure 3 and does not define the "other" reason for excluding n =96 studies. Upon review of rationale for the exclusion of some studies, the EAG noted a difference in reasons for exclusion that some studies excluded as "other" were due to "study design" or "population"
1.2 Were the eligibility criteria appropriate for the review question?	Yes	The updated eligibility criteria in CS Appendix B, Table 16 are appropriate for the NICE final scope.
1.3 Were eligibility criteria unambiguous?	Probably yes	The eligibility criteria were generally unambiguous, except regarding the publication year restriction. The company's study design criteria did not explicitly state publication year limits, yet the search strategy applied a publication filter from 2020–2024. This inconsistency may have led to the exclusion of relevant studies.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably yes	CS Appendix B, Table 16 updated eligibility criteria do not specify a publication year limit, yet the search strategy applied a 2020–2024 filter. The rationale for this restriction is unclear, and its appropriateness remains uncertain.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably yes	The search strategy applied English language restrictions, which may introduce bias by excluding non-English articles. However, this is a common limitation in SLRs. Additional restrictions included the exclusion of animal

		studies, editorials, reviews, letters, commentaries, case reports, and surveys. While appropriate for focusing on RCTs and observational studies, excluding reviews may have limited the identification of relevant referenced studies.
Concerns regarding specification of study eligibility criteria	Low	Efforts were made to align the review question and objectives with the decision problem. However, the application of publication filters may have excluded relevant studies. The absence of a pre-published protocol and lack of transparency regarding changes to eligibility criteria add to this concern.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	The CS states that the updated SLR (Nov 2024) search was consistent with the original search (Feb 2019) in which all databases and grey literature searches were performed to include Medline (PubMed), Embase, Cochrane, EconLit, University of York CRD, EconPapers, CEA Registry and proceedings of 5 named conferences. However, the company only reports three database search terms and results for all SLRs including the updated 2024 SLR (Medline (PubMed), Embase, and Cochrane - CS Appendix Table 47,48 and 49).
2.2 Were methods additional to database searching used to identify relevant reports?	Probably yes	Additional search methods were used such as grey literature searching, reference checking and hand searches as noted in the original SLR (Feb 2019). However, these were not carried out in the updated SLR (Nov 2024 - which is

		in line with the decision problem) nor reported in the original SLR (Feb 2019). The CS appendix provides the number of grey literature reports retrieved in the original SLR and states that similar methods were used in the updated SLR. However, the CS does not detail how grey literature was sought and reported, neither does it specify if additional searches of the specified databases were undertaken to identify systematic reviews or handsearching of these reviews to identify further reports. Therefore, full details of the supplementary searches or reviews, guidelines and grey literature examined are not reported.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably yes	The updated SLR search is in line with the decision problem (CS Appendix 1.1 Table 9, 10, 11 and 13). Relevant filters for randomised controlled trials, epidemiological, costs, and observational studies are also used and applied correctly. While the eligibility criteria were updated in SLR 2024, the search terms used are those of the original SLR (Feb 2019). This is appropriate to ensure a comprehensive search. Keywords/identifiers (kw) are not used in the Embase searches, which would have retrieved more results. Unfortunately, search terms and the numbers of results used for non-

		database sources are not provided. The methods used for non-database searching was not updated in the latest Nov 2024 update and the search terms and numbers of results of the 'pragmatic searches' are not provided.
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably Yes	The SLR update (Nov 2024) searches were restricted to records added to databases from 2020 to 2024 which is consistent with an update of the searches reported in the original submission. It is unclear how the records identified through other sources were retrieved i.e., conference proceedings or other grey literature. The studies are restricted by publication by the application of search filters, which is appropriate. Restrictions on language to studies published in English is appropriate.
2.5 Were efforts made to minimise errors in selection of studies?	Probably Yes	Record screening is assessed by two independent reviewers in both title/abstract screening and full text screening for the wider SLR. However, details of the final step alignment with the NICE decision problem are not reported.
Concerns regarding methods used to identify and/or select studies	Low concern	Given the review question and eligibility criteria as assessed in Domain 1, a substantial effort has been made to identify as many relevant studies as possible through a variety of search methods. However, only search results of three databases are reported and how records were identified from other sources are not reported.
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	Yes	Standardised form used, extraction by one reviewer and verification by a second reviewer.

3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	The characteristics of included studies was reported in the CS Appendix Table 18 and those within the NICE decision problem are summarised in CS document B, Section B.2.2 Table 5.
3.3 Were all relevant study results collected for use in the synthesis?	No	It is unclear the relevance of other studies identified in this review. The company does not provide a rationale for excluding the identified studies based on their relevance to the NICE decision problem.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes	The methodological quality of the included studies (non-randomised and non-controlled studies) in the SLR was assessed using the Quality Critical Appraisal Skills Programme (CASP) framework. However, NICE prefers more structured tools like ROBINS-I for non-randomised studies assessing interventions
3.5 Were efforts made to minimise error in risk of bias assessment?	Probably yes	All quality and risk of bias assessment were validated by a second reviewer and conflicts resolved by a third reviewer.
Concerns regarding methods used to collect data and appraise studies	Unclear concern	Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted in line with the scope. However, the CS did not present all the studies they essentially selected out using another set of criteria than their eligibility criteria.
4: Synthesis and findings		

4.1 Did the synthesis include all studies that it should?	No	No, the company did not include all relevant studies
4.2 Were all predefined analyses followed, or departures explained?	No information	There were no pre-defined analyses specified in the CS.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?		The company had only identified three eligible non-randomised RCTs to inform the clinical effectiveness (CS Appendix B, section B.2.2, all of which were related to the technology of the submission (brexu-cel). Therefore, no indirect or mixed treatment comparisons were conducted (CS Document B, section B.2.10).
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	N/A	See above
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	N/A	Not applicable
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	The company did not state potential confounders but performed subgroup analysis based on baseline characterises without controlling or adjusting for confounders. The population was not representative of real-world clinical settings as patients appeared to be young and fit. therefore, the EAG was unable to determine if the treatment centres were representative of the UK, NHS practice.
Concerns regarding the synthesis and findings	Unknown	There is insufficient information reported to make a judgement on the risk of bias. The company did not

		include all relevant studies, and there were no predefined analyses specified in the CS. The synthesis did not account for potential biases or address heterogeneity among studies.
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	Some concern	There are concerns regarding study selection, search strategy, synthesis, and adjusting for potential confounders, particularly in terms of unclear eligibility criteria and a population sample not reflective of UK clinical practice. The absence of a pre-published protocol, unexplained restrictions, and incomplete reporting of search methods contribute to some concerns about the risk of bias in this review.

6.5 *EAG technical details of changes made to the company's model*

In Table 33, we present the technical details of the changes made to the company model.

Table 37: EAG changes to the company model

Functionality (with using data validation-list)		
Main board	F143	Name: Population_approach Options: EAG approach: Using the ITT population, which includes all leukapheresed patients from SACT database. Company's approach: Using the mITT from ZUMA-2
Main board	F148	Name: time_horizon_approach Options:

		EAG approach: Using the 100 years minus the starting age as a time horizon Company's approach: Using the company's approach (fixed 50-year time horizon) 20y
Main board	F153	Name: Half_cycle_cor_approach Options: EAG approach Use of average health state occupancy for half-cycle correction Company's approach Using cycle midpoints
Main board	F158	Name: Cure_time_point_approach Options: EAG approach Using the 60-month LTS timepoint Company's approach Using the 48-month LTS timepoint. 36months
Main board	F163	Name: allo_SCT_approach Options: EAG approach Including alloSCT in both arms ([redacted]% in brexu-cel and [redacted]% in R-BAC) with updated costs Company's approach Including alloSCT in both arms ([redacted]% in brexu-cel and 31% in R-BAC) with updated costs SoC 15% Patients receiving alloSCT, SoC: 15.0% SoC 10% Patients receiving alloSCT, SoC: 10.0% brexu-cel0% approach
Main board	F168	Name: MRAF_approach Options: EAG approach using the MRAF of 3.00 Company's approach using the MRAF of 1.09 Third option Using the MRAF of 5.00 No SMR adjustment
Main board	F173	Name: IVIg_need_approach Options: EAG approach Using 38% for patients requiring IVIg therapy for a period of one years. Company's approach Using [redacted]% for patients requiring IVIg therapy for a period of one year. Third option Using 38% for patients requiring IVIg therapy for two years. 10% for two years
Main board	F178	Name: AE_source_approach Options: EAG approach Using the most updated incidence rates Company's approach Incidence rates that are reported in the main submission
Main board	F183	Name: CAR_T_tariff_approach Options: EAG approach Using the tariff costs for CAR-T infusion and monitoring, valued at £58,964 + ICU costs (with 27% for ICU) Company's approach Using the tariff costs for CAR-T infusion and monitoring, valued at £41,101 Bottom-up Estimating the CAR-T tariff cost based on different cost items (with 27% for ICU)
Main board	F188	Name: Utility_approach Options: EAG approach: Pre-Progression; GPU, Post-Progression: Direct TA502 value (0.68), LTS: GPU Company's approach: Pre-Progression; ZUMA-2 value ([redacted]), post-progression: [redacted], LTS: GPU EAG with lower LTS utility: Pre-Progression; [redacted], Post-Progression: Direct value from TA502 value (0.68), LTS: GPU*0.90 TA502: Pre-Progression; GPU, Direct TA502 value (0.68), LTS: GPU
Results (In proper tables)		
Main board	C114: M116	

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)

		=$C$12	=$G$12	=$F$12	=$E$12						
		=$C$11	=$G$11	=$F$11	=$E$11	=E116-E115	=F116-F115	=G116-G115	=H116/J116	=J116-(H116/20000)	=J116-(H116/30000)

Main board	C131: G134		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
			=IF(E133=E134,"OK","NO")	=IF(F133=F134,"OK","NO")	=IF(G133=G134,"OK","NO")
		Company's base case	[redacted]	[redacted]	[redacted]
		scenario	**=$H$116**	**=$J$116**	**=$K$116**

Population approach

Work sheet	Cell(s)	New value/formula/changes
Main board	A143: I144	Functionality for selecting the 'EAG' or 'Company' approach (Cell F143: with the name of Population_approach)
Main board	E209: J215	Putting the Patient characteristics table, with related calculation for some of the parameters

Patient characteristics	Name	Value	SD	Standard Error	
Population size in trial (N) (ITT)	Pop_size_SACT	135			
Female (%)	Female_SACT	0.23		0.036219495	Female_SACT_SE
Mean age at start (years)	Age_SACT	66	7.7	0.662710484	Age_SACT_SE
Mean bodyweight (kg) (from ZUMA-2 ITT)	Weight_SACT	81.8	16.8	1.445913783	Weight_SACT_SE
Mean height(cm) (from ZUMA-2 ITT)	Height_SACT	173.4	9.2	0.791809929	
Mean body surface area (m2)	BSA_SACT	((Height_SACT*Weight_SACT)/3600)^0.5	0.2323486	0.019997384	BSA_SACT_SE

Main board	L209: O214	Creating the table for Some parameters related to drug acquisition for adapting the model based on ITT

Some parameters related to drug acquisition for adapting the model based on ITT					
Parameters	Value	Incorporated into the model	Name	SE	Name
Infused patients (N from ITT)	95	=M211/Pop_size_SACT	Infuesed_patiants	0.00826110747042008	Infuesed_patiants_SE
N received Bridging therapy	=0.91*Pop_size_SACT	=M212/Pop_size_SACT	P_Bridging_ITT	=P_Bridging_ITT*(1-P_Bridging_ITT)/SQRT(Pop_size_SACT)	P_Bridging_ITT_SE
N received Conditioning chemo	95	=M213/Pop_size_SACT	P_Conditional_chemo_ITT	0.00826110747042008	P_Conditional_chemo_ITT_SE

		therapy / N received Leukapheresis: 119 / =1-(M211/M214) / P_Leukapher_Extra_ITT / P_Leukapher_Extra_ITT_SE
Main board	E48	@IF(Population_approach="EAG",Pop_size_SACT,(IFS(Survival!$E$12='Labels & constants'!$BE$4,'Labels & constants'!$BN$4,OR(Survival!$E$12='Labels & constants'!$BE$5,Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!$BN$5,OR(Survival!$E$12='Labels & constants'!$BE$6,Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!$BN$6)))
Main board	E50	@IF(Population_approach="EAG",Female_SACT,(IFS(Survival!$E$12='Labels & constants'!$BE$4,'Labels & constants'!$BI$4,OR(Survival!$E$12='Labels & constants'!$BE$5, Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!$BJ$4, OR(Survival!$E$12='Labels & constants'!$BE$6, Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!$BK$4)))
Main board	E53	IF(Population_approach="EAG",Age_SACT,63.2)
Main board	E55	@IF(Population_approach="EAG",Weight_SACT,(IFS(Survival!$E$12='Labels & constants'!$BE$4,'Labels & constants'!$BI$6, OR(Survival!$E$12='Labels & constants'!$BE$5, Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!$BJ$6, OR(Survival!$E$12='Labels & constants'!$BE$6, Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!$BK$6)))
Main board	E57	@IF(Population_approach="EAG",BSA_SACT,(IFS(Survival!$E$12='Labels & constants'!$BE$4,'Labels & constants'!$BI$7, OR(Survival!$E$12='Labels & constants'!$BE$5, Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!$BJ$7, OR(Survival!$E$12='Labels & constants'!$BE$6, Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!$BK$7)))
Main board	F50	@IF(Population_approach="EAG",Female_SACT_SE,(IFS(Survival!$E$12='Labels & constants'!$BE$4,'Labels & constants'!$BT$4, OR(Survival!$E$12='Labels & constants'!$BE$5, Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!$BT$5, OR(Survival!$E$12='Labels & constants'!$BE$6, Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!$BT$6)))
Main board	F53	@IF(Population_approach="EAG",Age_SACT_SE, (IFS(Survival!$E$12='Labels & constants'!BE4,'Labels & constants'!BO4,OR(Survival!$E$12='Labels & constants'!$BE$5, Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!BO5, OR(Survival!$E$12='Labels & constants'!$BE$6, Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!BO6)))
Main board	F55	@IF(Population_approach="EAG",Weight_SACT_SE,(IFS(Survival!$E$12='Labels & constants'!BE4,'Labels & constants'!BQ4, OR(Survival!$E$12='Labels & constants'!$BE$5, Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!BQ5, OR(Survival!$E$12='Labels & constants'!$BE$6, Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!BQ6)))
Main board	F57	@IF(Population_approach="EAG",BSA_SACT_SE,(IFS(Survival!$E$12='Labels & constants'!BE4,'Labels & constants'!BS4, OR(Survival!$E$12='Labels & constants'!$BE$5, Survival!$E$12='Labels & constants'!$BE$7),'Labels & constants'!BS5, OR(Survival!$E$12='Labels & constants'!$BE$6, Survival!$E$12='Labels & constants'!$BE$8),'Labels & constants'!BS6)))
Survival parameters	Mentioned in the table	

Relative survival models		brexu-cel OS (pooled RWE + ZUMA long term influence)	brexu-cel PFS (pooled RWE + ZUMA long term influence)	R-BAC OS (minus SCT)	R-BAC PFS (minus SCT)
Range used in company's model		S36:S56	D36:D56	AM36:AM56	AE36:AE56
exponential	AIC	1670.6	1767.2	152.4	143.4
	rate	-3.654	0.04735	0.0739	0.0921
gen gamma	AIC	1666.5	1732.5	148.7	144.4
	mu	3.5146	2.3707	2.445	2.091
	sigma	1.6345	1.8827	0.679	0.91
	Q	0.1889	-0.5527	0.388	0.206
gompertz	AIC	1668.6	1746.63	149.4	144.7
	shape	-0.01382	-0.04046	0.0697	0.0265
	rate	0.029452	0.06246	0.0391	0.0752
loglogistic	AIC	1667.1	1743.4	147.7	142.9
	shape	1.0381	1.001	2.379	1.851
	scale	29.1327	14.5633	10.312	7.471
lognormal	AIC	1664.83	1733.8	147	142.5
	meanlog	3.4365	2.71	2.32	2.005

		<table><tr><td></td><td>sdlog</td><td>0.557786</td><td>0.541312</td><td>-0.33129</td><td>-0.06828</td></tr><tr><td>weibull</td><td>AIC</td><td>1669.9</td><td>1756.7</td><td>147.4</td><td>143.7</td></tr><tr><td></td><td>shape</td><td>-0.108</td><td>0.8171</td><td>1.671</td><td>1.264</td></tr><tr><td></td><td>scale</td><td>3.751</td><td>23.8736</td><td>13.961</td><td>11.167</td></tr></table>
Survival parameters	B29	"EAG: Partition survival model (PSM) - Unweighted"
Survival parameters	Q29	"EAG: Partition survival model (PSM) - Unweighted"
Survival parameters	AC29	"SoC (Lit-based): EAG"
Survival parameters	AK29	"SoC (Lit-based): EAG"
Survival	E12	IF(Population_approach="EAG","EAG","Safety (n=68) (60m investigator assessed data cut)")
Survival	E13	IF(Population_approach="EAG","EAG","Safety (n=68) (60m investigator assessed data cut)")
Survival	E23	IF(AND(Population_approach="EAG",EAG_Source_Selected="SACT-ITT-Leukapheresed populatin-R-BAC OS and PFS from original company's model-Scenario"),"PFS McCulloch",IF(Population_approach="EAG","EAG","PFS McCulloch"))
Survival	E26	IF(AND(Population_approach="EAG",EAG_Source_Selected="SACT-ITT-Leukapheresed populatin-R-BAC OS and PFS from original company's model-Scenario"),"OS McCulloch",IF(Population_approach="EAG","EAG","OS McCulloch"))
Main board	E78	IF(Population_approach="EAG",Infuesed_patiants,0%)
Main board	E79	IF(Population_approach="EAG",P_Conditional_chemo_ITT,0%)
Main board	E80	IF(Population_approach="EAG",P_Leukapher_Extra_ITT,0%)
Main board	F78	IF(Population_approach="EAG",Infuesed_patiants_SE,0.00826110747042008)
Main board	F79	IF(Population_approach="EAG",P_Conditional_chemo_ITT_SE, 0.00826110747042008)
Main board	F80	IF(Population_approach="EAG",P_Leukapher_Extra_ITT_SE,0)
Main board	E83	IF(Population_approach="EAG", P_Bridging_ITT,25/68)
Main board	F83	IF(Population_approach="EAG",P_Bridging_ITT_SE,E83*(1-E83)/SQRT(68))
Main board	C77	Proportions with:
Inputs	C776	IF(Population_approach="EAG",Costs!J11,IF('Main board'!E33="Yes",0,Costs!J11))
Costs calcs	C8	IF(Population_approach="EAG",Inputs!N806*((Inputs!N768*(1-Inputs!N772)+Inputs!N813)),((Inputs!N768*(1-Inputs!N772)+Inputs!N813)))
Costs calcs	D8	IF(Population_approach="EAG",Inputs!N776*(Inputs!N808),(Inputs!N776+Inputs!N817))
Costs calcs	M8	IF(Population_approach="EAG",Inputs!N806*IF('Main board'!E33="Yes",'Main board'!F33,(Inputs!N780+Inputs!N825)),IF('Main board'!E33="Yes",'Main board'!F33,(Inputs!N780+Inputs!N825)))

Costs calcs	C14	IF(Population_approach="EAG",G534*Inputs!N807,G534)
Costs calcs	D14	IF(Population_approach="EAG",R534*Inputs!N807,R534)
Costs calcs	E14	IF(Population_approach="EAG",AC534*Inputs!N807,AC534)
Costs calcs	F14	IF(Population_approach="EAG",AN534*Inputs!N807,AN534)
Costs calcs	G14	IF(Population_approach="EAG",J530*Inputs!N807,J530)
Costs calcs	H14	IF(Population_approach="EAG",IF(G14>0,0,U530*Inputs!N807),IF(G14>0,0,U530))
Costs calcs	I14	IF(Population_approach="EAG",IF(G14+H14>0,0,U530*Inputs!N807),IF(G14+H14>0,0,U530))
Costs calcs	J14	IF(Population_approach="EAG",IF(G14+H14+I14>0,0,U530*Inputs!N807),IF(G14+H14+I14>0,0,U530))
Main board	I218	1.02
Main board	I219	4.5
Main board	J218	$G$105
Main board	J219	$G$107
Main board	K218	(I218/(calc_DpY/calc_DpM))*J218 EAG_Pretreatment_Infused_QALYs
Main board	K219	(I219/(calc_DpY/calc_DpM))*J219 EAG_Pretreatment_Uninfused_QALYs
Results vs SoC (Lit-based)	D33	IF(Population_approach="EAG",((EAG_Pretreatment_Infused_QALYs+IF(Inputs!$N$26='Labels & constants'!$AA$10,NA(),SUM(D34:D38)))*Infuesed_patiants)+(EAG_Pretreatment_Uninfused_QALYs*(1-Infuesed_patiants)),IF(Inputs!$N$26='Labels & constants'!$AA$10,NA(),SUM(D34:D38)))
Main board	M218	(I218/(calc_DpY/calc_DpM))
Main board	M219	(I219/(calc_DpY/calc_DpM))
Main board	N218	M218+M219 LYG_mITT_To_ITT_difference
Survival parameters	AN52	(INDEX('CODA output'!$B$5:$AAC$10004, MATCH(AO52, CODA_rows,0),MATCH($AK$31 &" " & AK51 & " " & AL52, CODA_names,0)))
Survival parameters	AF52	(INDEX('CODA output'!$B$5:$O$10004,MATCH(AG52,CODA_rows,0),MATCH($AC$32&" "&AC51&" "&AD52,CODA_names,0)))
CODA output	Columns: L,M, AN,AO	New parameters for Mu and Log Sigma (10000 samples for each parameter)

Patient distribution	AY19 - and then for other cells in this column	IF(AND(Population_approach="EAG",EAG_Source_Selected="SACT-ITT-Leukapheresed populatin-R-BAC OS and PFS from original company's model-Scenario"),(IFERROR($M19*CHOOSE(MATCH(AY$7,label_curves,0),
		EXP(-EXP(AZ$8)*$F19),
		1-((EXP(GAMMALN(EXP(AZ$8)))*GAMMA.DIST(EXP(AZ$9)*$F19,EXP(AZ$8),1,TRUE))/GAMMA(EXP(AZ$8))),
		IF($F19=0,1,IF(AZ$10>0,1,0)+IF(AZ$10>0,-1,1)*IFERROR(GAMMA.DIST((AZ$10^-2)*EXP(AZ$10*((LN($F19)-(AZ$8))/EXP(AZ$9))),AZ$10^-2,1,TRUE),0)),
		EXP((AZ$8/AZ$9)*(1-EXP(AZ$9*$F19))),
		1/(1+($F19/EXP(AZ$8))^EXP(AZ$9)),

		1-IFERROR(LOGNORM.DIST($F19,AZ$8,EXP(AZ$9),TRUE),0), EXP(- (($F19/EXP(AZ$8))^EXP(AZ$9)))),0)),IF(Population_approach="EAG",(IFERROR($M19*CHOOSE (MATCH(AY$7,label_curves,0), EXP(-EXP(AZ$8)*$F19), 1- ((EXP(GAMMALN(EXP(AZ$8)))*GAMMA.DIST(EXP(AZ$9)*$F19,EXP(AZ$8),1,TRUE))/GAM MA(EXP(AZ$8))), IF($F19=0,1,IF(AZ$10>0,1,0)+IF(AZ$10>0,-1,1)*IFERROR(GAMMA.DIST((AZ$10^- 2)*EXP(AZ$10*((LN($F19)-(AZ$8))/EXP(AZ$9))),AZ$10^-2,1,TRUE),0)), EXP((AZ$8/AZ$9)*(1-EXP(AZ$9*$F19))), 1/(1+($F19/EXP(AZ$8))^EXP(AZ$9)), 1-IFERROR(LOGNORM.DIST($F19,AZ$8,AZ$9,TRUE),0), EXP(- (($F19/EXP(AZ$8))^EXP(AZ$9)))),0)),(IFERROR($M19*CHOOSE(MATCH(AY$7,label_curves,0), EXP(-EXP(AZ$8)*$F19), 1- ((EXP(GAMMALN(EXP(AZ$8)))*GAMMA.DIST(EXP(AZ$9)*$F19,EXP(AZ$8),1,TRUE))/GAM MA(EXP(AZ$8))), IF($F19=0,1,IF(AZ$10>0,1,0)+IF(AZ$10>0,-1,1)*IFERROR(GAMMA.DIST((AZ$10^- 2)*EXP(AZ$10*((LN($F19)-(AZ$8))/EXP(AZ$9))),AZ$10^-2,1,TRUE),0)), EXP((AZ$8/AZ$9)*(1-EXP(AZ$9*$F19))), 1/(1+($F19/EXP(AZ$8))^EXP(AZ$9)), 1-IFERROR(LOGNORM.DIST($F19,AZ$8,EXP(AZ$9),TRUE),0), EXP(-(($F19/EXP(AZ$8))^EXP(AZ$9)))),0)))

Patient distribution	AT19 - and then for other cells in this column	IF(AND(Population_approach="EAG",EAG_Source_Selected="SACT-ITT-Leukapheresed populatin-R-BAC OS and PFS from original company's model-Scenario"),($M19*CHOOSE(MATCH(AT$7,label_curves,0),
		EXP(-$F19*EXP(AU$8)),
		1-
		((EXP(GAMMALN(EXP(AU$8)))*GAMMA.DIST(EXP(AU$9)*$F19,EXP(AU$8),1,TRUE))/GAM
		MA(EXP(AU$8))),
		IF($F19=0,1, IF(AU$10>0,1,0) + IF(AU$10>0,-1,1) * IFERROR(GAMMA.DIST((AU$10^-
		2)*EXP(AU$10*((LN($F19)-(AU$8))/EXP(AU$9))),AU$10^-2,1,TRUE),0)),
		EXP((AU$8/AU$9)*(1-EXP(AU$9*$F19))),
		1/(1+($F19/EXP(AU$8))^EXP(AU$9)),
		1-IFERROR(LOGNORM.DIST($F19,AU$8,EXP(AU$9),TRUE),0),
		EXP(-
		(($F19/EXP(AU$8))^EXP(AU$9))))),IF(Population_approach="EAG",($M19*CHOOSE(MATCH(A
		T$7,label_curves,0),
		EXP(-$F19*EXP(AU$8)),
		1-
		((EXP(GAMMALN(EXP(AU$8)))*GAMMA.DIST(EXP(AU$9)*$F19,EXP(AU$8),1,TRUE))/GAM
		MA(EXP(AU$8))),
		IF($F19=0,1, IF(AU$10>0,1,0) + IF(AU$10>0,-1,1) * IFERROR(GAMMA.DIST((AU$10^-
		2)*EXP(AU$10*((LN($F19)-(AU$8))/EXP(AU$9))),AU$10^-2,1,TRUE),0)),
		EXP((AU$8/AU$9)*(1-EXP(AU$9*$F19))),
		1/(1+($F19/EXP(AU$8))^EXP(AU$9)),
		1-IFERROR(LOGNORM.DIST($F19,AU$8,(AU$9),TRUE),0),
		EXP(-(($F19/EXP(AU$8))^EXP(AU$9))))),($M19*CHOOSE(MATCH(AT$7,label_curves,0),
		EXP(-$F19*EXP(AU$8)),
		1-
		((EXP(GAMMALN(EXP(AU$8)))*GAMMA.DIST(EXP(AU$9)*$F19,EXP(AU$8),1,TRUE))/GAM
		MA(EXP(AU$8))),
		IF($F19=0,1, IF(AU$10>0,1,0) + IF(AU$10>0,-1,1) * IFERROR(GAMMA.DIST((AU$10^-
		2)*EXP(AU$10*((LN($F19)-(AU$8))/EXP(AU$9))),AU$10^-2,1,TRUE),0)),
		EXP((AU$8/AU$9)*(1-EXP(AU$9*$F19))),
		1/(1+($F19/EXP(AU$8))^EXP(AU$9)),
		1-IFERROR(LOGNORM.DIST($F19,AU$8,EXP(AU$9),TRUE),0),
		EXP(-(($F19/EXP(AU$8))^EXP(AU$9)))))))

		Scenarios related to population
Main board	G143	Functionality of Sources of baseline data are utilized by EAG With name of EAG_Source_Selected Options including: SACT-ITT-Approved populatin-Scenario SACT-ITT-Leukapheresed populatin-R-BAC OS and PFS from original company's model-Scenario

ZUMA-2-ITT-Leukapheresed populatin-Scenario
O'Reilly-ITT-Leukapheresed populatin-Scenario

Main board E310 ZUMA-2-ITT-Leukapheresed populatin-Scenario

Patient characteristics	Value
Population size in trial (N) (ITT)-Leukapheresed	74
Female (%)	0.16
Mean age at start (years)	63.7
Mean bodyweight (kg) (from ZOMA-2 ITT)	81.8
Mean height(cm) (from ZOMA-2 ITT)	173.4
Mean body surface area (m2)	1.985

Main board H310 ZUMA-2-ITT-Leukapheresed populatin-Scenario

Some parameters related to drug acquisition for adapting the model based on ITT		
Parameters	Value	Incorporated into the model
Infused patients (N from ITT)	68	92%
N received Bridging therapy	28	0.378378378
N received Conditioning chemotherapy	69	93%
N received Leukapheresis	74	8%

Main board E326 O'Reilly-ITT-Leukapheresed populatin-Scenario

Patient characteristics	Value
Population size in trial (N) (ITT)-Leukapheresed	104
Female (%)	0.27
Mean age at start (years) (median)	68
Mean bodyweight (kg) (from ZOMA-2 ITT)	81.8
Mean height(cm) (from ZOMA-2 ITT)	173.4
Mean body surface area (m2)	1.985

Main board H326 O'Reilly-ITT-Leukapheresed populatin-Scenario

Some parameters related to drug acquisition for adapting the model based on ITT		
Parameters	Value	Incorporated into the model
Infused patients (N from ITT)	83	80%
N received Bridging therapy	94	0.903846154
N received Conditioning chemotherapy	83	80%
N received Leukapheresis	104	20%

Main board E342 SACT-ITT-Approved populatin-Scenario

Patient characteristics	Value
Population size in trial (N) (ITT)-approved population from SACT	135
Female (%)	0.23
Mean age at start (years)	66
Mean bodyweight (kg) (from ZOMA-2 ITT)	81.8
Mean height(cm) (from ZOMA-2 ITT)	173.4
Mean body surface area (m2)	1.985

<table>
<tr><td>Main board</td><td>H342</td><td>SACT-ITT-Approved populatin-Scenario
<table>
<tr><td>Some parameters related to drug acquisition for adapting the model based on ITT</td><td></td><td></td></tr>
<tr><td>Parameters</td><td>Value</td><td>Incorporated into the model</td></tr>
<tr><td>Infused patients (N from ITT)</td><td>95</td><td>70%</td></tr>
<tr><td>N received Bridging therapy</td><td>95</td><td>0.703703704</td></tr>
<tr><td>N received Conditioning chemotherapy</td><td>123</td><td>91%</td></tr>
<tr><td>N received Leukapheresis</td><td>104</td><td>9%</td></tr>
</table></td></tr>
<tr><td>Main board</td><td>G210</td><td>IF(EAG_Source_Selected="SACT-ITT-Approved populatin-Scenario",135,IF(EAG_Source_Selected="ZUMA-2-ITT-Leukapheresed populatin-Scenario",F311,IF(EAG_Source_Selected="O’Reilly-ITT-Leukapheresed populatin-Scenario",F327,119)))</td></tr>
<tr><td>Main board</td><td>G211</td><td>IF(EAG_Source_Selected="ZUMA-2-ITT-Leukapheresed populatin-Scenario",F312,IF(EAG_Source_Selected="O’Reilly-ITT-Leukapheresed populatin-Scenario",F328,0.23))</td></tr>
<tr><td>Main board</td><td>M211</td><td>IF(EAG_Source_Selected="ZUMA-2-ITT-Leukapheresed populatin-Scenario",I312,IF(EAG_Source_Selected="O’Reilly-ITT-Leukapheresed populatin-Scenario",I328,95))</td></tr>
<tr><td>Main board</td><td>M212</td><td>IF(EAG_Source_Selected="ZUMA-2-ITT-Leukapheresed populatin-Scenario",I313,IF(EAG_Source_Selected="O’Reilly-ITT-Leukapheresed populatin-Scenario",I329,0.91*Pop_size_SACT))</td></tr>
<tr><td>Main board</td><td>M213</td><td>IF(EAG_Source_Selected="ZUMA-2-ITT-Leukapheresed populatin-Scenario",I314,IF(EAG_Source_Selected="O’Reilly-ITT-Leukapheresed populatin-Scenario",I330,95))</td></tr>
<tr><td>Main board</td><td>M214</td><td>IF(EAG_Source_Selected="ZUMA-2-ITT-Leukapheresed populatin-Scenario",I315,IF(EAG_Source_Selected="O’Reilly-ITT-Leukapheresed populatin-Scenario",I331,119))</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">Time horizon</td></tr>
<tr><td>Main board</td><td>E29</td><td>First, we need to change the data validation condition
Second, IF(time_horizon_approach="EAG",100-E53,IF(time_horizon_approach="20Y",20,50))</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">half-cycle correction</td></tr>
<tr><td>Patient distribution</td><td>E19-then to the end</td><td>IF(Half_cycle_cor_approach="EAG",(IF(B19=0,0,E18+input_cycle_length)),AVERAGE(C19:D19))</td></tr>
<tr><td>Patient distribution</td><td>AB20 - then to the end</td><td>IF(Half_cycle_cor_approach="EAG",((IFNA(S20,0)+IFNA(S19,0))/2),IFNA(S20,0))</td></tr>
<tr><td>Patient distribution</td><td>AC20 - then to the end</td><td>IF(Half_cycle_cor_approach="EAG",(((Y20-S20)+(Y19-S19))/2),(Y20-S20))</td></tr>
<tr><td>Patient distribution</td><td>AD20 - then to the end</td><td>IF(Half_cycle_cor_approach="EAG",(((1-Y20)+(1-Y19))/2),(1-Y20))</td></tr>
<tr><td>Patient distribution</td><td>BD20 - then to the end</td><td>IF(Half_cycle_cor_approach="EAG",((AV20+AV19)/2),AV20)</td></tr>
<tr><td>Patient</td><td>BE20 - then</td><td>IF(Half_cycle_cor_approach="EAG",(((BA20-AV20)+(BA19-AV19))/2),(BA20-AV20))</td></tr>
</table>

<table>
<tr><td>distribution</td><td>to the end</td><td></td></tr>
<tr><td>Patient distribution</td><td>BF20 - then to the end</td><td>IF(Half_cycle_cor_approach="EAG",(((1-BA20)+(1-BA19))/2),(1-BA20))</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">Cure time point</td></tr>
<tr><td>Main board</td><td>Cell E222</td><td>=60 with name of EAG_Cure_time_point</td></tr>
<tr><td>Main board</td><td>Cell E224</td><td>=48 with name of Company_Cure_time_point</td></tr>
<tr><td>Inputs</td><td>C53 and C54</td><td>IF(Cure_time_point_approach="EAG",EAG_Cure_time_point,IF(Cure_time_point_approach="company",Company_Cure_time_point,36))</td></tr>
<tr><td>Patient distribution</td><td>S20- then to the end</td><td>IF(AND(PFS_cure = "Yes", OR(AND(F20>Inputs!$N$53, PFS_cure_choice = INDEX(label_PFS_cure_options, 1)), AND(S19 <= PFS_cure_percentage, PFS_cure_choice = INDEX(label_PFS_cure_options, 2)))),IF('Main board'!$H$26= "OS to PFS",$M20*S19*(1-J20),$M20*MIN(S19*(1-J20),Y20)), IF('Main board'!$H$26= "OS to PFS",$M20*MIN(S19,U20*T20,T20),$M20*MIN(S19,Y20,U20*T20,T20)))</td></tr>
<tr><td>Patient distribution</td><td>Y20 - then to the end</td><td>IF(AND(OS_cure = "Yes", OR(AND(F20>Inputs!$N$53, OS_cure_choice = INDEX(label_OS_cure_options, 1)), AND(Y19 <= OS_cure_percentage, OS_cure_choice = INDEX(label_OS_cure_options, 2)))),IF('Main board'!$H$26="OS to PFS",$M20*MAX(Y19*(1-J20),S20),$M20*Y19*(1-J20)),IF('Main board'!$H$26="OS to PFS",$M20*MAX(MIN(Y19,AA20*Z20,AA20),S20),$M20*MIN(Y19,AA20*Z20,Z20)))</td></tr>
<tr><td>Patient distribution</td><td>J19 - then to the end</td><td>INDEX('Input conversion'!$F$52:$F$172,MATCH(G19,'Input conversion'!$B$52:$B$172,1))/IF(AND(OR(OS_cure="Yes", PFS_cure="Yes"), B19 < Inputs!$N$53), 'Main board'!$E$67, 1)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">Proportion receiving alloSCT and associated costs</td></tr>
<tr><td>Main board</td><td>E229: H235</td><td>create table below:
<table>
<tr><th>Parameter</th><th>value</th><th>Name</th></tr>
<tr><td>Brexu-cel: % of population need alloSCT</td><td>[redacted]%</td><td>EAG_P_allo_SCT_Bexu</td></tr>
<tr><td>R-BAC: % of population need alloSCT</td><td>31.00%</td><td>EAG_P_allo_SCT_R_BAC</td></tr>
<tr><td>Costs of allo_SCT: Stem cell harvesting</td><td>£4,699.80</td><td>EAG_allo_SCT_harvesting_cost</td></tr>
<tr><td>Costs of allo_SCT: AlloSCT procedure</td><td>£66,744.65</td><td>EAG_allo_SCT_procedure_cost</td></tr>
<tr><td>Costs of allo_SCT: Follow-up, up to 24 months post alloSCT</td><td>£46,307.00</td><td>EAG_allo_SCT_Follow_up_cost</td></tr>
<tr><td>Costs of allo_SCT: Total cost</td><td>£117,751.45</td><td>EAG_allo_SCT_Total_cost</td></tr>
</table></td></tr>
<tr><td>Costs</td><td>S11</td><td>IF(allo_SCT_approach="EAG",EAG_P_allo_SCT_Bexu,IF(allo_SCT_approach="Brexu-cel 0%",0,[redacted]%))</td></tr>
<tr><td>Costs</td><td>S12</td><td>IF(allo_SCT_approach="EAG",EAG_P_allo_SCT_R_BAC,IF(allo_SCT_approach="SoC 15%",0.15,IF(allo_SCT_approach="SoC 10%",0.1,IF(allo_SCT_approach="Brexu-cel 0%",31%,31%))))</td></tr>
<tr><td>Costs</td><td>E205</td><td>IF(OR(allo_SCT_approach="EAG",allo_SCT_approach="Brexu-cel 0%",allo_SCT_approach="SoC 15%",allo_SCT_approach="SoC 10%"),EAG_allo_SCT_Total_cost,47508.3245520714)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">Mortality Rate Adjustment Factor (MRAF)</td></tr>
<tr><td>Main board</td><td>Cell E64</td><td>IF(OR(MRAF_approach="EAG", MRAF_approach="third_option"), "user input",IF(MRAF_approach="No SMR adjustment ","Background Mortality", "Maurer, 2014"))</td></tr>
<tr><td>Main board</td><td>E65</td><td>IF(MRAF_approach="EAG",3,5)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">IVIg Therapy Needs</td></tr>
</table>

Inputs	C928	IF(IVIg_need_approach="EAG",0.38,IF(IVIg_need_approach="38% for two years",0.38,IF(IVIg_need_approach="10% for two years",0.1,AE!E71)))
Costs	F289	IF(IVIg_need_approach="EAG",36903.2946428571*1,IF(IVIg_need_approach="38% for two years",36903.2946428571*2,IF(IVIg_need_approach="10% for two years",36903.2946428571*2,36903.2946428571*1)))
Adverse events source		
Main board	E241: J273	Put the new table of AEs

Adverse event grade 3 and above exept CRS with any grades.	CSR cohort 1 derived from Table 14.3.2.1.1a CSR and clarification responses TI14.3.3.1.1a Table	**Company submission in Table 25; AEs occurring in ≥ 5% of the ZUMA-2 cohort**	**Disutility**	**Duration (days)**	**Event cost (NHS England. 2022/23 National Cost Collection Data Publication)**
Cytokine release syndrome (CRS)	[redacted]	[redacted]	0.76	11.0	[redacted]
White blood cell count decreased	[redacted]	[redacted]	0.15	40.0	[redacted]
Anaemia	[redacted]	[redacted]	0.12	14.0	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	0.15	17.0	[redacted]
Hypotension	[redacted]	[redacted]	0.15	5.0	[redacted]
Hypoxia	[redacted]	[redacted]	0.11	2.0	[redacted]
Hypophosphataemia	[redacted]	[redacted]	0.15	16.0	[redacted]
Encephalopathy	[redacted]	[redacted]	0.15	12.0	[redacted]
Platelet Count decreased	[redacted]	[redacted]	0.11	50.0	[redacted]
Neutropenia	[redacted]	[redacted]	0.09	47.0	[redacted]
Pyrexia	[redacted]	[redacted]	0.11	2.0	[redacted]
Confusional state	[redacted]	[redacted]	0.15	7.0	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	0.15	7.0	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	0.15	7.0	[redacted]
Hypertension	[redacted]	[redacted]	0.15	5.0	[redacted]
Pneumonia	[redacted]	[redacted]	0.15	7.0	[redacted]
Hyponatraemia	[redacted]	[redacted]	0.15	7.0	[redacted]
Thrombocytopenia	[redacted]	[redacted]	0.11	63.0	[redacted]
Leukopenia	[redacted]	[redacted]	0.15	21.0	[redacted]
Febrile Neutropenia	[redacted]	[redacted]	0.09	47.0	[redacted]
Acute Kidney Injury	[redacted]	[redacted]	0.15	7.0	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	0.15	64.0	[redacted]
Sepsis	[redacted]	[redacted]	0.15	7.0	[redacted]
Lymphopenia	[redacted]	[redacted]	0.15	21.0	[redacted]
Hypocalcaemia	[redacted]	[redacted]	0.15	7.0	[redacted]
Hypogammaglobulinaemia	[redacted]	[redacted]	0.76	11.0	[redacted]
Hypokalaemia	[redacted]	[redacted]	0.15	7.0	[redacted]
Respiratory Failure	[redacted]	[redacted]	0.15	7.0	[redacted]
Infection (Pneumonia and Sepsis excluded)	[redacted]	[redacted]	0.22	15.1	[redacted]
Neurological event (including ICANS)	[redacted]	[redacted]	0.22	5.9	[redacted]
Diarrhoea	[redacted]	[redacted]	0.05	7.0	[redacted]
Hyperglycaemia	[redacted]	[redacted]	0.06	7.5	[redacted]

Main board	F274	SUM(F270:F273)

Main board	H274	(H270*F270)+(H271*F271)+(H272*F272)+(H273*F273)
Main board	I274	(I270*F270)+(I271*F271)+(I272*F272)+(I273*F273)
AE	C72	Not reported events
AE	E44- then to the end	IF(AE_source_approach="EAG",XLOOKUP(C44,'Main board'!$E$242:$E$274,'Main board'!$F$242:$F$274),M44)
Utilities	C65	Not reported events
Utilities	S37: S65	Copy the Company's original Disutility (positive)
Utilities	F37- then to the end	IF(AE_source_approach="EAG",XLOOKUP(C37,'Main board'!$E$242:$E$274,'Main board'!$H$242:$H$274),S37)
Main board	K242: K272 - then to the end	IFERROR(J242*F242,0)
CAR- T tariff costs		
Main board	G281	Costs!J11
Main board	G282	L276+(36903.2946428571*2*0.38)
Main board	G283	£47,094.16
Main board	G284	£0.00
Main board	G285	SUM(G281:G284) EAG_CAR_T_Bottom_up_cost
Main board	L281	27% EAG_Proportion_ICU
Main board	L282	£58,964 Updataed_CAR_T_tariff
Main board	F33	IF(CAR_T_tariff_approach="EAG",(Updataed_CAR_T_tariff+(EAG_Proportion_ICU*Costs!$F$36*Costs!E$203)),IF(CAR_T_tariff_approach="bottom-up",(EAG_CAR_T_Bottom_up_cost+(EAG_Proportion_ICU*Costs!$F$36*Costs!E$203)),41101))
Pre/Post-Progression, and LTS HRQoL Estimates		
Main board	G292	0.9508566+0.0212126*(1-input_female)-0.0002587*Inputs!$C$21-0.0000332*(Inputs!$C$21^2) EAG_Start_age_GP_Utility
Utilities	P29	IF(Utility_approach="company",'Input conversion'!$L$52,EAG_Start_age_GP_Utility)
Utilities	F21	P30
Main board	G293	0.68 EAG_Post_Progression
Main board	G294	0.9508566+0.0212126*(1-input_female)-0.0002587*(Inputs!$C$21+(Inputs!$C$53/12))-0.0000332*((Inputs!$C$21+(Inputs!$C$53/12))^2) EAG_LTS_GP_Utility
Main board	C103	IF((OR(Utility_approach="EAG",Utility_approach="EAG lower LTS UTILIT")),"User-adjustable",IF(Utility_approach="company","ZUMA-2 utilities","Literature-based utilities"))
Main board	E105	EAG_Start_age_GP_Utility
Main board	E106	IF(Utility_approach="EAG lower LTS UTILIT",EAG_LTS_GP_Utility*0.9,EAG_LTS_GP_Utility)
Main board	E107	EAG_Post_Progression
Main board	F105	Utilities!$G$29

Main board	F106	Utilities!$G$30
Main board	F107	Utilities!$G$31

6.6 *List of company and EAG cost-effectiveness analyses (applying confidential prices) and source of prices*

The EAG re-ran the company's base-case analysis and conducted its own base-case analysis to compare brexu-cel versus R-BAC (SoC) as the comparator, using the available PAS discounts for treatments. This report is provided separately in the document titled "EAG Confidential Appendix." In Table 38, we present the sources of the prices used in the analyses in the EAG Confidential Appendix document.

The EAG confidential appendix report includes the following analyses:

- Company's cost-effectiveness results applying confidential prices for comparator treatments
    - Deterministic base-case results,
    - Probabilistic sensitivity analysis results
    - Scenario analysis results
- EAG cost-effectiveness results applying confidential prices for comparator treatments
    - Deterministic base-case results,
    - Probabilistic sensitivity analysis results
    - Scenario analysis results

Table 38: Sources of prices used in EAG confidential appendix (provided separately)

Name	Dose per unit	Vial/Pack size	Source used in EAG confidential appendix
Brexu-cel			PAS provided by company
Fludarabine	50mg	1	eMIT
Cyclophosphamide	500mg	1	eMIT
Cyclophosphamide	1000mg	1	eMIT
Cyclophosphamide	2000mg	1	eMIT
Bendamustine	25mg	5	eMIT
Bendamustine	100mg	1	eMIT
Bendamustine	100mg	5	eMIT
Cytarabine	100mg	5	eMIT
Cytarabine	500mg	5	eMIT
Cytarabine	1000mg	1	eMIT
Cytarabine	2000mg	1	eMIT

Rituximab	100mg	2	High, low and midpoint of MPSC price
Rituximab	500mg	1	High, low and midpoint of MPSC price

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Title: *Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments (review of TA677): EAG Report [ID6325]: An addendum contains additional analyses*

Produced by	*Centre for Evidence and Implementation Science*
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Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 17/42/44.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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1 Additional analyses

Following the PMB1, NICE requested additional analyses. This document serves as an addendum to the main report and presents non-cPAS analyses. The following items are included in this addendum:

1.1- Revise the company's base case with using the company's most updated base case with applying the severity modifier

Following the clarification question stage, the company submitted additional analyses. After reviewing these alongside the company's responses to the EAG's questions (including points raised in the FAC response to issue 14), the EAG considered these as scenario analyses, however presented in Tables 28 and 29 of the main EAG report alongside the original company base case. Following discussions with the company on 16 June 2025, the non-cPAS addendum incorporates the updated company base case (the ICER of £50,270) with the severity modifier applied, as shown in Tables 1 and 2 in this addendum. No other changes were made to the company's base case.

Regarding the severity modifier, the EAG confirms that the company has provided shortfall calculations but has not submitted an updated model or base case applying the modifier. The company seems to seek flexibility in its use rather than a revised analysis. However, in this addendum, following NICE's request, a severity modifier of 1.2 (aligned with the company's shortfall calculation) is applied to the company's base case.

1.2- Revise the EAG base case using the updated CAR T-cell tariff and apply the severity modifier

Following confirmation from NHS England (NHSE) regarding the CAR T-cell therapy tariff for 2025/26, a tariff of £60,462 has been applied in this addendum. This tariff encompasses the costs associated with leukapheresis, in-hospital delivery of CAR T-cell therapy, management of in-hospital adverse events, monitoring for 100 days post-infusion, and associated training requirements. However, it does not include the costs related to conditioning and bridging chemotherapy (including acquisition, administration, and delivery), acquisition of the CAR T-cell product itself, subsequent treatments, or any subsequent allogeneic stem cell transplantation (allo-SCT).

With respect to the severity modifier, based on the EAG assessment, a severity modifier of 1.2 has been deemed appropriate for this analysis.

1.3- Scenario analyses to explore changes in the starting age

1.4 - Clarification of the scenario used to estimate CAR-T infusion and monitoring costs as a proxy for the CAR-T tariff

1.1 Revise the company's base case with applying the severity modifier

Table 1: Company's deterministic results*, with applying the severity modifier**

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
R-BAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,892	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay
* The most recently updated ICER from the company, prior to applying the severity modifier, was £50,270. (for more details see section 1 (Additional analyses))
**The analysis applies a severity modifier of 1.2. (for more details see section 1 (Additional analyses))

Table 2: Company's probabilistic results*, with applying the severity modifier**

Technologies	Total costs	Total QALY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
R-BAC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	£43,300	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay
*The company's ICER before applying the severity modifier was the most updated one (£50,270). (for more details see section 1 (Additional analyses))
**The analysis applies a severity modifier of 1.2. (for more details see section 1 (Additional analyses))

1.2 Revise the EAG base case using the updated CAR T-cell tariff and apply the severity modifier

Table 3: EAG's deterministic results, using the updated CAR T-cell tariff*

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
R-BAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£128,618	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay
* The updated CAR T tariff for 2025/26 is £60,462. (for more details see section 1 (Additional analyses))

Table 4: EAG's deterministic results, with applying the severity modifier

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
R-BAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,634	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay
*The analysis applies a severity modifier of 1.2. (for more details see section 1 (Additional analyses))

Table 5: EAG's deterministic results, using the updated CAR T-cell tariff* and applying the severity modifier**

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
R-BAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£107,181	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay
* The updated CAR T tariff for 2025/26 is £60,462. (for more details see section 1 (Additional analyses))
** The analysis applies a severity modifier of 1.2. (for more details see section 1 (Additional analyses))

Table 6: EAG's probabilistic results, using the updated CAR T-cell tariff* and applying the severity modifier**

Technologies	Total costs	Total QALY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
R-BAC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	£109,631	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay
* The updated CAR T tariff for 2025/26 is £60,462. (for more details see section 1 (Additional analyses))
** The analysis applies a severity modifier of 1.2. (for more details see section 1 (Additional analyses))

1.3 Scenario analyses to explore changes in the starting age

Table 7: Scenario analysis results based on EAG base case, to explore changes in the starting age

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Impact
EAG Base case (Using the updated CAR T-cell tariff* and apply the severity modifier* and mean age of 66 from SACT)		[redacted]	[redacted]	£107,181	-
Starting age	ZUMA-2 (cohort 1) Mean age: 63.2 years (It is used in the company's base case)	[redacted]	[redacted]	£96,774	-9.71%
	SACT- Median age: 67.5 years	[redacted]	[redacted]	£113,244	+5.66%
	O'Reilly et al. 2024***-median age: 68 years	[redacted]	[redacted]	£115,928	+8.16%

SACT: Systemic Anti-Cancer Therapy; EAG: external assessment group
* The updated CAR T tariff for 2025/26 is £60,462.
** The analysis applies a severity modifier of 1.2.
***O'Reilly MA, Wilson W, Burns D, Kuhnl A, Seymour F, Uttenthal B, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in the United Kingdom: A real-world intention-to-treat analysis. Hemasphere 2024;8(6):e87. http://dx.doi.org/10.1002/hem3.87

1.4 Clarification of the scenario used to estimate CAR-T infusion and monitoring costs as a proxy for the CAR-T tariff

Table 8 outlines the EAG's approach to estimating the costs of CAR-T infusion and monitoring based on individual resource components. As shown in the table below, there is a lack of evidence to support the inclusion of certain resource use and cost elements, particularly those related to monitoring and training. Additionally, some adverse events have not been assigned cost values. Due to these omissions, the EAG considers the current estimate to be an underrepresentation of the true cost.

Table 8: Clarification of the scenario used to estimate CAR-T infusion and monitoring costs

CAR-T Tariff components	Value	Formula/source
Leukapheresis	£1,927.09	CS, Company's model
Administration	£6,605.79	CS, Company's model
Hospitalization: ICU	£13,032.85	Proportion of ICU (27%) coms from RWE: O'Reilly et al. (2024) Other data are sourced from the CS, Company's model
Hospitalization: non-ICU	£7,561.10	CS, Company's model Other data are sourced from the CS, Company's model
Emergent AEs	£17,695.07	Incidences of AE: CSR cohort 1 derived from Table 14.3.2.1.1a CSR and clarification responses T14.3.3.1.1a Table Costs of AEs: Event cost (NHS England. 2022/23 National Cost Collection Data Publication)
IVIG	£14,023	IVIG proportion coms from Wang et al. (2023) (38% for one year), Other data are sourced from the CS, Company's model
All other costs occurring within the first 100 days post infusion (including monitoring and training)	£0.00	Not available
CAR-T infusion and monitoring total cost	£60,845*	-

CS: Company Submission; ICU: Intensive Care Unit; RWE: Real-World Evidence; AE: Adverse Event; CSR: Clinical Study Report; IVIG: Intravenous Immunoglobulin; NHS: National Health Service (UK)
*The EGA can confirm that there is a slight difference between this value and the value of £61,585 in Table 36 of the main report, due to the exclusion of some overlap between AEs, as the company mentioned in the FAC stage.

The EAG also notes that, when using this value as a proxy for the CAR-T tariff in the base-case model, the IVIG cost should be excluded to avoid double counting (already added). An updated scenario, based on the base-case analysis presented in Table 36 of the main report, is provided below. (Table 9)

Table 9: Updated Scenario for CAR-T Tariff Costs (Corresponding to Table 36 of the Main Report)

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Impact
EAG Base case*		[redacted]	[redacted]	£127,961	-
CAR-T tariff costs	Using the tariff costs for CAR-T infusion and monitoring, valued at £41,101 (company's approach)	[redacted]	[redacted]	£114,416	-10.59%
	Estimation of CAR-T infusion and monitoring costs based on individual components, used as a proxy for the CAR-T tariff	[redacted]	[redacted]	£116,924	-8.63%

EAG: external assessment group; ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years;
* The CAR T tariff presented in Table 36 of the main report is £58,964, and the analysis does not apply a severity modifier.

Single Technology Appraisal

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments [ID6325]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **1 May 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Clarity of reporting

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Substantial issue. The EAG report contains a variety of new analyses and evidence sources, not requested by the committee. The rationale and methodology followed is not clear. Company is unable to critically review these analyses without additional detail. Exampes include: The rationale for disregarding ZUMA-2 in base case is unclear The method of indentifying and selecting RWE data sets is not stated The methods of pooling RWE data sets is not stated	EAG modelling to use methods agreed by the commitee in TA677 *or* Provide sufficient rationale and detail about proposed changes to allow critical apprasial.	This is an update of TA677, justified by the new availability of data from ZUMA-2 and SACT. The addition of new data sources beyond this is inappropriate; the selection of these new data sources has not beeen clearly justified and the methods used for adjusting the analysis are not transparent enough to allow for critical appraisal.	Not a factual error. The EAG considers sufficient justification for these items is already provided in the EAG report or are not necessary: Disregarding ZUMA-2 2.2.5.1, 2.2.9, 3.2.3 Selection of RWE 3.2.3, note sources were identified by company. Method of pooling Not necessary, the re-created datasets were combined in a

Methods of “adjusting” comparator data to remove alloSCT outcomes not clear Methods of curve fitting not stated Rationale for changing the basecase population to leukapheresd patients is unclear A bottom-up costing of the NHSE tarrif is provided (the company do not have tariff details from NHSE)			straightforward manner. Method of adjusting comparator 2.4.2 Method of curve fitting Not necessary, standard approaches were used Rationale for using leukapheresed population 3.2.3 Bottom-up costing If this is referencing the EAG scenario analysis, CAR T costs were estimated by combining costs that were provided by the company with EAG preferred

			proportions of adverse events.

Issue 2 Evidence source for EAG modelling

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Substantial issue. The CDF Data Collection Arrangement for TA677 states that: "ZUMA-2 will be the source for the following outcomes: • 2-year Progression Free Survival (PFS): • 5-year Overall Survival (OS)" The EAG model presents OS and PFS from a pooled analysis of 3 RWE data sets, not from ZUMA-2.	EAG presents analysis that uses ZUMA-2 as the source for OS and PFS.	The current EAG model does not meet the requirements of the CDF Data Collection Agreement.	Not a factual error. The wording from the CDF Data Collection Arrangement does not refer to the use of data for survival extrapolation. Rather these time-points appear to be specified to investigate survival outcomes at these key points. Furthermore, the EAG maintains the use of ZUMA-2 follow-up to inform the survival extrapolations.

Issue 3 Inclusion of materials that NICE have not provided to the company

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Substantial issue. The EAG report contains previously unreported SACT analyses based on pre and post BSH guideline amendment. The company has not been provided with these analyses, although these materials have been requested multiple times. The CDF Data Collection Arrangement (section 9) specifies that reporting from SACT will be to NHS England, NHS improvement *and the sponsor* (our italics).	Provide a reference / source for figure 10 in the EAG report. Confirm these data were provided to NICE under an appropriate framework. The EAG report states that NHSE "were able to provide" these additional data but gives no other information. Provide the company with sufficient description of the new evidence provided and enough time to critically appraise the new evidence. Confirm that this new evidence will be made available to stakeholders including the company to comply with NICE's commitment to a fair and transparent process.	NICE has added potentially important new clinical evidence to the appraial without adequate description and without informing stakeholders Note that the company requested similar analysis as potentially important in understanding the SACT data, but the company's request was denied.	Not a factual error. The EAG has reproduced the output from the analysis as it was provided to the EAG. This analysis has not informed any cost-effectiveness modelling, and the EAG does not consider this a substantial issue. The analysis has now been shared with the company through the EAG report.

Issue 4 Misleading summary of bias assessment of ZUMA-2

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2.2.2. Substantial issue. The second sentence of paragraph 4 is misleading "However, the EAG notes that the subjects recruited were relatively fit patients with low ECOG PS and did not include patients with controlled viral infections. Clinical advice to the EAG states that such a population is not reflective of clinical practice" However, brexu-cel is only reimbursed in patients with low ECOG score (0-1) at infusion under the NHSE BluTeq Criteria.	Remove this reference to patients with low ECOG score	The summary sentence creates the impression in the real-world patients with higher ECOG score receive brexu-cel, while this is not the case and it is against the criteria for its reimbursement.	Not a factual error. A total of 12% of DESCAR and 13% of the US consortium have received brexu-cel with an ECOG score of 2 or higher. Additionally, our clinical expert has indicated that, while patients with higher ECOG performance status (PS) may not be initially recruited for brexu-cel infusion and leukapheresis due to limited available evidence—stemming from their exclusion in the ZUMA-2 trial—they will not be excluded if their ECOG PS score increases prior to infusion. In support of this, 2% of CDF patients

			and 6% of the O'Reilly et al. population pre-infusion were scored 2 or higher. Collectively, the evidence suggests that patients with higher ECOG scores should have been considered in the trial, given the proportions observed in real-world settings.
Section 2.2.2 Substantial issue. Final paragraph is misleading "The EAG also noted that patients were not randomly or widely recruited for the study. Instead, they were carefully selected based on specific eligibility criteria, which may limit how well the results apply to the wider R/R MCL patients". It is not possible to recruit 'randomly' and 'widely' for a	Please replace the existing sentence with "The EAG noted that patients were selected based on specific eligibility criteria, which might mean that the real-world population would be wider. However, careful selection and reimbursement criteria are also employed in the real-world setting."	Current wording implies the trial was not robustly set up which would be misleading to reviewers.	While the proposed issue may not constitute a factual inaccuracy, the EAG has refined the current text to enhance elucidation and clarity as follows: "The EAG notes that patients were carefully selected based on specific eligibility criteria, which may limit how well the results apply to the wider R/R MCL patients".

rare disease with low incidence. This statement undermines the robustness of the study.			

Issue 5 Modelling a population that includes patients who are not infused

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2.2.3; 2.2.4 Substantial issue. The EAG presented a model that estimates effectiveness from the point of leukapheresis, not the point of infusion.	EAG to present a model using the modified intent to treat (mITT) population, from the point of infusion, as in TA677.	The modified intent to treat (mITT) population was agreed by the appraisal committee in TA677.	Not a factual error. From the available documentation, the EAG understands no alternative populations to the mITT were considered by the appraisal committee in TA677. Given the strong potential for bias using mITT, the EAG maintains its preference to use the leukapheresed population.

Issue 6 Inaccurate description of McCulloch 2020 objectives

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2.2.4.3 Minor issue. In the first paragraph, the description of McCulloch 2020 is not correct. The EAG describe the study as “aimed to assess R-BAC as a bridge to alloSCT” this is factually inaccurate.	Please amend the description e.g. “aimed to analyse early clinical experience of using R-BAC post BTKi”	The description does not reflect the stated objectives of the study. The study aim was to assess the real world outcomes of a cohort of patients who had received R-BAC as standard of care for rrMCL in order to analyse early clinical experience of using R-BAC post BTKi.	The EAG has made minor revisions to the text to add further clarity. In summary, whilst McCulloch et al. does not explicitly state its objectives beyond broadly evaluating R-BAC, through consultation with the EAG clinical expert the EAG infers that the high proportion of patients consolidated with alloSCT suggests that the ability of R-BAC as a bridging therapy to alloSCT was a key interest to the authors. This is reinforced by the subsequent discussion and conclusion of the paper.

Issue 7 Unclear statement relating to sub-group analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2.2.7 Minor issue. The last sentence of the first paragraph seems to be misleading “This ongoing response rate also questions the plausibility of the company’s assumptions in the economic model”	Please remove this sentence.	Sub-group analysis was not conducted in the economic model.	The EAG has removed the sentence.

Issue 8 Misleading conclusions on clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2.5 Third bullet Substantial issue. The first sentence “The inadequate assessment of HRQoL, with unaccounted late-occurring safety issues which may impact the HRQoL.“ is not an accurate reflection of previous review.	Please remove this bullet.	Neither point is raised in the critique of ZUMA-2 provided earlier in the EAG report. The company is unclear what the statements refer to and the summary sentence is misleading.	Not a factual error. The issues raised are discussed in section 2.2.6.3 of EAG’s report.
Section 2.5 Fourth bullet Minor issue. The second part of sentence “There is a risk of long-term safety issues, *especially regarding secondary malignancies that may require close monitoring*” (our italics) is misleading as it implies specific concern over incidence of secondary malignancies with brexu-cel.	Please add the evidence-based conclusion “However, no cases of brexu-cel–related secondary cancers were reported in any of the ZUMA-2 data cuts (up to 60 months)” (as per conclusion of the safety summary [CS B.2.11.2.3])	There is no specific concern relating to secondary malignancies for brexu-cel.	Not a factual error. References 39, 40 and 41 were utilised for this concern, as stated in section 2.2.8.

Issue 9 Application of mortality adjustment to the LTS population

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.2.2. Substantial issue. EAG reports a Mortality Rate Adjustment Factor (MRAF) of [redacted] for patients post LTS. We are unable to replicate this number and believe it may be incorrect. EAG report does not describe how this figure was calculated so we cannot confirm. Separately, a MRAF of 3.0 is used - this value is from a population with substantial allo-SCT pre-treatment and not in line with the LTS population reported here.	Remove reference to a calculated MRAF of [redacted]. Use the cured population MRAF of 1.09 in the basecase (as justified in the CS and re-iterated in the company response to the EAG clarification Qs).	The mortality adjuster for long term survivors should be from an appropriate population that reflects the LTS status of the patients.	Not a factual error. The EAG can confirm the accuracy of its analysis, and that no change is required. The company's statement here is ignoring the limitations of the source of the 1.09 mortality ratio, which comes from a study of patients with DLBCL who did not receive CAR T therapy.

Issue 10 Correction of AEs

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.2.7 Table 19 Substantial issue. The addition of ICANS (30.9%) leads to a double count and is wrongly reported by the EAG as being missing in the original submission; in addition to this the data source used in the EAG report is not the most recent data used in the economic model (see below)	Please remove additional ICANS row and correct this in the EAG model. The text above the table should also be corrected.	ICANS terminology is not used in original submission and the company maintains this in the CS (see CS narrative around this); ICANS is a relatively new terminology introduced by ASTCT after the ZUMA-2 study protocol was approved. ICANS symptoms are already reported in Table 19 under confusional state and encepthalopathy (summing 11.8%+19.1% = 30.9%).	In response to clarification A20, the company provided Table 14.3.3.1.1a, which the EAG used with the most recent data where appropriate. For other reported AEs, the EAG referred to Table 14.3.2.1.1a from the CSR document. Additionally, Table 14.3.3.1.1a of clarification responses was cross-checked with the trial's 3-year follow-up publication (Wang et al., 2023), which reports updated events post-primary data cutoff. In A20, the company noted that no AEs were reported between October 2023 and the data cutoff (DCO) in April 2024. Regarding the

			ICANS and other items marked as "Not reported" in Table 19, the company did not provide clear information in the submission, and the EAG identified these items through other sources. However, the EAG still lacked sufficient clarity on their details. As a result, the associated QALY losses were not included in the base case analysis. The related cost estimates, however, were incorporated into the scenario analysis titled “Estimating the CAR-T tariff cost based on different cost items.” To enhance transparency, the EAG has added clarification below Table 19 and Table 36, and updated the relevant scenario analysis.
Section 3.2.7 Table 19.	AE rates should be updated to reflect the 48-month data cut used in the	Correct AE rates should be used in the EAG model.	Not a factual error. For information sources, refer to the above

Substantial issue. Firstly, tabulation of AEs does not appear to reflect underlying data source quoted by the EAG (i.e. Table 14.3.2.1.1a and Table 14.3.3.1) with double counting of neutropenia and thrombocytopaenia incidences, reported at [redacted]% and [redacted]% respectively. Secondly, the sources referenced by the EAG seem to be outdated (the 2019 CSR is referenced in the EAG report).	model with removal of double counting. The table reference should be **Table 14.3.18.1.1a.** Subject Incidence of Grade 3 or Higher KTE-X19-related Treatment-emergent Adverse Events by Preferred Term and Worst Grade (Cohort 1: KTE-X19) (Safety Analysis Set, N = 68) (DCO Oct 23) The text above Table 19 should also be corrected to remove any misleading critique of the CS data.		response to the company's query. The list of AEs is from the company submission (Table 45). Neutropenia and thrombocytopenia proportions are from the A20 clarification response, while platelet and neutrophil count decreases are from CSR Table 14.3.3.1.1a. The EAG used the company's TEAEs list (Table 49 in the CS) and assumed different definitions might relate to investigational events and Blood and lymphatic system disorders, as distinct categories for events (CSR Table 14.3.2.1.1a).

Issue 11 Incorrect tariff for CAR-T

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.2.8.1. Substantial issue. CAR-T tariff code. The EAG preferred number has no written reference and no known methodology.	As argued in the CS the correct tariff for rrMCL is £41,101 (in absence of evidence-based alternate)	No new proposed tariff has been supported by a written reference and/or sufficient methodology to allow it to be critically appraised. The existing cost should continue to be used (see CS for full rationale).	Not a factual error. The EAG has used a CAR-T tariff value which was accepted in a recent NICE appraisal of a CAR-T therapy (TA1048).

Issue 12 Correction of alloSCT costing

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.2.8.4. Minor issue. The alloSCT tariff codes in TA893 included paediatric inpatient codes; the company excluded these in their estimate. Secondly, the EAG estimate follows TA893 but the cost has not been inflated to the current cost year.	Update AlloSCT cost to current cost year; For Allo-SCT procedure cost, use cost codes relevant for adults rather than paediatric patients. See company response to EAG clarification Qs for suggested approach.	Costs should be in a consistent price base and reflect the population.	Not a factual error. The EAG has used an alloSCT cost of £117,751.45, based on the values reported in NICE TA893. This estimate (as used in NICE TA893) is appropriate for adult inpatient tariffs and aligns

			with the evidence base considered appropriate at the time of the assessment. The EAG acknowledges that the company used a lower cost (£47,508.32) in the original submission and subsequently updated it to £106,393.02 in response to EAG clarification question B14. However, the updated value remains below the TA893 estimate. The EAG base case assumes alloSCT has an equal probability in both arms of the model at a rate of 2.5% and hence any cost changes have a limited impact on the ICER. Furthermore, while the company recommends updating the alloSCT cost to the most recent price year and using adult-specific codes, the EAG has not

			had access to detailed cost breakdowns or robust data to support a revised estimate beyond that reported in TA893. Given that the EAG's selected cost is higher than the company's proposed update and that the difference has a negligible effect on ICER due to the low proportion of patients receiving alloSCT, the EAG considers the current approach appropriate and proportionate. Therefore, no amendment is proposed.

Issue 13 Removal of patient-generated utility data

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.2.7. Substantial issue. The EAG do not use the healthstate utilities from ZUMA-2 and this is a	Health-state utilities should be taken from ZUMA-2.	NICE state a preference for patient-generated utilities; utility data was generated in ZUMA-2 using NICE's preferred methods; the EAG	Not a factual error. The EAG maintains that applying the ZUMA-2 utility value of [redacted] for the 'Pre-progression (up

deviation from the NICE Reference Case.		argument of better health than general population is acknowledged but clinicians agree that CAR T population likely better health than general age-matched population.	to 60 months)' state is not appropriate for the base-case population. The utility value of [redacted] corresponds to a mean age of 63.2 years. This value exceeds the general population utility norm for that age, which is approximately [redacted], raising concerns about potential overestimation. In the EAG's base case, the population has a mean age of 66 years, for which the general population utility is 0.805. Given that health-state utilities are not expected to exceed general population norms, the EAG considers 0.805 to be a more appropriate and conservative estimate.

Issue 14 Non-use of updated model sent after clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 5.2. Table 33. Minor issue. The EAG analyses were run on the initial submission model (not the update provided to the EAG following clarification questions)	Perform EAG analysis using most current model.	To appropriately reflect the evidence presented and discussion to date.	Not a factual error. The EAG acknowledges that the EAG company's comment regarding Section 5.2, Table 33, and would like to clarify the rationale behind using the original submission model in our analyses. In response to EAG clarification questions (page 22), the company indicated that updates had been made to the model to account for: • A weighting for pre-infusion costs in patients not infused, potentially related to

			brexu-cel (see response to B2), • A correction to the uncertainty estimates around pre- and post-progression utility values (see response to B5), • An updated costing approach for alloSCT, including harvesting and follow-up costs (see response to B14). However, the company also stated in response to B2: *"The original submission is limited to the mITT population; this appraisal is the conclusion of this original submission, therefore there is no change to this."*

			The EAG was unclear whether the company fully supported the change they had made. Only in response to B14 did the company explicitly confirm an update to the base case, related to alloSCT costing. The EAG confirms that its analysis incorporated this updated cost, in alignment with TA893. Despite this, the company did not provide an updated base case that isolated the change to alloSCT costs or other changes, nor did it supply an updated CEAC curve or scenario analyses table reflecting a revised base case. Given these omissions, the EAG retained the original submission model as the

			basis for the EAG changes. Furthermore, incorporating the company's revisions has a small impact on the ICER. Therefore, the EAG considers that the original model remains the relevant version for the analyses presented. The EAG has updated tables 28 and 29 to also include new base case estimates, alongside new text in sections 4.1 and 5.2 to add clarity around the company base case and model changes.

Issue 15 Correction of SLR restrictions and limitations

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 6.4. Minor issue. There is misreporting in the Table EAG modified ROBIS evaluation of the company's SLR, ROBIS domain and signalling, question 2.4, as the previously updated SLR search strategy (referred to in the original submission) reported studies that were published up to January 2020 and the latest search updates (covering 2020 to 2024) picked up from the point where the previous search finished.	Exclude "The SLR update (Nov 2024) searches were restricted to records added to databases from 2020 to 2024. This is not appropriate, given that the original search strategy retrieved studies from 2019 of which some are relevant to the updated SLR criteria (Nov 2024) but excluded based on date. Therefore, any potentially eligible studies missed by the search in Feb 2019 would not have been picked up by this update search" Replace with : "The SLR update (Nov 2024) searches were restricted to records added to databases from 2020 to 2024 which is consistent with an update of the searches reported in the original submission."	To reflect accurate and appropriate updated SLR search dates.	The EAG have amended Section 2.4 of the ROBIS tool and changed the answer to 'probably yes' and made the suggested amendment.

Issue 16 Removal of effects of Allo-SCT on the survival of R-BAC patients was not reflected in the model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Minor issue. The incremental QALYs remained [redacted] after applying EAG assumption 5 (Main board F163).	Revise the formulas in the "Survival parameters" sheet so that the survival parameters used for the model can be updated when the EAG assumption is applied.	Updated survival of R-BAC patients should be applied if the effect of allo-SCT is removed.	Not a factual error. The EAG confirms that both cost and effect changes are reflected in the current base case analysis. However, the EAG would like to clarify that these changes are addressed in separate parts of the model. Specifically, assumption 5 (in the economic model) incorporates the cost impact by adjusting the proportion of patients receiving alloSCT, while the impact on survival is addressed in the population section, where the overall survival of R-BAC patients without alloSCT is applied. To enhance clarity, the EAG has amended the relevant section of the

			report by revising the text “Costs and effects of allo-SCT” to “Proportion receiving alloSCT and associated costs”.
Possible substantial issue. The estimated values of the log sigma (Survival parameters sheet, AE52, AM52) seem incorrect (potentially not log transformed)	Check if the survival parameters (log sigma) in the Excel model were reported correctly.	The log sigma values provided by the EAG ([redacted] for PFS, [redacted] for OS) in the Excel model are much larger than the estimates reported in the company submission, and these values would lead to higher QALYs for the R-BAC arm (rather than lower). It is possible that those parameter values were sigma instead of log sigma and this needs checking.	Not a factual error. The EAG is confident that the modelling is correct, as it has adjusted the relevant formula to account for the lack of log-transformation. This was done for ease of running the EAG’s probabilistic sensitivity analysis

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments (review of TA677): EAG Report [ID6325], section 2.2.6.2.2	Though the OS from the latest ZUMA-2 trial data cutoff has been published, the number of patients who had died (as opposed to censored) is not publicly available.	By the data cutoff, it was observed that [redacted] patients ([redacted]) had died, [redacted] had withdrawn, and [redacted] was lost to follow-up. According to the Kaplan-Meier (KM) estimates, there was a notable decline in survival from [redacted] at 30 months to [redacted] at 63 months. The most recent data indicated a survival rate of [redacted] at 66 months.	The EAG has not currently added the marking as requested to the EAG report, as it notes that this information is presented without confidential marking in the company submission (bottom of page 43), which the EAG has replicated. The information is also reported in this published abstract: https://doi.org/10.1182/blood-2024-198018

EAG information request

EAG information request to NHS England (NHSE) on brexucabtagene autoleucel (was KTE-X19) for treating relapsed or refractory mantle cell lymphoma - TA677 to help address clinical uncertainty raised by the NICE committee.

The dataset produced as part of the data collection agreement for this indication was used to answer the below questions from the company. Questions which couldn't be answered using the produced dataset haven't been answered. Therefore, answers are restricted by the agreed Data Collection Agreement. This dataset includes Blueteq applications and SACT data only.

Questions and answers

EAG – Q1:	Please report how many patients were classified according to sMIPI as low, intermediate, high, and missing.
NHSE response:	SACT does not collect this information.
EAG – Q2:	With respect to the Blueteq system, please confirm if there any NHS-affiliated databases reporting on brexu-cel administration as part of the Cancer Drugs Fund (CDF)? If yes, could you please provide patients' baseline characteristics, safety, and efficacy outcomes?
NHSE response:	None as part of CDF. The Reilly paper is a dataset collected by the CAR T haematologists.
EAG – Q3:	Please could you confirm the extent of overlap of the patient population with that reported by O'Reilly et al. (https://pubmed.ncbi.nlm.nih.gov/38873532/)
NHSE response:	Almost complete: 85 infused in Reilly, 92 in SACT.
EAG – Q4:	Please confirm how many people were leukapheresed out of the n=142 (or 135 after duplicate removal).
NHSE response:	Not known.
EAG – Q5:	Please confirm reasons for n=45 who did not apply for brexu-cel infusion. Please provide breakdown. E.g. manufacturing failure = X, ineligible=X, death=X. Please provide an overview of the reasons for ineligibility.
NHSE response:	Not known, please refer to Reilly.
EAG – Q6:	If possible, please provide a Kaplan Meier plot for Overall Survival from date of leukapheresis, for all leukapheresed patients.

NHSE response:	Not possible as date of leukapheresis is not known, please see Reilly.
EAG – Q7:	If possible, please provide a Kaplan Meier plot for Overall Survival from date of leukapheresis application, for all patients who were approved for leukapheresis.
NHSE response:	Please see Reily.
EAG – Q8:	Please confirm the average duration between leukapheresis CDF application, and leukapheresis administration.
NHSE response:	Not known.
EAG – Q9:	Please confirm the average duration between infusion Blueteq application and infusion administration.
NHSE response:	Due to outliers the mean duration between the Blueteq approval date and the infusion date in SACT is not meaningful. In the majority of cases, both dates are the same. Provided the median time from approval date to infusion. The median duration between the Blueteq approval date and the infusion date in SACT was 0 days.
EAG – Q10:	Please confirm whether the access to brexu-cel is likely to be faster if approved for routine use (rather than managed access via CDF/Blueteq application). If so, what is the likely impact.
NHSE response:	There is no potential for faster access in routine use compared with the CDF.
EAG – Q11:	Please clarify how duplications were noticed at infusion stage, when detecting for duplicates had already been carried out at leukapheresis stage.
NHSE response:	Multiple forms were completed by the trust and deduplicated prior to analysis as per our methodology (described in the final report).
EAG – Q12:	Please provide any information subsequent use of IVIg or allo-SCT after brexu-cel infusion.
NHSE response:	Not known.
EAG – Q13:	Please confirm why 3 infused patients are not in SACT.
NHSE response:	All missing records were followed up by NHSE, but information on three cases were not submitted by the relevant trust/s at the point of the final report being produced.
EAG – Q14:	Please provide details on the bridging therapies for all patients approved, e.g. bottom of Table 5 in current CDF report (rather than just for the infused patients as currently provided).
NHSE response:	SACT collects prior and subsequent treatments, but this was not a requirement in the DCA and therefore not included in the produced

	dataset. Blueteq data items capturing additional information on bridging therapies were included in the DCA.
EAG – Q15:	Please provide any information that will be helpful for estimating pre-infusion costs, relating to leukapheresis, bridging and conditioning therapy stages for the leukapheresed population. (i.e. proportion of people at each stage [out of n=135], the average total costs at each stage [or resources used, drugs used, dosing, duration]).
NHSE response:	Not known.
EAG – Q16:	Please provide a comparison of overall survival (e.g. KM plot) for patients who applied for brexu-cel leukapheresis before vs after August 2022 (ideally n=135 from leukapheresis, but n=92 from infusion would be okay).
NHSE response:	SACT and Blueteq do not capture the date of leucapheresis. Only the infusion date can be confirmed from SACT. This indication is a small cohort, therefore when stratified by time it is unlikely to be meaningful. However, in response to this question it has been calculated (Table 1) although we caution use. The results show no significant difference. Please note that the follow-up period for the two cohorts differs: ≤ August 2022 cohort: the maximum follow-up was 44.2 months; the minimum follow-up was 24.8 months. ≥ September 2022 cohort: the maximum follow-up was 24.8 months; the minimum follow-up was 11.9 months. Median survival amongst patients who received the infusion ≤ August 2022 is 25.7 months. Median survival amongst patients who received the Infusion ≥ September 2022 was not reached. See Table 1 and Figure 1. All patients were traced for their vital status on 25 September 2024 – see addendum in final report.
EAG – Q17:	Please provide details on number of people requiring ICU post-infusion, and their average duration. If possible, please also provide details on other hospitalisation and monitoring post-infusion within the first 100 days.
NHSE response:	Not known.
EAG – Q18:	If possible, please provide a Kaplan Meier plot for time to Next Treatment data.
NHSE response:	Not a requirement in the DCA.

Table 1: Overall survival at 6, 12 and 18-month intervals

Time period	Overall survival (%)					
	Infusion date ≤ August 2022 (N=49)			Infusion date ≥ September 2022 (N=43)		
	(%)	Lower Confidence Interval (LCI)	Upper Confidence Interval (UCI)	(%)	Lower Confidence Interval (LCI)	Upper Confidence Interval (UCI)
6 months	90%	82%	99%	77%	65%	90%
12 months	76%	64%	89%	74%	62%	89%
18 months	59%	47%	75%	69%	57%	85%

Figure 1: Kaplan-Meier survival plot (N=92) – split by infusion date in SACT

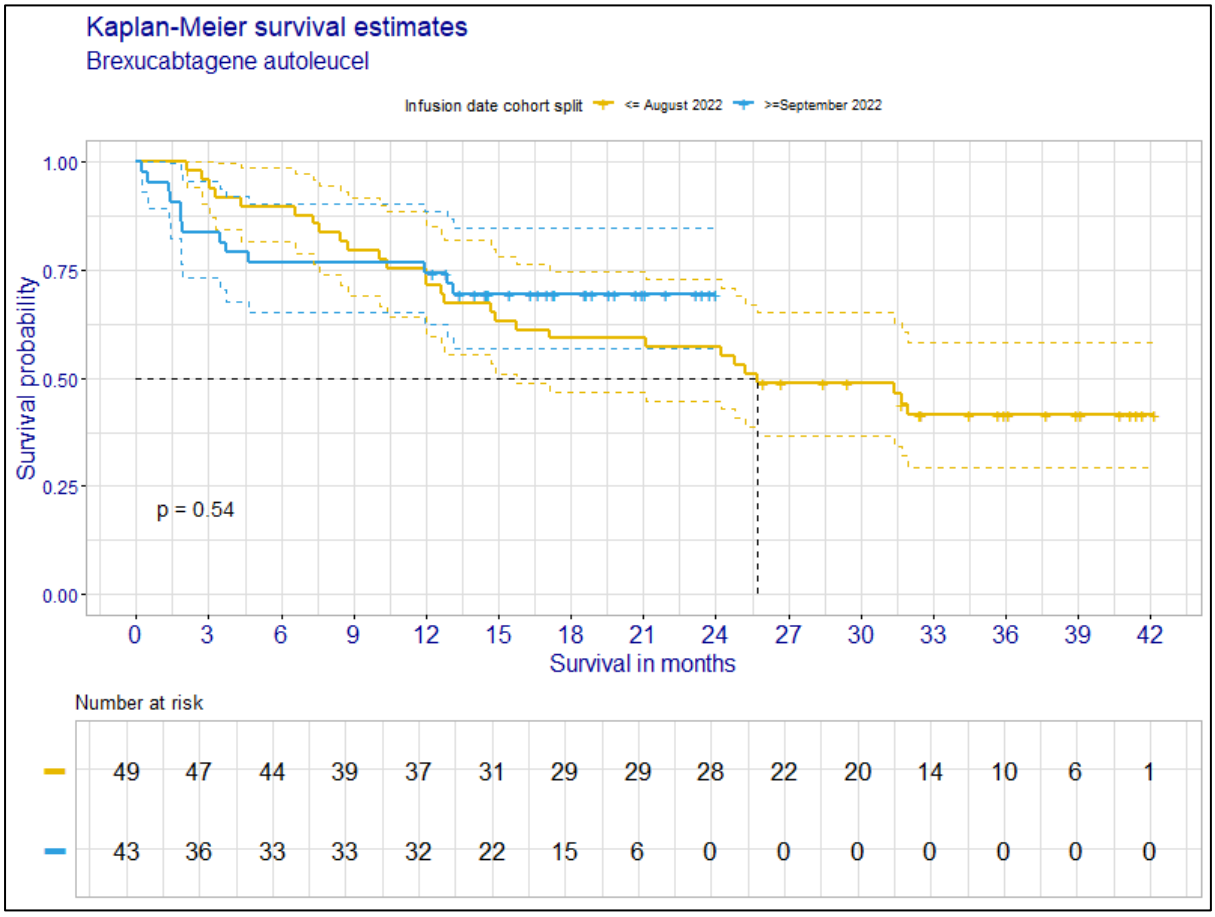

Table 2: Additional questions from EAG

	Brexucabtagene autoleucel infusion captured in SACT N=92
Median age, years (range) Mean age, years (SD)	Median (67.5 years, range 41, 78) Mean (66 years, standard deviation 7.7 years)
Median weight, kg (range) Mean weight, kg (SD)	Not included in the DCA.
Median height, cm (range) Mean height, cm (SD)	Not included in the DCA.
Male, n (%)	71 (77%)
Stage IV disease, n (%)	Stage not captured in SACT
ECOG 0, n (%)	15 (16%)
ECOG 1, n (%)	33 (36%)
ECOG ≥2, n (%)	2 (2%)
ECOG Missing	42 (46%)
Simplified MIPI, n (%) Low risk Intermediate risk High risk Missing	Not captured in SACT
Ki-67 proliferation index, median (range), % ≥ 30% ≥ 50%	Not captured in SACT
TP53 mutation, n/N (%) Unmutated Not available	Not captured in SACT
Bone marrow involvement, n (%)	Not captured in SACT
Splenic involvement	Not captured in SACT
POD24	Not captured in SACT
LDH, n (%) >ULN ≤ULN Not available	Not captured in SACT

Extranodal disease, n (%)	Not captured in SACT
Bulky disease (≥10 cm), n (%)	Not captured in SACT
MCL morphology, n (%) Classical Blastoid Pleomorphic Other/unknown	Not captured in SACT
Median no. of prior therapies (range) ≥ 3 prior therapies, n (%) <3 prior therapies, n (%)	Not included in the DCA.
Prior anthracycline, n (%) Prior bendamustine	Not included in the DCA.
Prior anti-CD20 mAb, n (%)	Not known
Prior auto-SCT, n (%)	25 (27%)
Prior allo-SCT	14 (15%)
Prior BTKi, n (%) Ibrutinib Acalabrutinib	 89 (97%) 1 (1%)
Relapse Refractory	45 (49%) 47 (51%)
BTKi relapsed or refractory disease, n (%) Refractory to BTKi Relapse during BTKi Relapse after BTKi BTKi intolerant	Not captured in SACT
Received specific bridging therapy, n (%)	91%
e.g. Ibrutinib Acalabrutinib Dexamethasone Methylprednisolone	5 (5%)
Ibrutinib plus steroid Acalabrutinib plus steroid (more to be added)	4 (4%)

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS England

Brexucabtagene autoleucel (was KTE-X19) for treating relapsed or refractory mantle cell lymphoma – data review

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

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

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

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

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

National Disease Registration Service
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NHS England

Contents

1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of brexucabtagene autoleucel (was KTE-X19) for treating relapsed or refractory mantle cell lymphoma. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended the commissioning of brexucabtagene autoleucel through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England have evaluated the real-world treatment effectiveness of brexucabtagene autoleucel in the CDF population, during the managed access period. This report presents the results of the use of brexucabtagene autoleucel in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

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

The collection and follow up of real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 97% of patients and 75% of patient outcomes reported in the SACT dataset. NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma in the CDF. Patient NHS numbers were used to link Blueteq applications to NDRS' routinely collected SACT data to provide SACT treatment history.

Between 19 January 2021 and 30 September 2023, 97 applications for brexucabtagene autoleucel were identified in the Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 92 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

92/95 (97%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

At data cut off, outcomes were expected for all 92 patients, having all been identified as receiving the single infusion. Of the 92 patients, 69 had an outcome as completed as prescribed in the SACT dataset.

The median OS was 31.7 months. OS at 6 months was 84% [95% CI: 74%, 90%], 12 months OS was 74% [95% CI: 63%, 82%], OS at 18 months was 60% [95% CI: 47%, 70%], OS at 24 months was 57% [95% CI: 44%, 68%] and OS at 30 months was 51% [95% CI: 37%, 64%].

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

Conclusion

This report analysed SACT real-world data for patients treated with brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma in the CDF. It evaluates OS and treatment outcomes for all patients treated with brexucabtagene autoleucel for this indication.

Introduction

Mantle cell lymphoma (ICD-10: C83.1) accounts for 0.2% of all cancer diagnoses in England. In 2021, 566 patients were diagnosed with Mantle cell lymphoma (males 425, females 141)[2].

Brexucabtagene autoleucel therapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory mantle cell lymphoma in adults who have previously had a Bruton's tyrosine kinase (BTK) inhibitor, only if the conditions in the managed access agreement are followed[3].

2. Background to this report

Using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England's ambitions of monitoring cancer care and outcomes across the patient pathway. NHS England produces routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access using Systemic Anti-Cancer Therapy (SACT) data collected by the National Disease Registration Service (NDRS).

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

NHS England analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NDRS.

NICE Appraisal Committee review of brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma [TA677]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of brexucabtagene autoleucel (Gilead Sciences Ltd) in treating relapsed or refractory mantle cell lymphoma [TA677] and published guidance for this indication in February 2021[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma through the CDF for a period of up to 35 months, from January 2021 to December 2023. The drug will be funded through the CDF until NICE publish their final guidance.

During the CDF funding period, results from a clinical trial (ZUMA-2[7]) evaluating brexucabtagene autoleucel in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the ZUMA-2 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the ZUMA-2 clinical trial[7].

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

- immaturity of progression-free, post-progression and overall survival data
- quality of life experienced by long-term survivors
- age at treatment initiation

NHS England have calculated overall survival, other uncertainties listed above will be included in the ZUMA-2 clinical trial results.

Approach

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

This report includes patients with approved CDF applications for brexucabtagene autoleucel, approved through Blueteq® and followed up in the SACT dataset collected by NDRS in NHS England.

3. Methods

CDF applications – identification of the cohort of interest

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

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

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

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

Brexucabtagene autoleucel clinical treatment criteria

- for leucapheresis and manufacture of CAR-T cells:
    - application for leucapheresis and treatment with brexucabtagene autoleucel - modified CAR-T cells is initiated by a consultant haematologist or medical oncologist specifically trained and accredited in the use of systemic anti-cancer therapy and working in an accredited CAR-T cell treatment centre and who is a member of the National CAR-T Clinical Panel for MCL and a member of the treating trust's MCL and CAR-T cell multidisciplinary teams.
    - Patient has a confirmed histological diagnosis of MCL with documentation of either cyclin D1 overexpression or the presence of the translocation t(11:14) and this diagnosis has been confirmed by a designated lymphoma stem cell transplant centre.
- patient has relapsed or refractory MCL defined by one of the following:
    - Refractory disease is defined as being either progressive disease as the best response to the last line of systemic therapy or stable disease as the best response after at least 2 cycles of the last line of therapy with stable disease duration lasting no longer than 6 months from the last dose of the last line of systemic therapy.
    - Relapsed disease is defined as disease that responded partially or completely to the last line of therapy and has since progressed.
    - Progressive disease must be defined radiologically as per RECIST version 1.1 and be based on CT or MR scans. Progressive disease cannot be defined on just an increased SUV on a PET scan; in such a circumstance, RECIST version 1.1 criteria for progressive disease must be met.
    - Neither radiotherapy nor steroids can be counted as a line of therapy.
- patient has been previously treated for MCL with one of the following cytotoxic chemotherapy regimens: an anthracycline-containing regimen or a bendamustine-containing regimen or a regimen containing high dose cytarabine with or without cisplatin/carboplatin.
- patient has been previously treated with at least one anti-CD20 monoclonal antibody unless there is clear documentation of the determination of CD20 negative disease.
- patient has not had stem cell transplantation (SCT) or has had an autologous or allogeneic SCT.
- patient has been previously treated for MCL with a BTK inhibitor (such as ibrutinib or acalabrutinib) and that the patient progressed either during treatment or following discontinuation of the BTK inhibitor.
- patient has not previously been treated with an anti-CD19 antibody-drug conjugate or if previously treated with an anti-CD19 antibody-drug conjugate that a biopsy of the relapsed/refractory disease has been done and has been shown to be CD19 positive.
- patient does not have known active CNS involvement by the lymphoma.
- patient is aged 18 years or older on the date of approval for brexucabtagene autoleucel by the National MCL CAR-T Clinical Panel.
- patient has an ECOG performance score of 0 or 1.
- patient has sufficient end organ function to tolerate treatment with CAR-T cell therapy.
- patient has either had no previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy or the patient has been treated with doses of genetically modified autologous or allogeneic T cell immunotherapy within an abandoned dosing cohort in a first in human dose-escalation phase I clinical trial.

- prior to infusion of brexucabtagene autoleucel, 4 doses of tocilizumab are available for use in this patient in the event of the development of cytokine release syndrome.
- brexucabtagene autoleucel -modified CAR-T cell therapy is to be otherwise used as set out in its Summary of Product Characteristics (SPC).
- approval for the use of brexucabtagene autoleucel has been formally given by the National MCL CAR-T cell Clinical Panel.
- following national approval for use of brexucabtagene autoleucel there has been local CAR-T cell multidisciplinary team agreement that this patient continues to have the necessary fitness for treatment and fulfils all the treatment criteria listed here.

In addition to the above eligibility criteria, for infusion of CAR-T cell therapy the following must be satisfied:

- patient has an ECOG performance score of 0 or 1 or 2.
- patient has required one of the following bridging therapies in between leucapheresis and CAR-T cell infusion:
    - no bridging therapy at all or
    - corticosteroids only or
    - ibrutinib monotherapy (only for those patients who previously discontinued a BTK inhibitor without disease progression) or
    - chemo(immuno)therapy only or
    - radiotherapy only or
    - corticosteroids and ibrutinib (only for those patients who previously discontinued a BTK inhibitor without disease progression) only or
    - corticosteroids and chemo(immuno)therapy or
    - corticosteroids and radiotherapy or
    - chemo(immuno)therapy and radiotherapy ± corticosteroids.

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

CDF applications - de-duplication criteria

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

1. If two trusts apply for the brexucabtagene autoleucel infusion used to treat relapsed or refractory mantle cell lymphoma for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for the brexucabtagene autoleucel infusion used to treat relapsed or refractory mantle cell lymphoma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for the brexucabtagene autoleucel infusion used to treat relapsed or refractory mantle cell lymphoma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

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

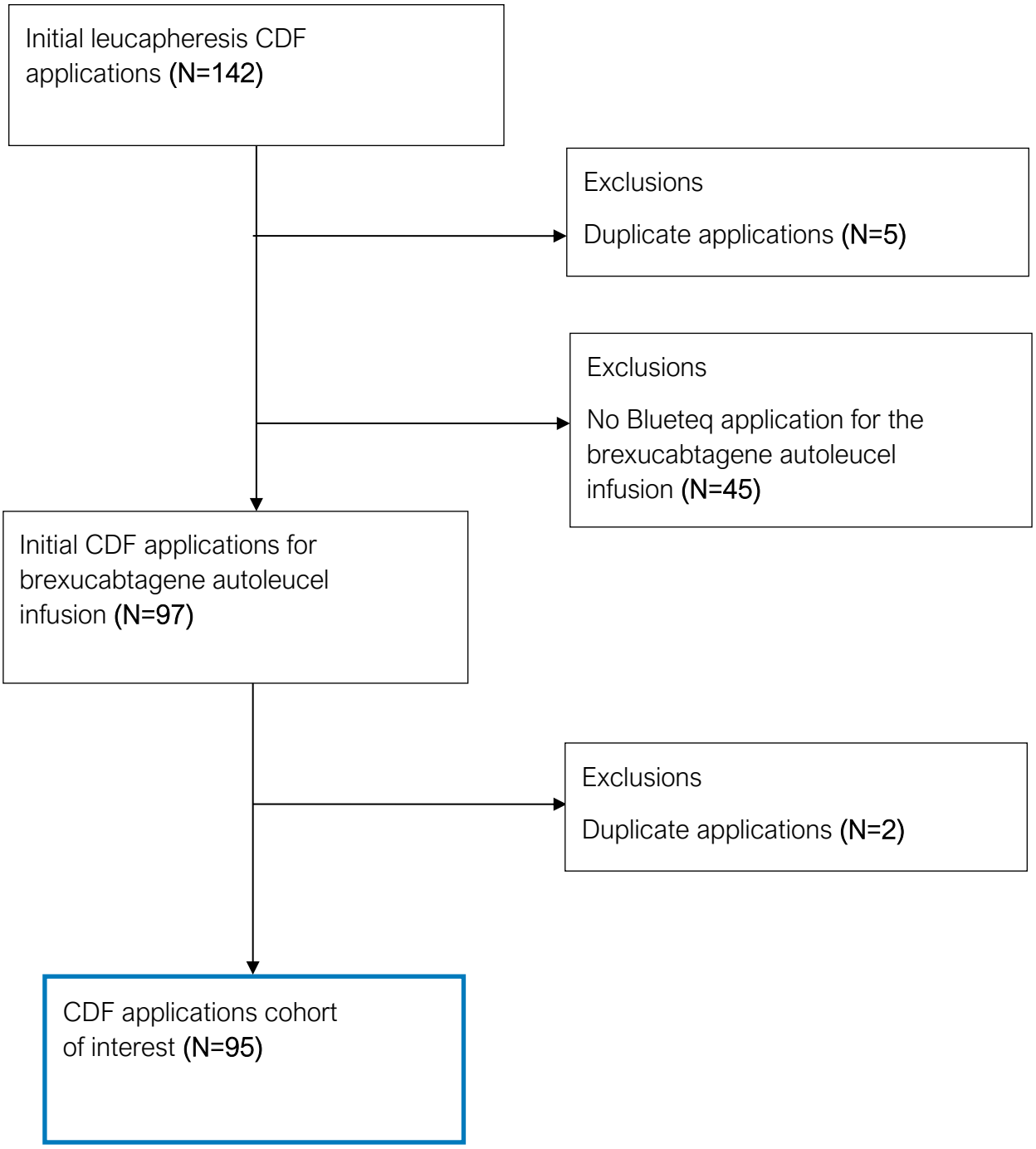
The CDF applications included in these analyses are from 19 January 2021 to 30 September 2023. A snapshot of SACT data was taken on 6 January 2024 and made available for analysis on 15 January 2024 and includes SACT activity up to 30 September 2023. Tracing the patients' vital status was carried out on 12 January 2024 using the Personal Demographics Service (PDS)[1].

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

There were 142 CDF funding applications for leucapheresis between 19 January 2021 and 30 September 2023, relating to 137 unique patients.

There were 97 applications for CDF funding for the brexucabtagene autoleucel infusion, used to treat relapsed or refractory mantle cell lymphoma between 19 January 2021 and 30 September 2023 in the NHS England Blueteq database. This relates to 95 unique patients after the exclusion of two duplicate applications.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for the brexucabtagene autoleucel infusion for treating relapsed or refractory mantle cell lymphoma between 19 January 2021 and 30 September 2023



Linking CDF cohort to SACT

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

Addressing clinical uncertainties

Overall survival (OS)

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

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

Additional explanation of these dates is provided below:

Start date of regimen

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

Start date of cycle

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

Administration date

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

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

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

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

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

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

Lost to follow-up:

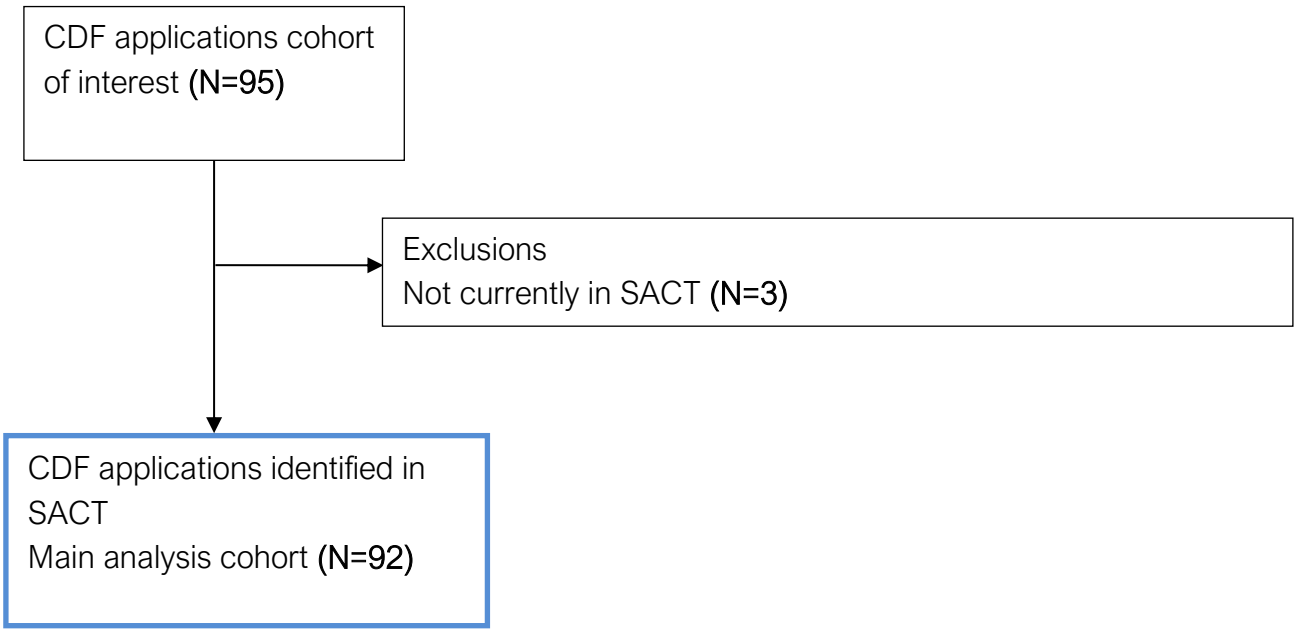
Where we cannot determine whether a patient is alive or not on the censor date; this happens when a patient cannot be successfully traced, for example, because they have emigrated or because important identifiers such as NHS number or date of birth contain errors, the patient's record will be censored at their last known treatment date in SACT. This is the date the patient was last known to be alive.

4. Results

Cohort of interest

Of the 95 applications for CDF funding for the brexucabtagene autoleucel infusion for treating relapsed or refractory mantle cell lymphoma, three patients were missing from the SACT dataset[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for brexucabtagene autoleucel infusion for treating relapsed or refractory mantle cell lymphoma between 19 January 2021 and 30 September 2023



A maximum of 95 brexucabtagene autoleucel infusion records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 97% (92/95) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender, start date of regimen and start date of cycle. Administration is 99% complete and performance status at the start of regimen is 54% complete.

Table 1: Completeness of key SACT data items for the brexucabtagene autoleucel infusion cohort (N=92)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	99%
Performance status at start of regimen	54%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment for this indication. All 92 patients have received a single infusion of brexucabtagene autoleucel and as such, a treatment completed as prescribed outcome is expected. Of the 92 patients that have received the single infusion, 69 have an outcome summary recorded in the SACT dataset 75% (69/92).

Table 2: Completeness of outcome summary for patients that have ended treatment (N=92)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	75%

Completeness of Blueteq key variables

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

Table 3: Completeness of Blueteq key variables (N=92)

Variable	Completeness (%)
Refractory or relapsed MCL	100%
Previously treated for MCL	100%
Stem cell transplant (SCT)	100%
Previously treated for MCL with a BTK inhibitor	100%
Previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy	100%
Bridging therapy in between leucapheresis and CAR-T cell infusion	100%

Patient characteristics

The median age of the 92 patients receiving the brexucabtagene autoleucel infusion for treatment of relapsed or refractory mantle cell lymphoma was 67.5 years. The median age in males and females was 69 and 67 years respectively.

Table 4: Patient characteristics (N=92)

Patient characteristics[b]			
		N	%
Gender	Male	71	77%
	Female	21	23%
Age	<40	0	0%
	40 to 49	3	3%
	50 to 59	16	17%
	60 to 69	39	42%
	70 to 79	34	37%
	80+	0	0%
Performance status at the start of regimen	0	15	16%
	1	33	36%
	2	2	2%
	3	0	0%
	4	0	0%

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

Patient characteristics[b]			
	Missing	42	46%

Blueteq data items

Table 5 shows the distribution of Blueteq data items.

Table 5: Distribution of key Blueteq data items (N=92)

Blueteq data items		N	%
Refractory or relapsed MCL	Has received 2 or more lines of systemic therapy for MCL and was refractory to the last line of systemic therapy	47	51%
	Has received 2 or more lines of systemic therapy for MCL and relapsed after the last line of systemic therapy	45	49%
Previously treated for MCL	Has been previously treated with an anthracycline-containing regimen	56	61%
	Has been previously treated with a bendamustine-containing regimen	17	18%
	Has been previously treated with a high dose cytarabine-containing regimen with or without cisplatin/carboplatin	19	21%
Stem cell transplantation (SCT)	Has not had SCT	53	58%
	Has had autologous SCT	25	27%
	Has had allogeneic SCT	14	15%
Previously treated for MCL with a Bruton's tyrosine kinase (BTK) inhibitor	Has been previously treated with ibrutinib	89	97%
	Has been previously treated with another BTK inhibitor	2	2%
	Has been previously treated with acalabrutinib	1	1%

Blueteq data items		N	%
Previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy	No previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy	91	99%
	Previously treated with doses of genetically modified autologous or allogeneic T cell immunotherapy within an abandoned dosing cohort in a first in human dose-escalation phase I clinical trial	1	1%
Bridging therapy in between leucapheresis and CAR-T cell infusion	Chemo(immuno)therapy only	42	46%
	Corticosteroids and chemo(immuno)therapy	12	13%
	Radiotherapy only	11	12%
	Chemo(immuno)therapy and radiotherapy ± corticosteroids	10	11%
	No bridging therapy at all	8	9%
	Ibrutinib monotherapy (only for those patients who previously discontinued a Bruton's tyrosine kinase (BTK) inhibitor without disease progression)	5	5%
	Corticosteroids and ibrutinib (only for those patients who previously discontinued a BTK inhibitor without disease progression) only	4	4%
	Corticosteroids only	0	0%
	Corticosteroids and radiotherapy	0	0%

Treatment outcomes

Of the 92 patients with CDF applications, all patients have completed treatment after receiving a single infusion of brexucabtagene autoleucel. Of the 92 patients, 35 (38%) patients had died by the end of the follow-up period (12 January 2024).

Table 6: Treatment outcomes for patients that received the brexucabtagene autoleucel infusion for treating relapsed or refractory mantle cell lymphoma (N=92)[c,d,e]

Treatment outcome	Frequency	Percentage
Completed treatment – received single infusion and are still alive	57	62%
Completed treatment – died after single infusion	35	38%
Total	92	100%

[c] Figures may not sum to 100% due to rounding.
[d] Table 6 presents the outcome summary data for patients that have received the brexucabtagene autoleucel infusion for the treatment of relapsed or refractory mantle cell lymphoma.
[e]

Overall survival (OS)

Of the 92 patients with a treatment record in SACT, the minimum follow-up was 3.4 months (103 days) from the last CDF application. Patients were traced for their vital status on 12 January 2024. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time was 11.4 months (346 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

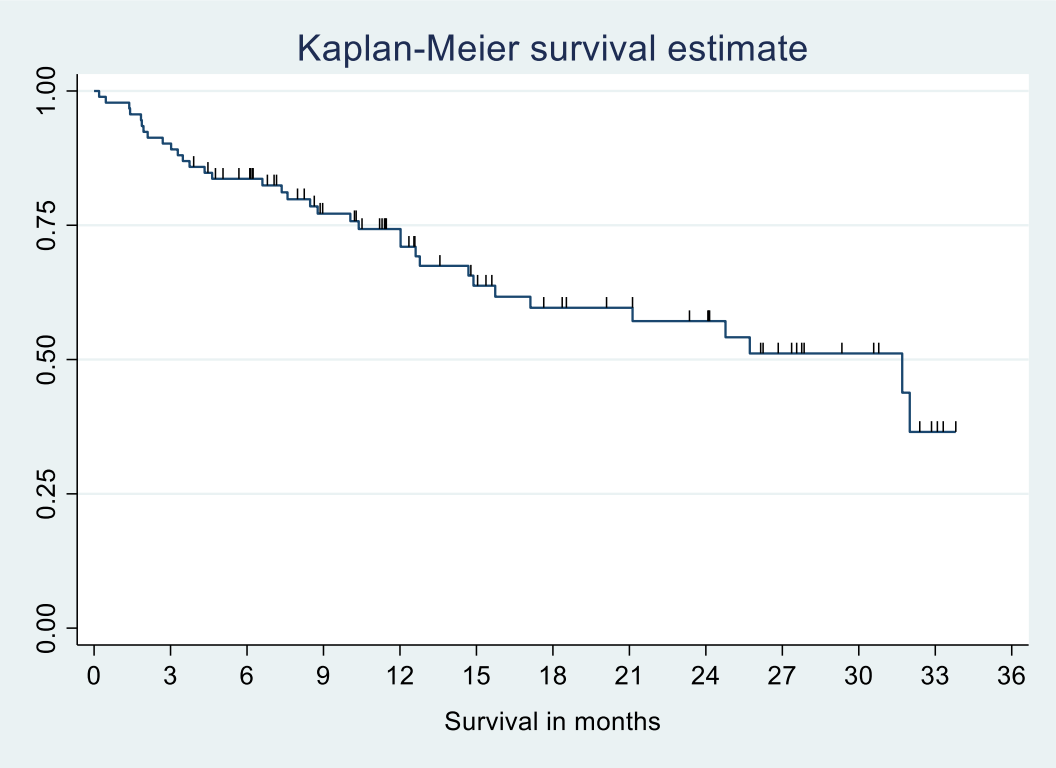
Table 7: OS at 6, 12, 18, 24, and 30-month intervals[f]

Time period	OS (%)
6 months	84% [95% CI: 74%, 90%]
12 months	74% [95% CI: 63%, 82%]
18 months	60% [95% CI: 47%, 70%]
24 months	57% [95% CI: 44%, 68%]
30 months	51% [95% CI: 37%, 64%]

[f] Survival by time interval.

Figure 3 provides the Kaplan-Meier curve for OS, censored at 12 January 2024. The median survival was 31.7 months[g] (964 days)

Figure 3: Kaplan-Meier survival plot (N=92)



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

Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 35.7 months (1,086 days), all patients were traced on 12 January 2024.

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

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Number at risk	92	83	72	55	45	35	28	25	21	14	9	2

Table 9 shows that for all patients who received treatment, 57 were still alive (censored) at the date of follow-up and 35 had died (events).

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

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Censored	57	57	52	40	32	26	23	20	17	12	7	2
Events	35	26	20	15	13	7	5	5	4	2	2	0

Sensitivity analysis
6-months follow up

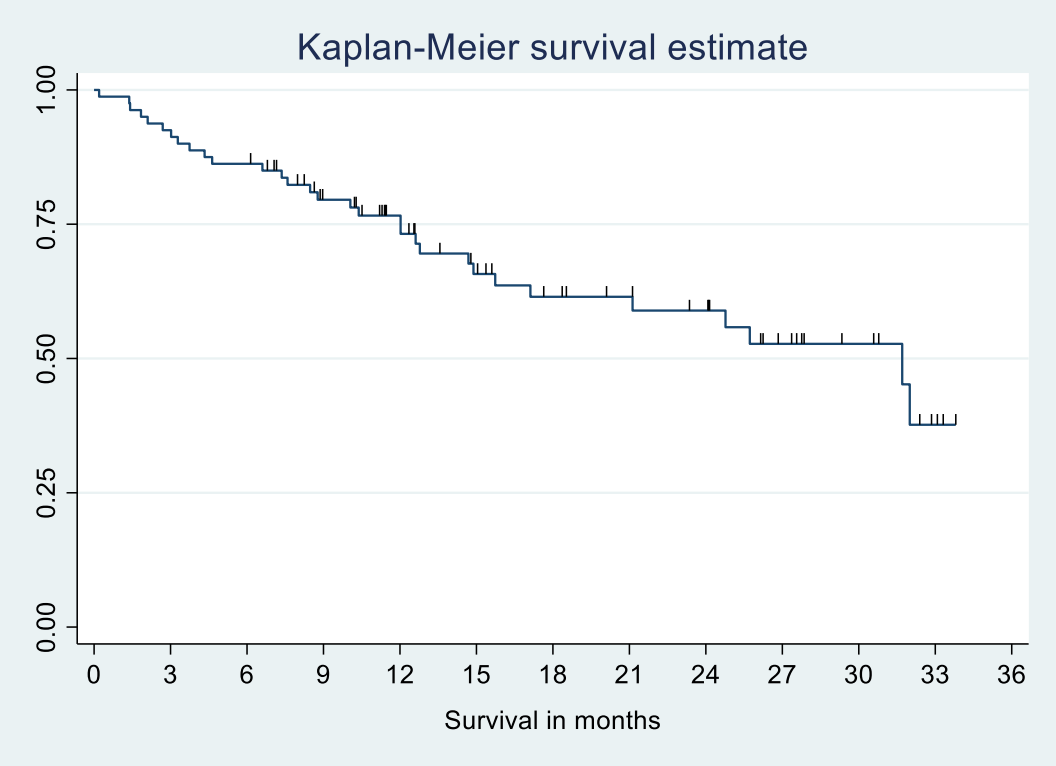
Overall survival (OS)

Sensitivity analyses were also carried out for OS on a cohort with at least six months follow-up. To identify the cohort, CDF applications were limited from 19 January 2021 to 12 July 2023.

Following the exclusions above, 80 patients (87%) were included in these analyses. The median follow-up time was 12.6 months (383 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 12 January 2024. The median survival was 31.7 months[h] (964 days)

Figure 4: Kaplan-Meier survival plot (N=80)



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

Table 10 and Table 11 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 35.7 months (1,086 days), all patients were traced on 12 January 2024.

Table 10: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Number at risk	80	74	69	55	45	33	28	25	21	14	9	2

Table 11 shows that for all patients who received treatment, 49 were still alive (censored) at the date of follow-up and 31 had died (events).

Table 11: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Censored	49	49	49	40	32	26	23	20	17	12	7	3
Events	31	25	20	15	13	7	5	5	4	2	2	0

Table 12: Median OS, full cohort and sensitivity analysis[i]

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort:
N	92	80
OS	31.7 months (964 days)	31.7 months (964 days)

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

5. Conclusions

95 patients received the brexucabtagene autoleucel infusion for the treatment of relapsed or refractory mantle cell [TA677] through the CDF in the reporting period (19 January 2021 and 30 September 2022). 92 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 97%.

Patient characteristics from the SACT dataset show that 77% (N=71) of patients who received brexucabtagene autoleucel infusion for the treatment of relapsed or refractory mantle cell were male, 23% (N=21) of patients were female. Most of the cohort were aged between 60 and 79, 79%, (N=73), and 55% (N=51) of patients had a performance status between 0 and 2 at the start of their regimen.

The median age of the 92 patients was 67.5 years. The median age in males was 69 years and in females the median age was 67 years.

At data cut off, outcomes were expected for all 92 patients, having all been identified as receiving the single infusion. Of the 92 patients, 69 had an outcome as completed as prescribed in the SACT dataset.

The median OS was 31.7 months. OS at 6 months was 84% [95% CI: 74%, 90%], 12 months OS was 74% [95% CI: 63%, 82%], OS at 18 months was 60% [95% CI: 47%, 70%], OS at 24 months was 57% [95% CI: 44%, 68%], and OS at 30 months was 51% [95% CI: 37%, 64%].

Sensitivity analysis was carried out on OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results were consistent with the full analysis cohort.

6. References

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7. Addendum

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma [TA677]

Subsequent to provision of the initial draft of this report to NICE and Gilead Sciences Ltd, NHS England were requested to supply a refresh of OS.

Of the 92 patients with a treatment record in SACT, the minimum follow-up was 11.9 months (362 days) from the last CDF application. Patients were traced for their vital status on 25 September 2024. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time was 17.2 months (522 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

The maximum follow-up period for survival was 44.2 months (1,345 days), all patients were traced on 25 September 2024.

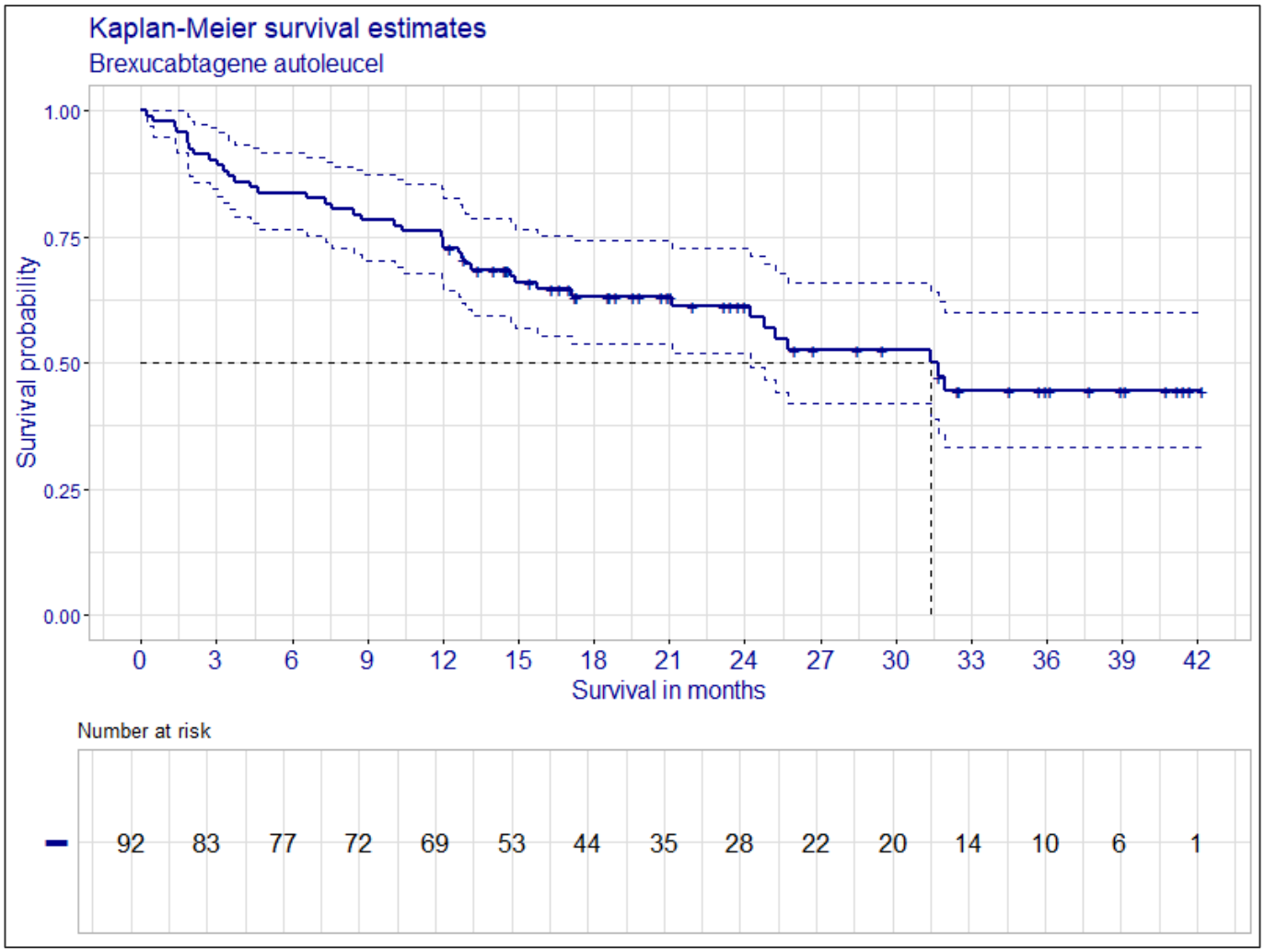
By the end of the follow-up period, 25 September 2024, 41 patients had died, and 51 patients were still alive.

Table 1: OS at 6, 12, 18, 24 and 36-month intervals

Time period	OS (%)
6 months	84% [95% CI: 76%, 92%]
12 months	75% [95% CI: 67%, 84%]
18 months	63% [95% CI: 54%, 74%]
24 months	61% [95% CI: 52%, 73%]
36 months	45% [95% CI: 33%, 60%]

Figure 1 provides the Kaplan-Meier curve for OS, censored at 25 September 2024. The median survival was 31.4 months[10] (955 days)

Figure 1: Kaplan-Meier survival plot (N=92)



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