NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma [ID1313]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma [ID1313]

Contents:
The following documents are made available to consultees and commentators:

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

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

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Lymphoma Action
   b. Royal College of Physicians

4. **Expert personal perspectives** from:
   a. Dr Andrew Davies – clinical expert, nominated by Kite Gilead
   b. Dr Toby Eyre – clinical expert, nominated by Royal College of Physicians
   c. Stephen Scowcroft – patient expert, nominated by Lymphoma Action
   d. Peter English – patient expert, nomination by Lymphoma Action

5. **Evidence Review Group report** prepared by Centre of Reviews and Dissemination, University of York

6. **Evidence Review Group – factual accuracy check**

7. **Final Technical Report**

8. **Technical engagement response from Kite, a Gilead company**
   a. Revised table 1 of company response

9. **Technical engagement responses from experts:**
   a. Dr Toby Eyre – clinical expert, nominated by Royal College of Physicians

10. **Evidence Review Group critique of company response to technical engagement** prepared by Centre of Reviews and Dissemination, University of York
    a. ERG addendum

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

Document B

Company evidence submission

April 2020

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

B.1.1. Decision problem

The submission covers the technology's anticipated full marketing authorisation for this indication, as summarised in Table 1, alongside other aspects of the decision problem to be addressed.

Of note, the draft summary of product characteristics (SmPC) provided in Appendix C describes a broader indication of "adult patients with relapsed or refractory mantle cell lymphoma". Early conversations with the European Medicines Agency (EMA) indicate that the approved marketing authorisation will align to the anticipated wording detailed in Table 1, that is, "adult patients with relapsed or refractory mantle cell lymphoma who have previously received a BTK inhibitor" to better reflect the trial data supporting KTE-X19 in this patient group.

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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 relapsed or refractory mantle cell lymphoma who have received at least two previous lines of therapy	Adult patients with relapsed or refractory mantle cell lymphoma who have previously received a BTK inhibitor	Population description aligned with the anticipated marketing authorisation.
Intervention	KTE-X19	KTE-X19	Not applicable
Comparator(s)	Established clinical management including but not limited to: • Chemotherapy with or without rituximab • Allogeneic haemopoietic stem cell transplant	Established clinical management including but not limited to: • Chemotherapy with or without rituximab	Allogeneic stem cell transplant is not a relevant comparator. It would not be used as an alternative treatment to KTE-X19 for patients who have relapsed or demonstrated refractoriness after receiving a BTKi. Rather, it may be used to consolidate a response to BTKi treatment in a minority of responding patients at second-line. In contrast, KTE-X19 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: BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor.			

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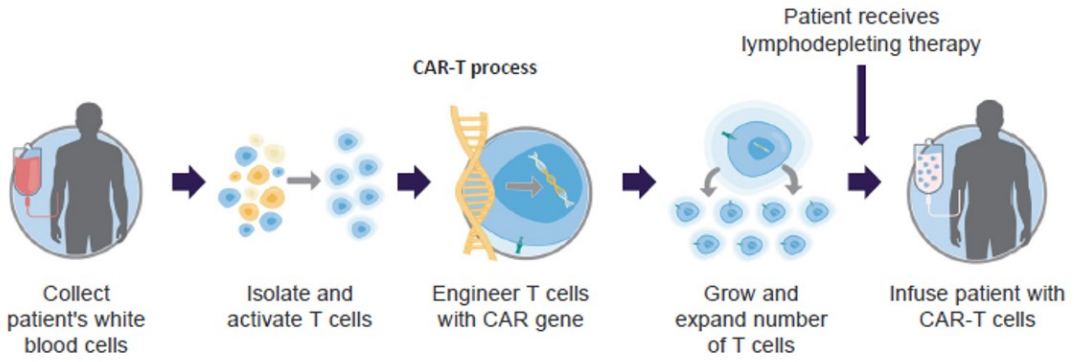
B.1.2. Description of the technology being appraised

KTE-X19 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 mantle cell lymphoma (MCL).[1] KTE-X19 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.

The CAR construct used in KTE-X19 is a single-chain antibody fragment directed against CD19 linked to CD3ζ and CD28 T-cell activating domains. Unique to the production of KTE-X19 compared with axicabtagene ciloleucel (KTE-C19; Yescarta®) 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 internally referenced to as the XLP process (hence the KTE-**X**19 product nomenclature), compared with the **C**LP process of axicabtagene ciloleucel (KTE-**C**19) manufacturing. Table 2 summarises these stages of the manufacturing process. Regulatory authorities (the US Food and Drug Administration [FDA] and the 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 KTE-X19	CLP process for axicabtagene ciloleucel
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.	Peripheral blood mononuclear cells fraction is enriched for mononuclear cells using Ficoll based separation in a closed automated system
T-cell stimulation	Co-stimulation is provided by exogenous anti-CD28 antibody	Co-stimulation is provided by other cell types present in the peripheral blood mononuclear cells fraction

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 KTE-X19 technology. The draft SmPC is provided in Appendix C.

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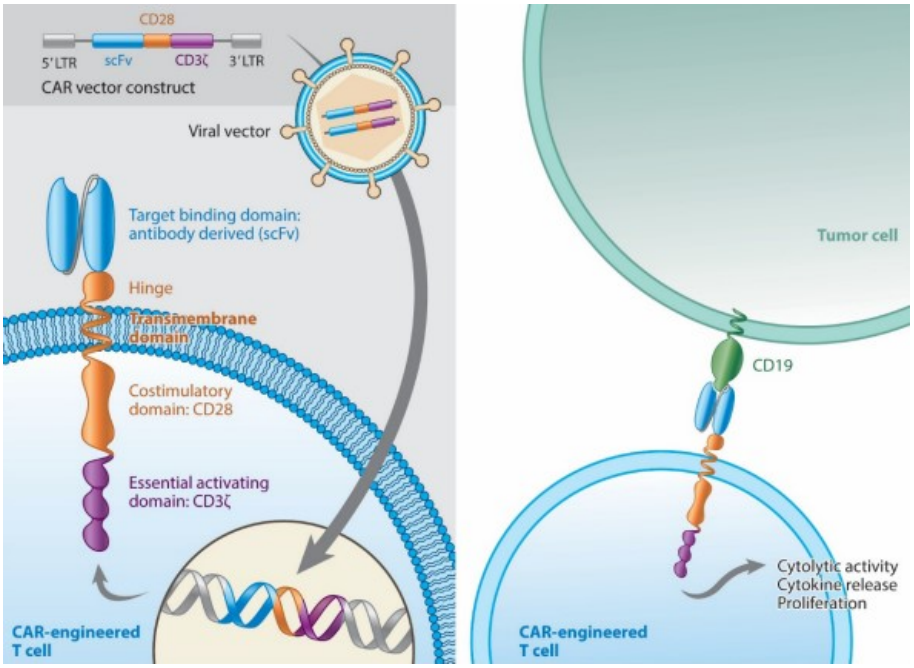
Table 3: Technology being appraised

Approved name	KTE-X19
Mechanism of action	KTE-X19 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 KTE-X19, 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 [redacted] and is currently ongoing. Positive opinion from the CHMP is expected in [redacted] and anticipated regulatory approval is expected [redacted].
Indication	Anticipated marketing authorisation: [redacted]
Method of administration and dosage	KTE-X19 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 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 KTE-X19.
List price and average cost of a course of treatment	List price: [redacted] Average cost of a course of treatment including leukapheresis, bridging therapy, conditioning chemotherapy and administration: [redacted]
Patient access scheme	Not applicable
Key: BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CAR T-cell, chimeric antigen receptor T-cell; CHMP, Committee for Human Medicinal Products; 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. 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] Approximately 560 people are diagnosed with MCL in the UK each year, representing approximately 5% of all people diagnosed with NHL.[14] In the UK population, MCL typically affects older men, with a median age at diagnosis of 72.9 and a male:female ratio of 2.6:1[15]

NHLs are categorised as low or high grade depending on how likely they are to grow and spread; that is, how aggressive the cancer is. MCL is normally classed as a high grade lymphoma in that it is fast growing (although it can also occasionally behave as a low grade lymphoma); as a result, it is often widespread at diagnosis.[16]. 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.[17] Unusually for lymphoma, MCL can also be found in the blood (see Section B.1.2).

Like most cancers, more advanced stage disease is generally associated with worse prognosis, but a more specific assessment of risk tool adopted to estimate prognosis and help guide treatment decisions in MCL is the Mantle Cell Lymphoma International Prognostic Index (MIPI). Table 4 summarises this tool which allows risk to be calculated as low, medium or high based on a computed formula or a simplified score-based index (s-MIPI). Dependent on risk category, 5-year survival estimates 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.[18]

Further prognostic factors in MCL include Ki-67 proliferation index ≥ 50%, blastoid morphology, *TP53* mutation and bulky disease (area of lymphoma over 5cm).[19, 20] 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.[20]

B.1.3.2. Outcomes for relapsed and refractory MCL patients

Unlike more common high-grade NHLs (e.g. DLBCL), MCL is generally incurable with current treatment. Despite good potential for response with early-line treatment regimens, patients inevitably relapse, and with each subsequent treatment line there is worsening prognosis.

A recent report from the Haematological Malignancy Research Network (HMRN) provides data on UK patients diagnosed with MCL between September 2004 and August 2017.[21] 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.[21] Although absolute survival estimates have changed over time with the introduction of novel agents – most notably rituximab at first-line and ibrutinib at second-line – this trend of reduced life expectancy with progressive treatment lines has remained. Similar observations are seen in other real-world evidence sets across Europe and the US.[22, 23]

In a more recent UK real-world analysis of patients receiving ibrutinib at first relapse (n = 169) as per current standard of care treatment in the second-line setting (see Section B.1.3.4), the estimated median survival was 23.9 months.[24] However, the prognosis for patients who have relapsed or are refractory to ibrutinib is extremely poor. In the same real-world analysis, 40% of patients progressed within 1 year of starting ibrutinib treatment and median survival post-ibrutinib was only 3.6 months, with 35.2% of patients dying within 1 month of documented relapse.[24] Although in part this will be a result of patients not being fit enough for further therapy, there have been no novel therapies introduced at later-line settings such that even for those patients who are fit enough, there are no effective treatment options (see Section B.1.3.4). Of the 53 patients surviving beyond 1 month, median survival post-ibrutinib was 7.5 months and 21.9% of patients lived beyond 1 year.[24]

B.1.3.3. Burden of disease

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).[16] Depending on where the lymphoma spreads, other symptoms may include

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loss of appetite, diarrhoea, sickness, anaemia and fatigue.[25] Further additional symptoms relating to extranodal spread can also be observed, dependent on site.

Such physical burden can impact patients' normal daily activity, with functional well-being scores as per the Functional Assessment of Chronic Illness Therapy – General (FACT-G) reduced in the relapsed or refractory (r/r) MCL population compared with general norms.[26-28] A similar trend of reduced scores are seen when comparing reported European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) scores in r/r MCL patients with general norms: global quality of life scores = 61.8 versus 66.1; physical function scores = 78.4 vs 85.1; role function scores = 76.3 vs 84.3; social function scores = 76.3 vs 86.2.[29, 30]

Evidence on the impact of multiple relapses on patient quality of life in MCL is scarce, but it can be expected that a continued reduction in quality of life is observed with each subsequent treatment line, given the worsening prognosis. In follicular lymphoma (FL), a UK cross-sectional study showed patients with relapsed FL had lower physical, emotional, functional and social wellbeing scores as per the Functional Assessment of Chronic Illness Therapy – Lymphoma (FACT-LYM) compared with newly diagnosed, responding or disease-free patients.[31] The mental impact on patient and carer quality of life is likely to be particularly high when effective treatment options have been exhausted. At this time, patients not only face the realisation that treatment has failed but they must prepare themselves and their loved one for the possibility of death.[32] This has been reported in patient and carer surveys with caregivers citing 'stress regarding whether treatment will be successful and fear of the patient dying' as an impact of r/r MCL.[33]

B.1.3.4. Clinical care pathway

Figure 2 depicts the active care pathway for advanced MCL in current practice, according to the British Society for Haematology (BSH) guidelines and the NICE pathway.[34, 35] Not represented in this pathway are patients who present with indolent disease; such patients would be managed with a 'watch and wait' approach until their disease advanced to a stage warranting treatment, at which point they would enter the pathway depicted.[36]

As can be seen from this pathway, treatment options at first-line and first relapse (second-line) are well established. When suitable, patients are treated with a high-dose cytarabine regimen followed by auto-SCT with or without rituximab maintenance.[37] Patients for whom an auto-SCT is unsuitable are generally treated with immunochemotherapy, most commonly one of the following regimens with or without rituximab maintenance:

- 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)

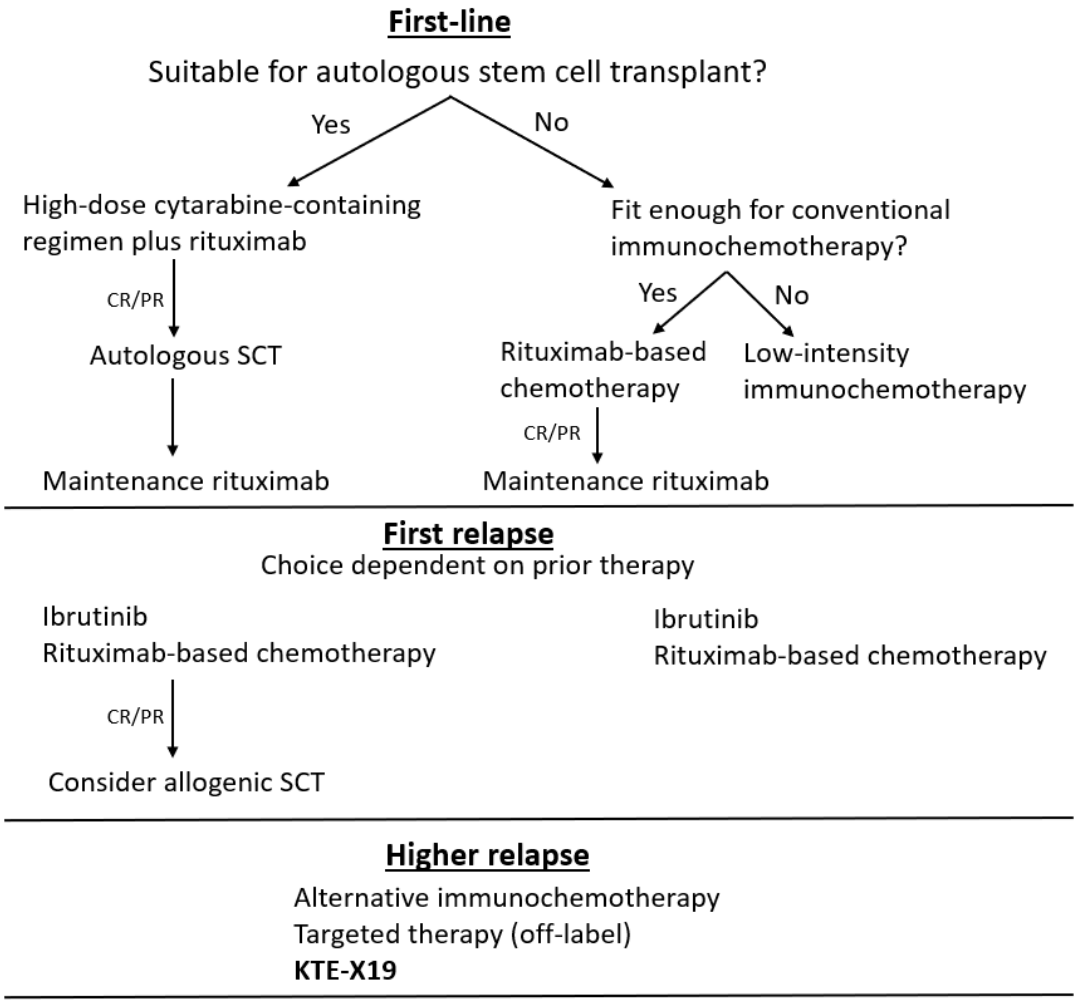
Ibrutinib, a Bruton tyrosine kinase inhibitor (BTKi), provided a major advance in relapse treatment when licensed in 2013 and is the most likely treatment to be used at first relapse (second-line setting), for which it is routinely reimbursed by National Health Service (NHS) England.[36-38] Ibrutinib-induced remission may be consolidated with allogeneic stem cell transplant (allo-SCT) in a minority of patients (those considered young and fit enough for transplant and with a suitably matched cell donor) but only while they are still responding to ibrutinib (outcomes are considerably worse if performed later[39]).[36]

Treatment options at higher relapse (third- and later-line setting) are not well established. An alternative immunochemotherapy to that adopted at first-line could be tried, but responses are almost always inferior at later lines and rapid progression is normally observed.[37] In a recently reported observational study of R-BAC use post-BTKi failure across UK and Italian centres (n=36), most patients responded to treatment (83%), but median progression-free survival (PFS) was only 10.1 months (8.6 months with censoring for transplant) and median overall survival (OS) was 12.5 months.[40] Other observational studies of mixed chemotherapy use post-BTKi failure report response rates ranging from 20% to 48%, and median OS estimates ranging from 6 to 10 months.[41-44] Venetoclax has been suggested as a non-chemotherapy alternative in MCL (despite not being licensed in this indication), but when used after ibrutinib failure, durable response has not been observed.[45] Lenalidomide is also the subject of ongoing research, but early data suggest low response rates (29%) in the post-BTKi setting.[46] For patients who do respond well to third-line

immunochemotherapy, there is the option to consolidate remission with allo-SCT but clinical experts estimate less than 30% of patients treated at third-line receive allo-SCT consolidation in this setting (<15% and <30% estimates provided on consultation).[47] Generally, the aim is to achieve sufficient response with ibrutinib at second-line for allo-SCT consolidation rather than consider such consolidation in the third-line setting.

The proposed positioning of KTE-X19 within the clinical care pathway is as a higher-relapse treatment option (third- or later-line setting) post-ibrutinib, in accordance with the anticipated marketing authorisation. Figure 2 depicts this proposed positioning.

Figure 2: Clinical care pathway of patients for advanced MCL and proposed placement for KTE-X19



Key: BSH, British Society of Haematology; CR, complete response; MCL, mantle cell lymphoma; PR, partial response; SCT, stem cell transplant.
Source: Adapted from the BSH guidelines[34] and NICE pathway for MCL.[35]

B.1.3.5. Summary of unmet medical need

MCL is a rare but aggressive disease that is generally incurable with current treatment. Approximately 560 people are diagnosed with MCL in the UK each year, representing approximately 5% of all people diagnosed with NHL.[14] Despite good potential for response with early-line treatment regimens, patients inevitably relapse, and with each subsequent treatment line there is worsening prognosis. In the UK, the 5-year relative survival from diagnosis of MCL is 41.9%.[15]

There is no true 'standard of care' treatment following BTKi failure. As no therapies have been prospectively assessed in the post-ibrutinib setting (until KTE-X19), there is no single intervention with proven clinical effectiveness, and no recommended standard of care. An individualised approach is instead adopted based on age, co-morbidities, performance status, response and toxicity with prior therapy and patient and physician preferences.[34] Patients are typically treated with an alternative immunochemotherapy to that adopted at first-line but with limited expectation of response and long-term benefit, with patients unlikely to survive beyond a year. Across observational studies of r/r MCL patients who have progressive disease despite receiving BTKi, therapy, median survival estimates are typically less than a year (range: 3.6 to 12.5 months).[24, 40-44]

Adult patients with r/r MCL who have previously received a BTKi clearly represent a patient group with significant unmet medical need in clinical practice. KTE-X19 offers an innovative treatment option with the potential for long-term survivorship to this group that could become established clinical management and thus a true 'standard of care' treatment option if recommended for use.

B.1.4. Equality considerations

No equality issues are foreseen.

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B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to KTE-X19.

B.2.2. List of relevant clinical effectiveness evidence

Table 5 summarises the clinical effectiveness evidence supporting KTE-X19 for the treatment of r/r MCL, which comes from the Phase II ZUMA-2 study.

Table 5: Clinical effectiveness evidence

<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 KTE-X19 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">KTE-X19</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 KTE-X19.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Overall survival
• Progression-free survival
• Response rate
• Adverse effects of treatment
• Health-related quality of life</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Incidence of anti-CD19 CAR antibodies
• Levels of anti-CD19 CAR T-cells in blood
• Levels of cytokines in serum
• Minimal residual disease (post-hoc analysis)</td></tr>
<tr><td colspan="6">Key: BTKi, Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma.
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.</td></tr>
</table>

As ZUMA-2 is a single-arm study, comparator data are sourced from the literature base and subsequent indirect treatment comparison (ITC). These data are detailed in Section B.2.9.

Further comparator data will become available during the appraisal process from (i) Public Health England real-world data from the Systemic Anti-Cancer Therapy (SACT) database, and (ii) an ongoing retrospective chart review that is currently in conduct across Europe (including the UK), but these are not available for inclusion within this primary submission (as an artefact of expedited appraisal timelines in England due to the need for an urgent review of this innovative new therapy).The anticipation is that these data would provide supportive analyses to further validate the base case results presented (see Section B.3.7) but would not change the base case approach.

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

Table 6 provides a summary of the trial methodology for ZUMA-2.

It is important to note that not all patients enrolled to the ZUMA-2 trial received treatment with KTE-X19 at the target dose, although these are the patients informing the anticipated marketing authorisation and for whom ZUMA-2 data are published. Figure 3 provides a summary of patients enrolled and treated across different cohorts and highlights those of relevance to this appraisal and discussed in detail throughout this submission (aligning to ZUMA-2 data publications).

Patients initially enrolled to ZUMA-2 received axicabtagene ciloleucel (Yescarta). This trial arm was closed following the development of the XLE manufacturing process described in Section B.1.2 and all patients subsequently enrolled to ZUMA-2 received KTE-X19. The axicabtagene ciloleucel trial arm is not relevant to this appraisal and is not discussed any further in this submission.

Following early observation of high expansion of CAR-T cells with the initial target dose of KTE-X19 (see Section B.2.4), a second cohort for a reduced dose of KTE-X19 was opened (Cohort 2) and patients enrolled prior and subsequent were designated Cohort 1. The data presented in this submission are for patients from

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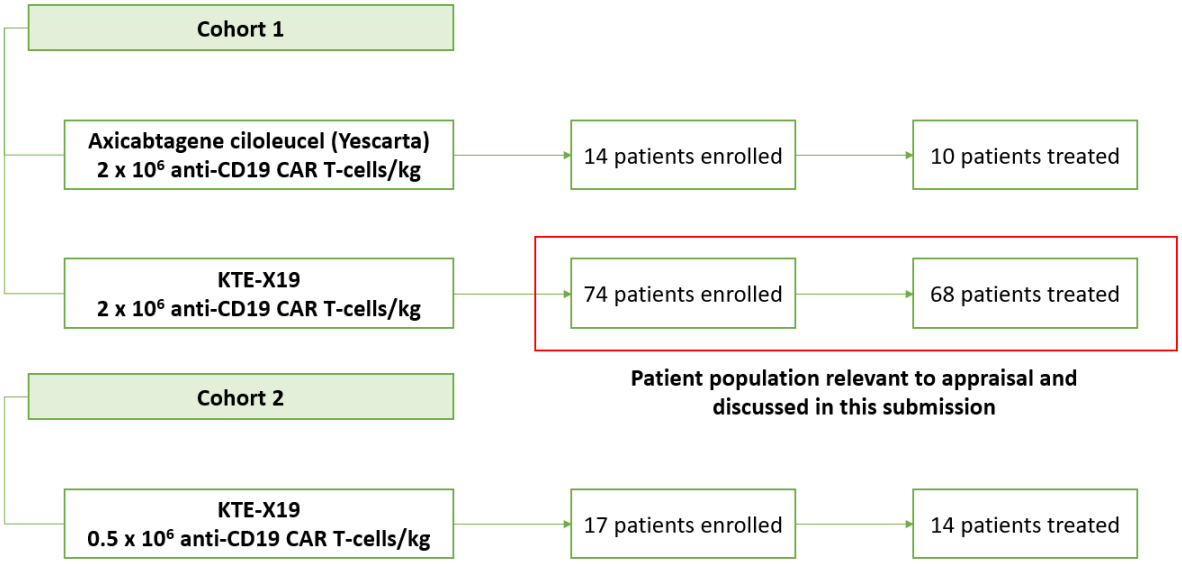
Cohort 1 who received the KTE-X19 product at the licence applied dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight, herein referred to as Cohort 1. Within this cohort, 74 patients were enrolled and for analyses purposes referred to as the Full Analysis Set (FAS); 68 patients were treated and for 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 KTE-X19 in Cohort 1 were to form the basis for statistical hypothesis testing of the primary endpoint and referred to as the inferential analysis set (IAS).

Figure 3: Patient cohorts of ZUMA-2



Key: CAR T-cell, chimeric antigen receptor T-cell.
Source: Adapted from ZUMA-2 CSR[48]

Each patient was to proceed 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. Allowance for retreatment is based on clinical experience reported in two studies conducted at the peadiatric and surgery branch of the National Cancer Institute where six patients in total have been re-treated upon progression. Three of the re-treated patients in these studies (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression.[49, 50]

All patients were to be evaluated for disease response by an Independent Radiology Review Committee (IRRC) per the Internal Working Group (IWG) Lugano Classification[17] (primary endpoint). Response assessments were also to be determined by the site investigators (secondary endpoint). Due to initial patients enrolled to Cohort 1 being assessed by the investigators as per the IWG 2007 Criteria for Malignant Lymphoma[51], and subsequent maintenance of this approach for consistency purposes, investigator-assessed response in Cohort 1 is based on this rather than the Lugano Classification. Other secondary endpoints included additional efficacy analyses (best objective response [BOR], duration of response [DOR], PFS and OS), safety analyses and health-related quality of life (HRQL) outcomes.

Table 6: 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 KTE-X19 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 KTE-X19 infusion • History of allo-SCT • Prior CD19-targeted therapy, with the exception of patients who received KTE-X19 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 KTE-19 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 KTE-X19 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 – Cohort 2 patients were to receive a target dose of 0.5 x 10^6 anti-CD19 CAR T-cells/kg, with a maximum dose of 0.5 x 10^8 anti-CD19 CAR T-cells/kg for patients ≥ 100kg – Patients who achieved a PR or CR had the option to receive a second course of conditioning chemotherapy and KTE-X19 if their disease subsequently progressed > 3 months after the initial KTE-X19 infusion, providing the relapse was confirmed to be CD19-positive • Post-treatment assessment: beginning at Week 2 (± 2 days) and completing at Month 3 (± 1 week) • Long-term follow-up period: beginning at Month 6
Settings and locations where the data were collected	• Patients were to be hospitalised for treatment with KTE-X19 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 KTE-X19-related non-haematological toxicities had returned to Grade ≤ 1 or baseline. Patients were also to remain hospitalised for ongoing KTE-X19-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 KTE-X19 infusion used for bridging therapy • Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after KTE-X19 infusion unless used to manage KTE-X19-related toxicities. Other medications that may interfere with evaluation of KTE-X19 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 KTE-X19 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 KTE-X19 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 used in the economic model/specified in the scope	• 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 for Cohort 1 and Lugano Classification for Cohort 2, 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 KTE-X19 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 KTE-X19 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 • HRQL, 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; allo-SCT, 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; HRQL, 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[48]	

B.2.3.1. Baseline characteristics

Table 7 provides a summary of baseline characteristics, including demographic and clinical characteristics, and bridging therapy needs in Cohort 1. Equivalent data for Cohort 2 are provided in Appendix L.

The populations from KTE-X19 Cohort 1 presented here are:

- **The Full Analysis Set (FAS):** The 74 patients that were enrolled into Cohort 1 with the intention to treat them with KTE-X19 at a dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight

- **The Modified Intent-to-treat (mITT) group:** The 68 patients in Cohort 1 who received KTE-X19 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
- **The Inferential analysis set (IAS):** The first 60 patients in Cohort 1 who were treated with KTE-X19. This analysis set was used for the hypothesis testing of the primary endpoint at the time of the primary analysis. Primary analysis was to be conducted when these 60 patients had the opportunity to be assessed for response 6 months after the Week 4 disease assessment

Across all treated patients (mITT group), 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 KTE-X19, 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.[52]

Table 7: Baseline characteristics of patients in ZUMA-2 (Cohort 1)

	KTE-X19		
	FAS (n = 74)	**mITT (n = 68)**	**IAS (n = 60)**
Median age, years (range)	65 (38-79)	65 (38-79)	[redacted]
Age ≥ 65 years, n (%)	43 (58)	39 (57)	[redacted]
Male, n (%)	62 (84)	57 (84)	[redacted]
Stage IV disease, n (%)	64 (86)	58 (85)	[redacted]
ECOG 0/1, n (%)	74 (100)	68 (100)	[redacted]
Intermediate/high-risk s-MIPI, n (%)	43 (58)	38 (56)	[redacted]
Ki-67 proliferation index at diagnosis, n/N (%)			
≥ 30%	40/49 (82)	40/49 (82)	[redacted]
≥ 50%	34/49 (69)	34/49 (69)	[redacted]

TP53 mutation, n/N (%)	6/36 (17)	6/36 (17)	[redacted]
Bone marrow involvement, n (%)	38 (51)	37 (54)	[redacted]
Extranodal disease[a], n (%)	43 (58)	38 (56)	[redacted]
MCL morphology[b], n (%)			
Classical	40 (54)	40 (59)	[redacted]
Blastoid	19 (26)	17 (25)	[redacted]
Blastoid or Pleomorphic	23 (31)	21 (31)	[redacted]
Other	1 (1)	1 (1)	[redacted]
Median no. of prior therapies (range)[c]	3 (1-5)	3 (1-5)	[redacted]
≥ 3 prior therapies, n (%)	60 (81)	55 (81)	[redacted]
Prior anthracycline or bendamustine, n (%)	73 (99)	67 (99)	[redacted]
Prior anti-CD20 mAb, n (%)	74 (100)	68 (100)	[redacted]
Prior auto-SCT, n (%)	31 (42)	29 (43)	[redacted]
Prior BTKi, n (%)	74 (100)	68 (100)	[redacted]
Ibrutinib	62 (84)	58 (85)	[redacted]
Acalabrutinib	18 (24)	16 (24)	[redacted]
Both	6 (8)	6 (9)	[redacted]
Relapsed or refractory disease, n (%)	74 (100)	68 (100)	[redacted]
Relapse after auto-SCT	31 (42)	29 (43)	[redacted]
Refractory to most recent prior therapy	29 (39)	27 (40)	[redacted]
Relapse after most recent prior therapy	14 (19)	12 (18)	[redacted]
BTKi relapsed or refractory disease, n (%)	74 (100)	68 (100)	[redacted]
Refractory to BTKi	46 (62)	42 (62)	[redacted]
Relapse during BTKi	20 (27)	18 (26)	[redacted]
Relapse after BTKi	5 (7)	5 (7)	[redacted]
BTKi intolerant[d]	3 (4)	3 (4)	[redacted]
Received bridging therapy, n (%)	[redacted]	25 (37)	[redacted]
Ibrutinib	[redacted]	14 (21)	[redacted]
Acalabrutinib	[redacted]	5 (7)	[redacted]
Dexamethasone	[redacted]	12 (18)	[redacted]
Methylprednisolone	[redacted]	2 (3)	[redacted]
Ibrutinib plus steroid	[redacted]	4 (6)	[redacted]
Acalabrutinib plus steroid	[redacted]	2 (3)	[redacted]

Key: auto-SCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IAS, inferential analysis set; 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[48]; Wang et al. 2020.[4]

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

Table 8 provides a summary of the statistical analysis and definitions of analysis sets in ZUMA-2.

The study was to evaluate two doses of KTE-X19. Cohort 1 was to include at least 60 and up to approximately 80 patients treated with KTE-X19; 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[53], Kite, a Gilead company added Cohort 2 to ZUMA-2 to evaluate the safety and efficacy of a 4-fold lower dose of KTE-X19. 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 KTE-X19 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 KTE-X19 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-

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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 KTE-X19 and had the opportunity to be assessed for response 6 months after the Week 4 disease assessment. Analysis sets relevant to KTE-X19 cohorts are detailed in Table 8; the analysis set used for hypothesis testing was the IAS that included the first 60 patients in Cohort 1 who were treated with KTE-X19. 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 8. 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.[44, 54] 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[55]). Full details of this meta-analysis and the studies included are provided in Section B.2.9.

Table 8: Summary of statistical analyses for ZUMA-2

Hypothesis objective	The ORR to KTE-X19 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.

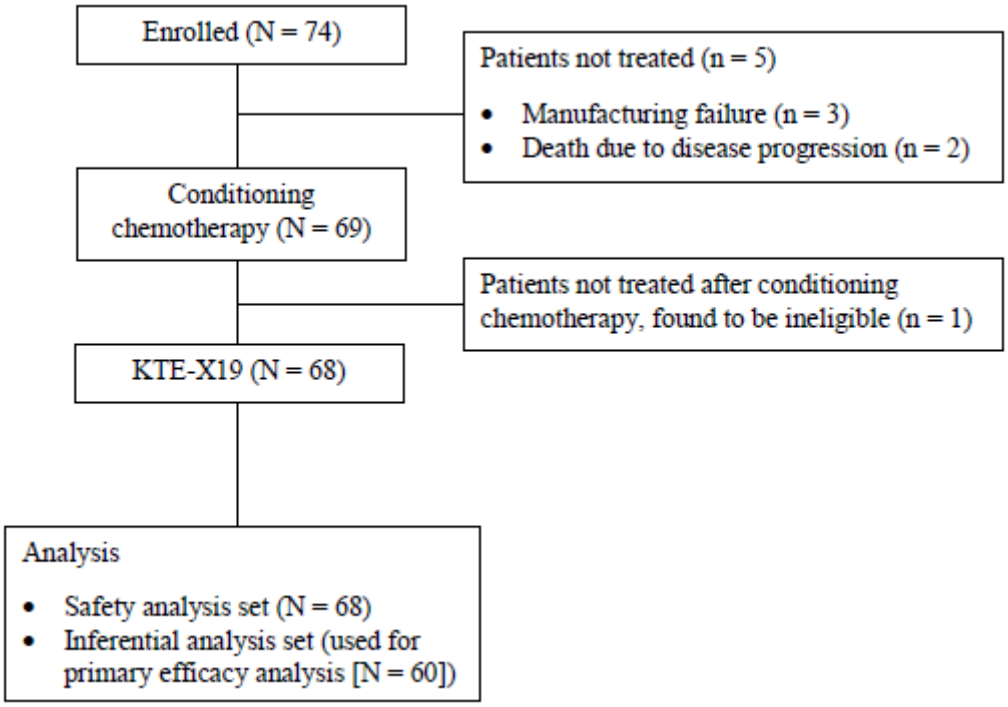
	Wilson's method, the Agresti–Coull method and the modified Jeffrey's method were used in sensitivity analyses. Time-to-event estimates were calculated using the Kaplan–Meier approach and KM plots, estimates and 2-sided 95% CIs generated. Proportion of patients alive and proportion of patients alive and 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 **KTE-X19 Cohort 1:** FAS: all patients enrolled with the intention to treat with KTE-X19 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 KTE-X19 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 KTE-X19 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 KTE-X19 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; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant. **Source:** ZUMA-2 CSR.[48]	

B.2.4.1. Patient disposition data

Figure 4 provides a summary of patient disposition data for Cohort 1. KTE-X19 was successfully manufactured for 71 patients leukapheresed (96%) and administered to 68 patients (92%). Of the three patients for whom KTE-X19 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 KTE-X19 to the study site was 16 days (range: [redacted] days); the median time from leukapheresis to administration of KTE-X19 to the patient was [redacted] days (range: [redacted] days).[4, 48] Two patients who had successful manufacturing of KTE-X19 died from progressive disease before receipt of conditioning chemotherapy (Figure 4). After the receipt of conditioning chemotherapy, one patient with ongoing atrial fibrillation was deemed to be ineligible for KTE-X19 infusion.[4]

Figure 4: Patient disposition data for Cohort 1 of ZUMA-2 (KTE-X19)



Source: Wang et al. 2020.[4]

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

Quality assessment of ZUMA-2 was conducted using the Downs and Black checklist, full details of which are provided in Appendix D.

Within the context of a single-arm study design, the overall risk of bias in ZUMA-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). The single-arm design does however necessitate a need for ITC to provide relative effect estimates required for decision making that is associated with higher uncertainty than a controlled trial would stipulate. This is further discussed in Section B.2.9. In terms of intervention, patients treated with KTE-X19 in Cohort 1 reflect the administration and dosing practice of KTE-X19 expected in clinical practice, and that of the anticipated 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 KTE-X19, 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). This is further discussed in Section B.2.13.

B.2.6. Clinical effectiveness results of the relevant trials

KTE-X19 cohorts and analysis sets for which data are presented are summarised in Table 9.

Table 9: Summary of data available across KTE-X19 cohorts and analysis sets

Cohort	Analysis set	n	Data available	Submission location
Cohort 1	IAS	60	Efficacy	Section B.2.6
Cohort 1	mITT	68	Efficacy	Section B.2.6
Cohort 1	FAS	74	Efficacy	Appendix L
Cohort 1	mITT	68	HRQL	Section B.2.6
Cohort 2	mITT	14	Efficacy	Appendix L

Key: FAS, full analysis set; HRQL, health-related quality of life; IAS, inferential analysis set; mITT, modified intent-to-treat.
Notes: FAS includes all patients enrolled to the KTE-X19 phase of the study; IAS includes the first 60 patients in Cohort 1 who were treated with KTE-X19; mITT includes all patients treated with KTE-X19 and can be applied to Cohort 1 that provides data for KTE-X19 at a target dose of 2 x 10^6 CAR T-cells/kg body weight as per the anticipated marketing authorisation or Cohort 2 that provides data for KTE-X19 at a target dose of 0.5 x 10^6 CAR T-cells/kg body weight.

The populations from Cohort 1 for which data are presented throughout the rest of this section are:

- **The Inferential analysis set (IAS):** The first 60 patients in Cohort 1 who were treated with KTE-X19. This analysis set was used for the hypothesis testing of the primary endpoint at the time of the primary analysis. Primary analysis was to be conducted when these 60 patients had the opportunity to be assessed for response 6 months after the Week 4 disease assessment
- **The Modified Intent-to-treat (mITT) group:** The 68 patients in Cohort 1 who received KTE-X19 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

Primary analyses are based on a data cut-off date of 24 July 2019. At this time, the median follow-up among the patients in the primary efficacy analysis set (IAS) was 12.3 months (range: 7.0–32.3 months), but the first 28 patients treated (47%) had at least 24 months follow-up with a median follow-up of 27.0 months (range: 25.3–32.3).[4] The median follow-up among the patients in the mITT group was [redacted] months (range: [redacted] months).[48]

B.2.6.1. Response and duration of response

Table 10 summarises response data for both the IAS and the mITT group.

Table 10: Summary of response using central assessment (IRRC) per IWG Lugano classification (Cohort 1)

	KTE-X19	
	mITT (n = 68)	**IAS (n = 60)**
Objective response rate (CR + PR), n (%) [95% CI]	[redacted]	56 (93) [redacted]
p-value vs historical control rate	[redacted]	[redacted]
Best objective response		
Complete response rate, n (%) [95% CI]	[redacted]	40 (67) [redacted]
Partial response, n (%) [95% CI]	[redacted]	16 (27) [redacted]

	KTE-X19	
	mITT (n = 68)	**IAS (n = 60)**
Stable disease, n (%) [95% CI]	[redacted] [redacted]	2 (3) [redacted]
Progressive disease, n (%) [95% CI]	[redacted] [redacted]	2 (3) [redacted]
Time to response		
Median time to response, months (range) Initial response Complete response	 [redacted] [redacted]	 1.0 (0.8–3.1) 3.0 (0.9–9.3)

Key: CI, confidence interval; CR, complete response; CSR, clinical study report; IAS, inferential analysis set; IRRC, Independent Radiology Review Committee; IWG, International Working Group; mITT, modified intent-to-treat; ORR, objective response rate; PR, partial response.
Notes: CIs are reported as per the Clopper–Pearson method used for primary analyses.
Source: Wang et al. 2020[4]; ZUMA-2 CSR[48, 56]

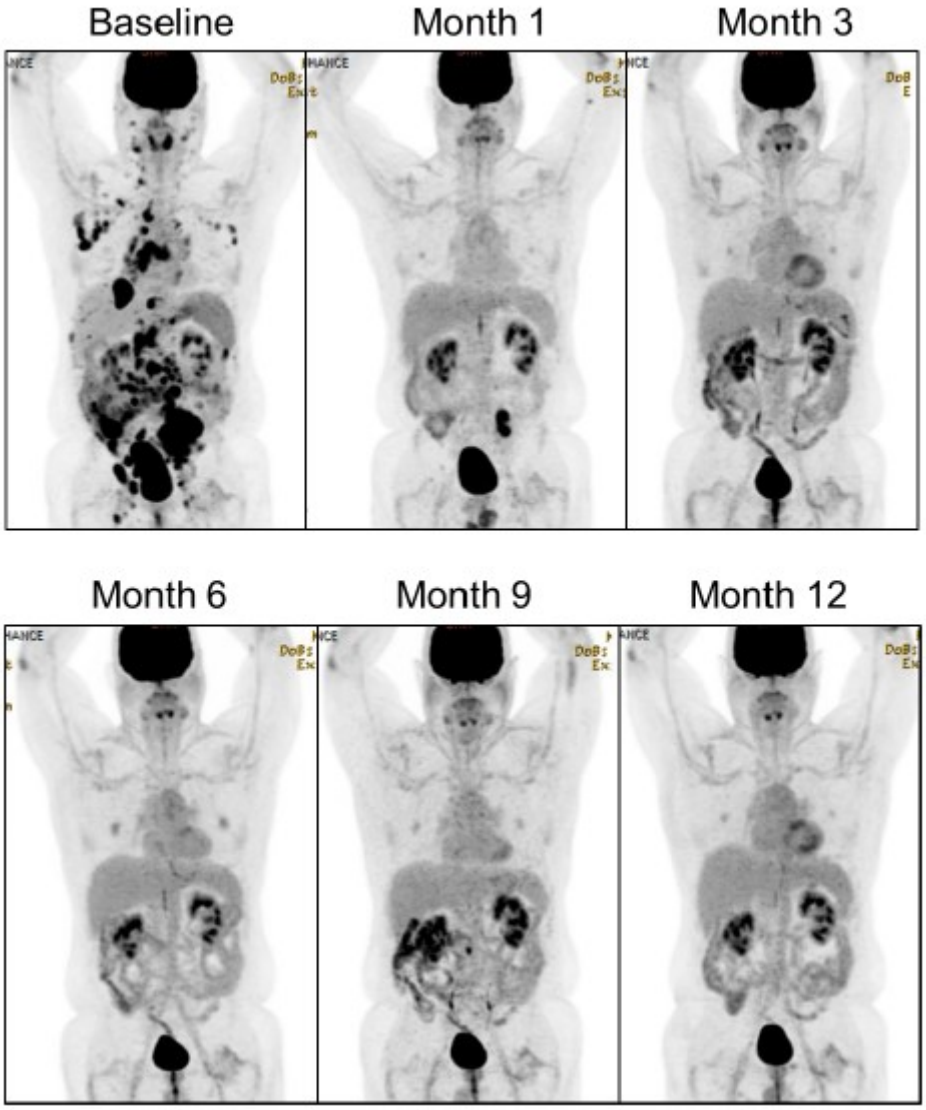
B.2.6.1.1. Inferential analysis set

The ORR using central assessment (IRRC) per Lugano classification (primary endpoint) was 93%, with a complete response (CR) rate of 67%.[4] The ORR was significantly higher than the prespecified historical control rate (25%) at a 1-sided alpha level of 0.025 (p [redacted]) and thus the primary endpoint of ZUMA-2 was met.[48]

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, 24 (57%), including 21 with an initial PR and 3 with stable disease, subsequently had a CR.[4] The median percentage change in SPD, representative of change in tumour burden from baseline at Month 12 was [redacted]%.[48]

Figure 5 presents representative positron emission tomography (PET) scans of a patient presenting with multi-compartmental MCL who achieved PR at Month 1 and CR at Month 3 and remains in remission 18 months later.

Figure 5: Representative PET scans of complete response



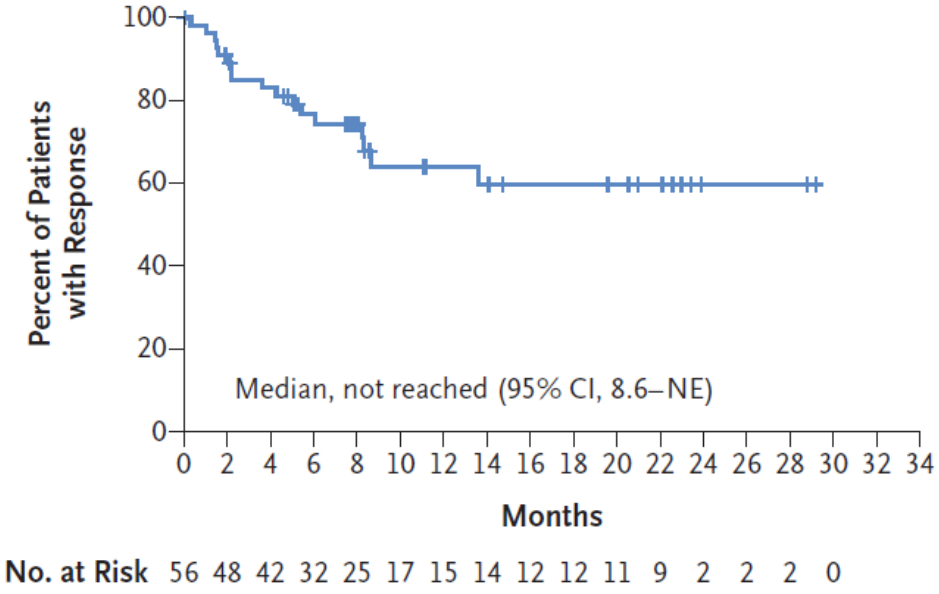
Key: PET, positron emission tomography.
Source: Wang et al. 2020.[4]

The ORR using investigator assessment per IWG 2007 Criteria for Malignant Lymphoma (secondary endpoint) was 88%, with a CR rate of 70%.[4] High concordance was observed between response rates determined through central assessment (IRRC) and those determined through investigator assessment (95%; kappa coefficient 0.7).[4]

Figure 6 shows the median DOR has not been reached after a median follow-up of [redacted] months (95% CI: [redacted]) using central assessment (IRRC) per the Lugano

classification (secondary endpoint); the estimated proportion of patients with durable response of at least 12 months is [redacted]%.[48] Of patients with ≥ 24 months follow-up at the time of analysis, almost half of responding patients ([redacted]%) remain in response; the longest observed DOR to date is [redacted] months.[48]

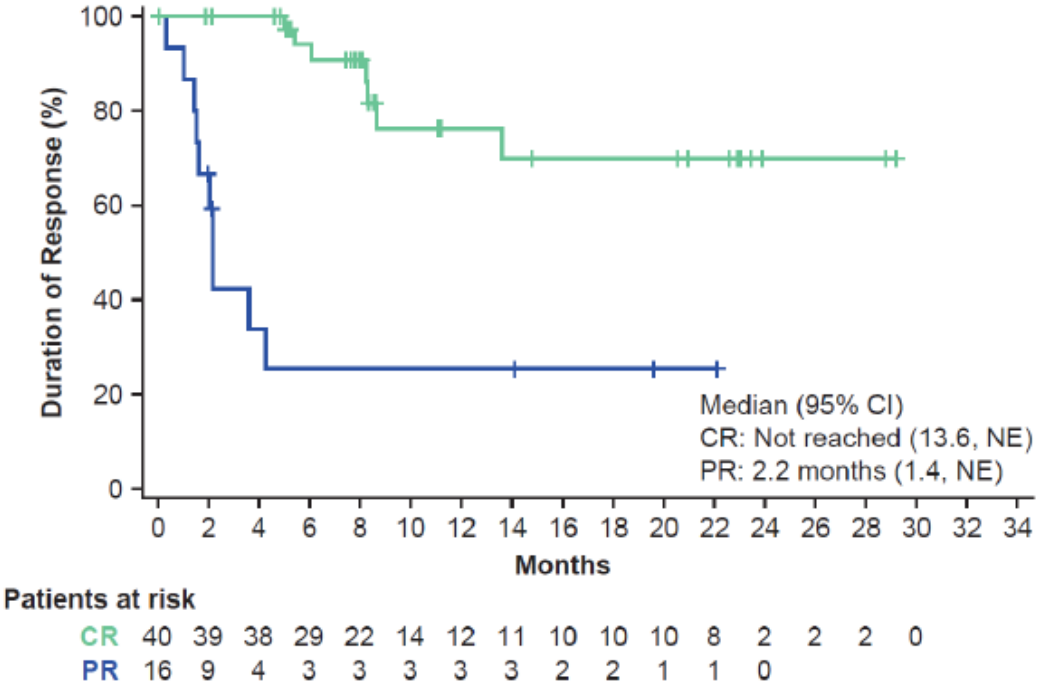
Figure 6: Duration of response using central assessment (IRRC) per IWG Lugano classification (inferential analysis set)



Key: CI, confidence interval; IRRC, Independent Radiology Review Committee.
Source: Wang et al. 2020.[4]

At the time of primary analysis providing a maximum follow-up of [redacted] months in patients who had a response (n=56), 61% of responding patients and 78% of patients with a CR are in remission.[4] Figure 7 shows the DOR based on response type (PR vs CR), and shows a substantial extension in DOR for patients experiencing a CR to KTE-X19 treatment (compared to patients experiencing a PR).

Figure 7: Duration of response by type of response (PR vs CR) using central assessment (IRRC) per Lugano classification (inferential analysis set)



Key: CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; NE, not estimable.
Source: Wang et al. 2020 (supplementary appendix).[4]

B.2.6.1.2. Modified intent-to-treat group

The ORR using central assessment (IRRC) per Lugano classification (primary endpoint) was [redacted]%, with a complete response (CR) rate of [redacted]%.[56] The ORR was significantly higher than the prespecified historical control rate (25%) at a 1-sided alpha level of 0.025 (p [redacted]). Among [redacted] patients who initially had a PR or stable disease, [redacted] ([redacted]%) subsequently had a CR.

The ORR using investigator assessment per IWG 2007 Criteria for Malignant Lymphoma (secondary endpoint) was [redacted]%, with a CR rate of [redacted]%.[56] High concordance was observed between response rates determined through central assessment (IRRC) and those determined through investigator assessment ([redacted]%).

Figure 8 shows the median DOR has not been reached after a median follow-up of [redacted] months (95% CI: [redacted]) using central assessment (IRRC) per the Lugano

classification (secondary endpoint); the estimated proportion of patients with durable response of at least 12 months is [redacted]%.[56]

Figure 8: Duration of response using central assessment (IRRC) per IWG Lugano classification (Cohort 1; modified intent-to-treat group)

[redacted]

Key: CI, confidence interval; CSR, Clinical Study Report; IRRC, IRRC, Independent Radiology Review Committee; NE, not estimable.
Source: ZUMA-2 CSR.[56]

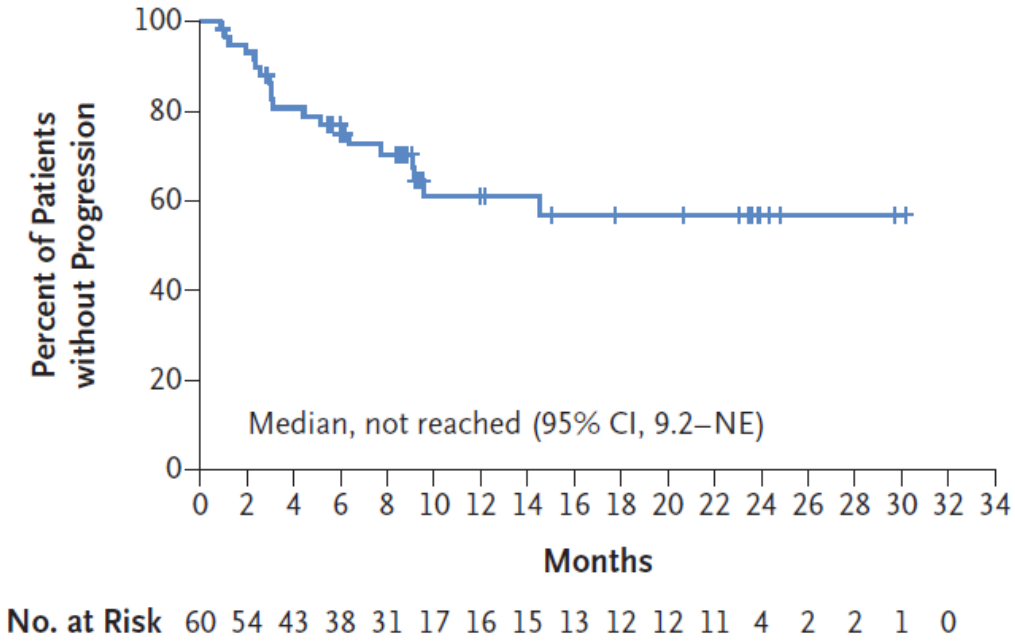
B.2.6.2. Progression-free survival

B.2.6.2.1. Inferential analysis set

Figure 9 shows that the median PFS has not been reached after a median follow-up of 12.3 months using central assessment (IRRC) per Lugano classification (secondary endpoint).

At the time of primary analysis providing a maximum follow-up of 32.3 months, [redacted] patients ([redacted]%) had progressed or died; the estimated 12-month PFS rate was 61% and the estimated 24-month PFS rate was [redacted]%.[4, 48] Among patients who achieved a CR, the estimated 12-month PFS rate was [redacted]%; among those who achieved a PR, the estimated 12-month PFS rate was [redacted]%.[48]

Figure 9: Progression-free survival using central assessment (IRRC) per IWG Lugano classification (inferential analysis set)



Key: CI, confidence interval; IRRC, Independent Radiology Review Committee; PFS, progression-free survival.
Source: Wang et al. 2020.[4]

B.2.6.2.2. Modified intent-to-treat group

Figure 10 shows that the median PFS has not been reached after a median follow-up of [redacted] months using central assessment (IRRC) per Lugano classification (secondary endpoint).

At the time of primary analysis providing a maximum follow-up of [redacted] months, [redacted] patients ([redacted]%) had progressed or died; the estimated 12-month PFS rate was [redacted]% and the estimated 24-month PFS rate was [redacted]%.[56] Among patients who had a response (n = [redacted]), progressive disease developed in 14.[4, 56]

Figure 10: Progression-free survival using central assessment (IRRC) per IWG Lugano classification (Cohort 1; modified intent-to-treat group)

Key: CI, confidence interval; CSR, Clinical Study Report; IRRC, Independent Radiology Review Committee; NE, not estimable.
Source: ZUMA-2 CSR.[56]

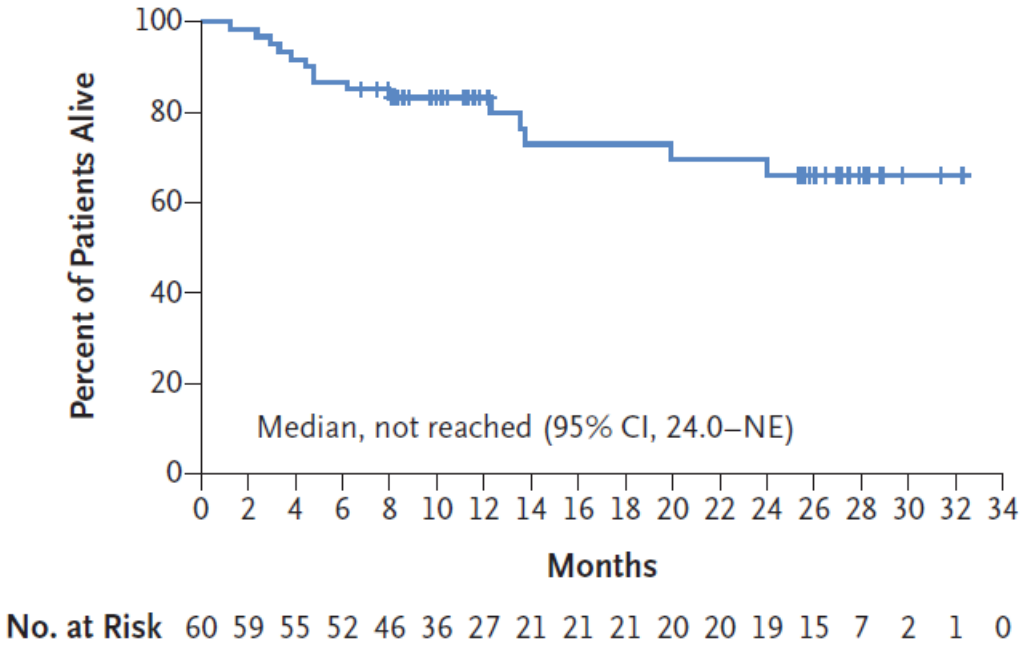
B.2.6.3. Overall survival

B.2.6.3.1. Inferential analysis set

Figure 11 shows that the median OS has not been reached after a median follow-up of 12.3 months (secondary endpoint). At the time of primary analysis providing a maximum follow-up of 32.3 months, [redacted] patients ([redacted]%) had died; the estimated 12-month OS rate was 83%, and the estimated 24-month OS rate was [redacted]%.[4, 48]

An additional analysis of OS for patients with ≥ 24 months follow-up at the time of the primary analysis (n = 28) demonstrated a 24-month OS rate of [redacted]% ([redacted]/28 patients alive).[48] The median OS was [redacted] despite this follow up of at least 2 years, and the longest observed survival to date is [redacted] months.

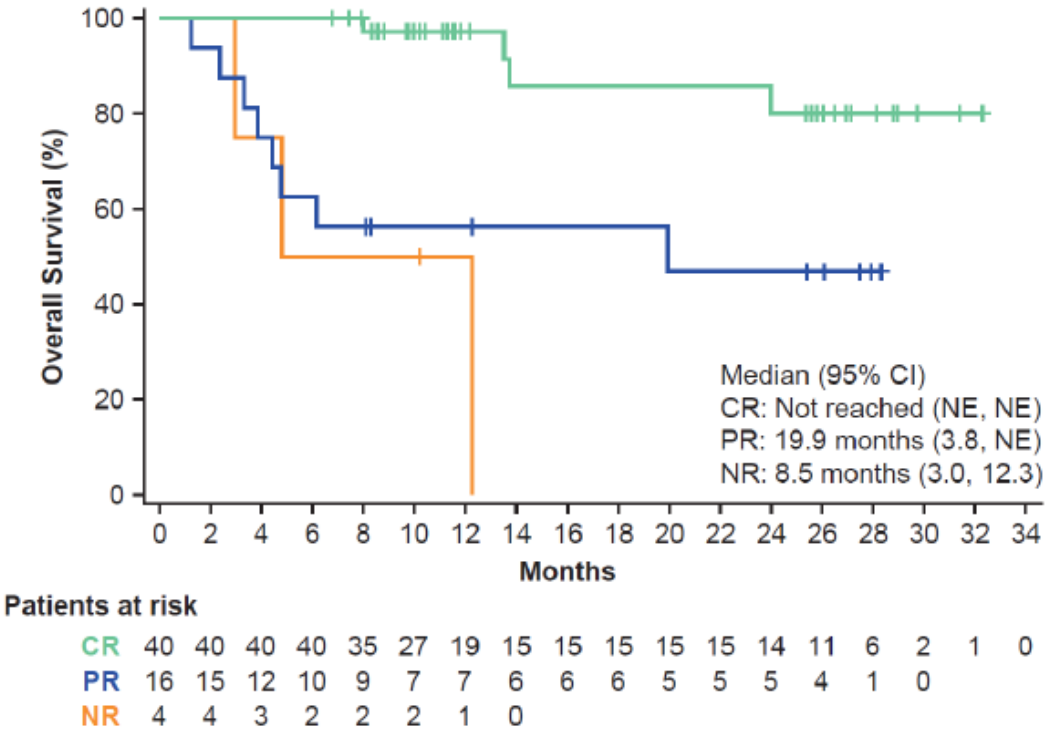
Figure 11: Overall survival (inferential analysis set)



Key: CI, confidence interval; OS, overall survival.
Source: Wang et al. 2020.[4]

Among patients who achieved a CR (n = 40), only [redacted] patients ([redacted]%) had died at data cut-off; the estimated 12-month OS rate was [redacted]%, and the estimated 24-month OS rate was [redacted]%.[48] Figure 12 presents OS by best objective response, and shows a substantial extension to life for patients experiencing a CR to KTE-X19 treatment (compared to patients experiencing a PR).

Figure 12: Overall survival by best objective response using central assessment (IRRC) per Lugano classification (inferential analysis set)



Key: CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; NE, not estimable; NR, no response; PR, partial response.
Source: Wang et al. 2020 (supplementary appendix).[4]

B.2.6.3.2. Modified intent-to-treat group

Figure 13 shows that the median OS has not been reached after a median follow-up of [redacted] months (secondary endpoint). At the time of primary analysis providing a maximum follow-up of [redacted] months, 16 patients (24%) had died; the estimated 12-month OS rate was [redacted]%, and the estimated 24-month OS rate was [redacted]%.[4, 56]

Figure 13: Overall survival (Cohort 1; modified intent-to-treat group)

Key: CI, confidence interval; CSR, Clinical Study Report; NE, not estimable.
Source: ZUMA-2 CSR.[56]

Among patients who achieved a CR (n=[redacted]), only [redacted] patients ([redacted]%) had died at data cut-off; the estimated 12-month OS rate was [redacted]%, and the estimated 24-month OS rate was [redacted]%.[56]

B.2.6.4. Health-related quality of life

Table 11 summarises EQ-5D scores. Decreases from baseline in patient-reported HRQL were shown at Week 4 (reflecting the period when patients are most likely to experience acute treatment-related toxicity) but better scores in mobility, self-care, usual activities and overall health (according to the EQ-5D visual analogue scale [VAS]) were observed by Month 3, with overall health returning to baseline status or better in most patients by Month 6.[4]

Table 11: 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)
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; 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 (all of whom were in the IAS and thus all analysis groups). 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 negative results at Month 6.[4]

B.2.6.6. Retreatment

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.[4] 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].[48]

[redacted]

[redacted] in the IAS and [redacted] in the Cohort 1 mITT group had an allo-SCT while in a KTE-X19-induced remission; a further [redacted] started a new anti-cancer therapy (non-SCT) prior to progressive disease post-KTE-X19.[48] [redacted] in total ([redacted]%) received subsequent anti-cancer therapy post-progression, most commonly [redacted] ([redacted]%) or [redacted] ([redacted]%) (Table 12).

Table 12: Subsequent anti-cancer therapies (Cohort 1; modified intent-to-treat)

	KTE-X19 (n = 68)
Subsequent anti-cancer therapy, n (%)	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]

Key: CSR, clinical study report.
Source: ZUMA-2 CSR.[48]

B.2.7. 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.

Efficacy outcomes in high-risk subgroups showed that KTE-X19 may benefit patients who typically have a poor prognosis, including the post-hoc subgroup of patients with *TP53* mutation: a group who respond particularly poorly to conventional therapy.[37] At

the time of primary analysis, an ongoing response was observed in approximately 60% of patients across high-risk subgroups. However, it should be noted that patient numbers in several subgroups are small, and interpretation should therefore be limited to trend analyses and considered only for exploratory purposes. Table 13 summarises high-risk subgroup analyses; subgroup analyses of ongoing response and PFS in key subgroups are provided in Appendix E.

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Table 13: Efficacy outcomes in high-risk subgroups using central assessment (IRRC) per IWG Lugano classification (Cohort 1)

	Inferential analysis set (n = 60)					mITT (n = 68)
	ORR, n/N (%) [95% CI]	CR, n/N (%) [95% CI]	Median DOR, months [95% CI]	6-month PFS rate, % [95% CI]	6-month OS rate, % [95% CI]	ORR, n/N (%) [95% CI]
MCL morphology						
Classical	32/35 (91)	22/35 (63)	Not reached	73	86	[redacted]
	[77, 88]	[45, 79]	[8.2, NE]	[54, 85]	[69, 94]	
Pleomorphic	4/4 (100)	3/4 (75)	Not reached	75	100	[redacted]
	[40, 100]	[19, 99]	[1.6, NE]	[13, 96]	[NE]	
Blastoid	13/14 (93)	9/14 (64)	8.6	69	71	[redacted]
	[66, 100]	[35, 87]	[2.0, NE]	[36, 87]	[41, 88]	
TP-53 mutation						
Detected	6/6 (100)	6/6 (100)	Not reached	100	100	[redacted]
	[54, 100]	[54, 100]	[5.4, NE]	[NE]	[NE]	
Undetected	30/30 (100)	20/30 (67)	Not reached	76	83	[redacted]
	[88, 100]	[47, 83]	[8.3, NE]	[56, 88]	[64, 93]	
Ki-67 index						
< 50%	14/14 (100)	9/14 (64)	Not reached	79	86	[redacted]
	[77, 100]	[35, 87]	[3.6, NE]	[47, 93]	[54, 96]	
≥ 50%	30/32 (94)	25/32 (78)	Not reached	84	91	[redacted]
	[79, 99]	[60, 91]	[8.3, NE]	[66, 93]	[74, 97]	

Key: IRRC, Independent Radiology Review Committee; MCL, mantle cell lymphoma; mITT, modified intent-to-treat.
Source: Wang et al. 2020 (supplementary appendix)[4]; ZUMA-2 CSR.[56]

B.2.8. Meta-analysis

Meta-analysis is not required for KTE-X19 as a single study provides data for this intervention. However, meta-analysis has been performed to provide pooled estimates for a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes (see Section B.1.3.4).

B.2.8.1. Included studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to 'standard of care'.

Table 14 summarises the eight studies deemed suitable for pooling in the meta-analysis, for which primary outcomes were pre-determined as OS, PFS and ORR; these studies are further detailed in Appendix D.

Table 14: Summary of trials included in the meta-analysis

Study ID	Study design	Population (n)	Treatment (n)	OS	PFS	ORR
Dreyling 2016[41]	Prospective RCT follow-up	Adults with r/r MCL whose disease had progressed on ≥ 1 rituximab-based regimens and ibrutinib (n = 40)	Mixed ST Most common included rituximab, bendamustine or anthracycline	-	-	✓
Epperla 2017[42]	Retrospective RW follow-up – US	Adults with MCL whose disease had progressed on ibrutinib (n = 29)	Mixed ST Most common included BORT, LEN or bendamustine	-	-	✓
Eyre 2019[45]	Retrospective CUP – UK	Adults with r/r MCL whose disease had progressed on ≥ 2 regimens including BTKi (n = 20)	Venetoclax	✓	✓	✓
Jain 2018[43]	Retrospective RW follow-up – US	Adults with MCL whose disease had progressed on ibrutinib (n = 36)	Mixed ST Most common included rituximab, BORT, LEN, bendamustine or anthracycline	✓[a]	-	✓

Study ID	Study design	Population (n)	Treatment (n)	OS	PFS	ORR
Martin 2016[44]	Retrospective Trial / RW follow-up – US, UK, Germany & Poland	Adults with MCL whose disease had progressed on ibrutinib (n = 73)	Mixed ST Most common included rituximab, LEN, cytarabine, bendamustine, BORT or anthracycline	✓	-	✓
McCulloch 2019[57]	Retrospective RW follow-up – UK & Italy	Adults with r/r MCL whose disease had progressed on BTKi (n = 29)[b]	R-BAC	✓	✓	✓
Regny 2019[58]	Retrospective RW follow-up – France	Adults with r/r MCL whose disease had progressed on ibrutinib (n = 12)	RiBVD	-	-	✓
Wang 2017[46]	Retrospective RW follow-up – US & UK	Adults with MCL whose disease had progressed on ibrutinib (n = 58)	Lenalidomide-based	-	-	✓

Key: BORT, bortezomib; BTKi, Bruton tyrosine kinase inhibitor; CUP, compassionate use program; LEN, lenalidomide; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R-BAC, rituximab, bendamustine and cytarabine; RCT, randomised controlled trial; RiBVD, rituximab, bendamustine, bortezomib and dexamethasone; r/r, relapsed or refractory; RW, real world; ST, subsequent therapy.
Notes: [a], survival time measured from ibrutinib discontinuation; [b], data included from conference presentation available at the time of meta-analysis – study since published in full with additional data.[40]

B.2.8.2. Meta-analysis methodology

A two-step approach to meta-analysis was taken for OS and PFS outcomes:

- Step one – various parametric survival distributions were fitted, and the most appropriate distribution chosen based on Akaike information criterion (AIC) and visual inspection
- Step two – parameter estimates were synthesised with a multivariate meta-analysis model as proposed by Achana et al.[59] to provide a time-varying treatment effect

These analyses were performed in a Bayesian framework, which involved data, a likelihood distribution, a model with parameters, and prior distributions.

OS and PFS were assessed up to 60 months, which reflected the longest follow-up for the external studies. Mean survival was defined as the AUC of the survival function from 0 to 60 months. For estimating absolute treatment effects, both fixed- and random-effects models were fit to the data.

For the ORR outcome, analysis was performed based on the proportion of patients experiencing the event of interest (a response). Both fixed- and random-effects meta-analysis models were used to estimate a pooled ORR using the approach proposed by DerSimonian and Laird.[60] The analyses were performed in a frequentist framework.

Further details of the meta-analysis methodology are provided in Appendix D.

B.2.8.3. Meta-analysis results

Results for the fixed-effects models are presented in this section, as these were considered most appropriate for use in the subsequent indirect treatment comparison (see Section B.2.9) given the small number of studies included and the pooling of patient characteristics by means of weighted averages. Results of the random-effects models are provided in Appendix D.

B.2.8.3.1. Overall survival

According to the model selection process, the best fitting survival distribution for 'standard of care' OS was log normal. Alternative survival distributions and AIC scores for all distributions are provided in Appendix D.

Table 15 summarises the pooled OS estimates for a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes.

Figure 14 shows the fitted Kaplan–Meier curve for OS when all included studies (mixed subsequent therapy, venetoclax or R-BAC) were meta-analysed. Median survival is estimated at [redacted] months; estimated 12-month and 24-month OS rates are [redacted]% and [redacted]%, respectively.

Figure 15 shows the fitted Kaplan-Meier curve for OS when all included studies with Time 0 set at the time of subsequent therapy initiation were meta-analysed. Median

survival is estimated at [redacted] months; estimated 12-month and 24-month OS rates are [redacted]% and [redacted]%, respectively.

Figure 14: Kaplan–Meier plot of fixed-effects meta-analysis (log normal model) of overall survival curves – all included studies (mixed subsequent therapy, venetoclax or R-BAC)

Key: R-BAC, rituximab, bendamustine and cytarabine.

Figure 15: Kaplan–Meier plot of fixed-effects meta-analysis (log normal model) of overall survival curves – all included studies with Time 0 set at time of subsequent therapy

Key: R-BAC, rituximab, bendamustine and cytarabine.

Figure 16 shows the fitted Kaplan–Meier curve for OS when only mixed subsequent therapy studies were meta-analysed. Median survival is estimated at [redacted] months; estimated 12-month and 24-month OS rates are [redacted]% and [redacted]%, respectively.

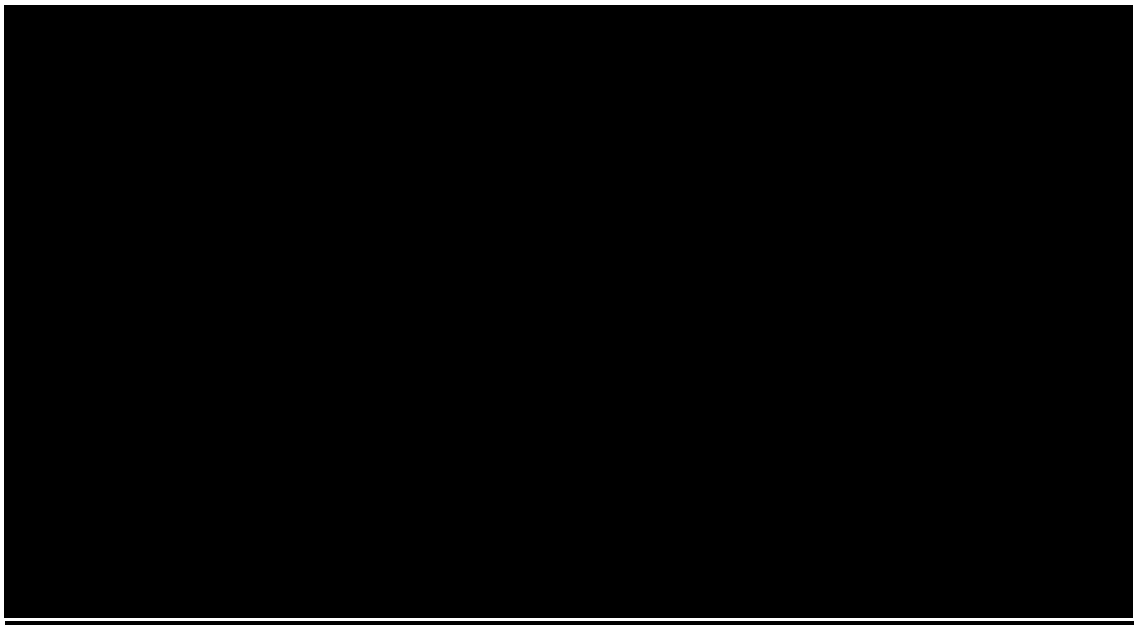
Figure 16: Kaplan–Meier plot of fixed-effects meta-analysis (log normal model) of overall survival curves – mixed subsequent therapy studies

[redacted]

Figure 17 shows the fitted Kaplan–Meier curve for OS when mixed subsequent therapy or R-BAC studies were meta-analysed. Median survival is estimated at [redacted] months; estimated 12-month and 24-month OS rates are [redacted]% and [redacted]%, respectively.

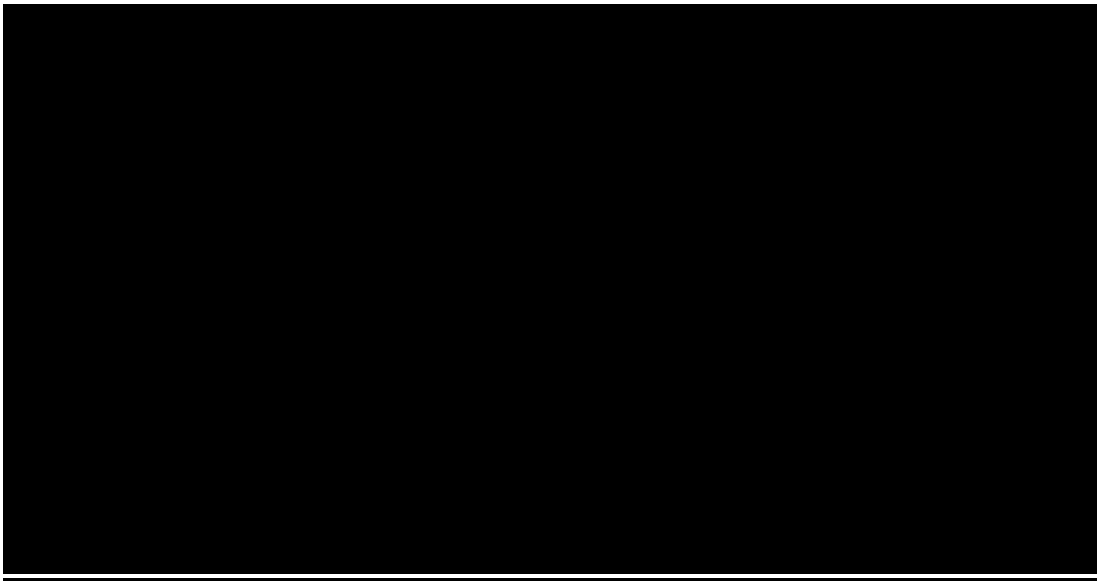
Figure 18 shows the fitted Kaplan–Meier curve for OS when mixed subsequent therapy or R-BAC studies with Time 0 set at the time of subsequent therapy initiation were meta-analysed. Median survival is estimated at [redacted] months; estimated 12-month and 24-month OS rates are [redacted]% and [redacted]%, respectively.

Figure 17: Kaplan–Meier plot of fixed-effects meta-analysis (log normal model) of overall survival curves – mixed subsequent therapy or R-BAC studies



Key: R-BAC, rituximab, bendamustine and cytarabine.

Figure 18: Kaplan–Meier plot of fixed-effects meta-analysis (log normal model) of overall survival curves – mixed subsequent therapy or R-BAC studies with Time 0 set at time of subsequent therapy



Key: R-BAC, rituximab, bendamustine and cytarabine.

Table 15: Survival estimate summary of fixed-effects meta-analysis (log normal model) of overall survival curves

	All included studies (mixed ST, venetoclax or R-BAC)	All included studies with Time 0 set at time of ST	Mixed ST studies	Mixed ST or R-BAC studies	Mixed ST or R-BAC studies with Time 0 set at time of ST
Mean survival, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median survival, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival rate, % (95% CI)					
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; R-BAC, rituximab, bendamustine and cytarabine; ST, subsequent therapy.

B.2.8.3.2. Progression-free survival

As was the case for OS, according to the model selection process, the best-fitting survival distribution for 'standard of care' PFS survival was log normal. Alternative survival distributions and AIC scores for all distributions are provided in Appendix D.

Figure 19 shows the fitted Kaplan–Meier curve for PFS when all included studies (venetoclax or R-BAC) were meta-analysed. Median PFS is estimated at [redacted] months; estimated 12-month and 24-month PFS rates are [redacted]% and [redacted]%, respectively.

Figure 19: Kaplan–Meier plot of fixed-effects meta-analysis (log normal model) of progression-free survival curves – all included studies (venetoclax or R-BAC)

[redacted]

Key: R-BAC, rituximab, bendamustine and cytarabine.

Table 16 summarises the pooled PFS estimates for a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes.

Table 16: Progression-free survival estimate summary of fixed-effects meta-analysis (log normal model) of progression-free survival curves

	All included studies (venetoclax or R-BAC)
Mean survival, months (95% CI)	[redacted]
Median survival, months (95% CI)	[redacted]
Survival rate, % (95% CI)	
6 months	[redacted]
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
Key: CI, confidence interval; R-BAC, rituximab, bendamustine and cytarabine.	

B.2.8.3.3. Response

Table 17 summarises the pooled response estimates for a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes.

When all included studies (mixed subsequent therapy, venetoclax, R-BAC, RiBVD or lenalidomide based) were meta-analysed, the ORR is estimated at [redacted]%, with a CR rate of [redacted]%. When only mixed subsequent therapy studies were meta-analysed, the ORR is estimated at [redacted]%, with a CR rate of [redacted]%.

When all included studies providing OS and ORR data (mixed subsequent therapy, venetoclax or R-BAC) were meta-analysed, the ORR is estimated at [redacted]%, with a CR rate of [redacted]%. When only mixed subsequent therapy studies providing OS and ORR data were meta-analysed, the ORR is estimated at [redacted]%, with a CR rate of [redacted]%.

Table 17: Response estimate summary of fixed-effects meta-analysis

	All included studies (mixed ST, venetoclax, R-BAC, RiBVD or LEN-based)	Mixed ST studies	All included studies with OS and ORR data (mixed ST, venetoclax or R-BAC)	Mixed ST studies with OS and ORR data
ORR, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
CR rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PR rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; LEN, lenalidomide; ORR, overall response rate; OS, overall survival; PR, partial response; R-BAC, rituximab, bendamustine and cytarabine; RiBVD, rituximab, bendamustine, bortezomib and dexamethasone; ST, subsequent therapy.

B.2.8.4. Meta-analysis conclusions

Pooled estimates for a 'standard of care' comparator based on studies providing post-BTKi treatment survival outcomes demonstrated median OS times ranging from [redacted] months (depending on included studies). Associated 12-month and 24-month OS rate estimates ranged from [redacted]% to [redacted]% and from [redacted]% to [redacted]%, respectively. On consultation, clinical experts noted that these broadly reflect their expectations for survival of r/r MCL patients receiving further treatment post ibrutinib, estimating 2-year survival with current care at ~10-20%.[47]

Pooled estimates for a 'standard of care' comparator based on studies providing post-BTKi treatment PFS outcomes demonstrated a median PFS of [redacted] months. Associated 12-month and 24-month PFS rate estimates are [redacted]% and [redacted]%, respectively. Pooled estimates for a 'standard of care' comparator based on studies providing post-BTKi treatment response outcomes demonstrated ORRs ranging from [redacted]% to [redacted]%, with CR and PR rates ranging from [redacted]% to [redacted]% and from [redacted]% to [redacted]%, respectively (depending on included studies).

These outcomes are markedly reduced compared with survival and response outcomes for KTE-X19 from ZUMA-2. Indirect treatment comparisons (ITC) formally exploring comparative effectiveness are presented in Section B.2.9. Uncertainties relating to the meta-analysis and subsequent ITC are also discussed in this section.

B.2.9. Indirect and mixed treatment comparisons

In the context of the evidence base available (single-arm trial data), a mixed treatment comparison was not feasible.

The ITCs therefore took the form of (i) naïve (unadjusted) comparison and (ii) matching-adjusted indirect comparison (MAIC).

B.2.9.1. Matching-adjusted indirect comparison methodology

A four-step approach to MAIC was taken for PFS and OS outcomes:

- **Step one** – A logistic propensity score model was used to estimate weights for the ZUMA-2 individual patient-level data (IPD) such that the weighted mean baseline characteristics of interest matched those reported in the 'standard of care' comparator studies
- **Step two** – Observed outcomes from ZUMA-2 were reweighted to facilitate pairwise comparisons of KTE-X19 versus 'standard of care' across the balanced study populations
- **Step three** – Various parametric survival distributions were fitted, and the most appropriate distribution chosen based on AIC and visual inspection
- **Step four** – Parameter estimates were synthesised with a multivariate pairwise meta-analysis model, to estimate relative treatment effects of KTE-X19 versus 'standard of care'

OS and PFS were assessed up to 33 months, which reflected the longest follow-up for ZUMA-2. Mean survival was defined as the AUC of the survival function from 0 to 33 months. Please note: this means that the mean survival estimates for 'standard of care' in the ITCs differed from those reported in the meta-analysis based on the AUC of the survival function from 0 to 60 months.

A three-step approach to MAIC was taken for the ORR outcome. Steps one and two were identical to those taken for PFS and OS outcomes:

- **Step three** – Reweighted outcomes for KTE-X19 were compared with the pooled ORR from the meta-analysis using weighted contingency table methods

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B.2.9.1.1. Selection of baseline characteristics of interest (covariates)

A targeted literature review was conducted to identify potential prognostic factors in patients with r/r MCL. Identified factors were listed along with other commonly reported baseline characteristics across studies for clinical validation.

The resulting list of baseline characteristics of interest considered within the MAIC, by order of relevance, were:

1. Number of prior therapies
2. Prior auto-SCT
3. Duration on prior BTKi therapy
4. Response to prior BTKi therapy (ORR)
5. MIPI or simplified-MIPI (low, intermediate, high)
6. Morphologic variants (blastoid)
7. Ki67 (≥ 30%, ≥ 50%)
8. Disease staging (Stage 3, Stage 4)
9. Prior BTKi therapy (ibrutinib)
10. Sex (male)
11. Extranodal disease
12. Bone marrow involvement

Of note, age, ECOG performance status, lactate dehydrogenase and white blood cell count were not included in this list as independent variables as these characteristics are used to calculate MIPI risk, which was reported by at least one of the comparator studies. In addition, *TP53* mutation, bulky disease and primary refractory disease status were identified as potential prognostic factors but had to be excluded from the final list of baseline characteristics of interest due to lack of reporting across studies.

Preliminary findings of the MAIC when the full list of baseline characteristics of interest considered above were included in the analyses demonstrated a low effective sample size (ESS; n = 11.1) and an unexpected shift in the weighted OS curve (upward shift; further discussed in Section B.2.9.4). The list of baseline characteristics considered within the MAIC were therefore reduced (through internal expert consultation).

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The final list of baseline characteristics of interest included within the MAIC, by order of relevance, were:

1. Number of prior therapies
2. Prior auto-SCT
3. Duration on prior BTKi therapy
4. Response to prior BTKi therapy (ORR)
5. MIPI or simplified-MIPI (low, intermediate, high)
6. Morphologic variants (blastoid)

Further details of the MAIC methodology are provided in Appendix D.

B.2.9.2. Matching-adjusted indirect comparison results and naïve comparison

Results for comparisons using the mITT analysis set of Cohort 1 from ZUMA-2 are presented in this section, as these were considered most appropriate for use in the subsequent economic modelling (see Section B.3). Results for comparisons using the IAS are provided in Appendix D. All scenarios considered in the meta-analysis with regard to included studies were taken through to the MAIC.

B.2.9.2.1. Matched baseline characteristics

Table 18 presents the baseline characteristics of patients enrolled to ZUMA-2 before and after matching to the ‘standard of care’ comparator studies providing post-BTKi treatment survival outcomes.

Table 18: Baseline characteristics of patients in ZUMA-2 (Cohort 1; mITT) before and after matching to comparator studies

Scenario	No. of SOC studies	Baseline patient characteristics							ESS
		No. of prior therapies	Prior auto-SCT, %	Prior BTKi duration[a]	Prior BTKi ORR, %	MIPI low, %	MIPI intermediate, %	Blastoid variant, %	
ZUMA-2	-	3.32	43	7.0	38	42	44	25	68
OS scenario: all included studies (mixed ST, venetoclax or R-BAC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS scenario: all included studies with Time 0 set at time of ST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS scenario: mixed ST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS scenario: mixed ST or R-BAC studies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26	31	19
OS scenario: mixed ST or R-BAC studies with Time 0 set at time of ST	2	2.8	20	4.7	53	19	25	-	18
PFS scenario: all included studies (venetoclax or R-BAC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR scenario: all included studies (mixed ST, venetoclax, R-BAC, RiBVD or LEN-based)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR scenario: mixed ST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Auto-SCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; ESS, effective sample size; LEN, lenalidomide; MIPI, Mantle Cell Lymphoma International Prognostic Index; mITT, modified intent-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R-BAC, rituximab, bendamustine and cytarabine; RiBVD, rituximab, bendamustine, bortezomib and dexamethasone; SOC, standard of care; ST, subsequent therapy.
Notes: Grey cells present data from the ZUMA-2 trial prior to matching; [a], matched on median of each scenario.

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B.2.9.2.2. Overall survival

According to the model selection process, the best-fitting survival distributions for KTE-X19 OS varied between Gompertz and log normal. Alternative survival distributions and AIC scores for all distributions are provided in Appendix D.

Table 19 summarises the indirect comparison results, including outcomes of the naïve (unadjusted) comparison and the MAIC for KTE-X19 versus a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes.

Figure 20 shows the parametric survival curves for OS when all included studies (mixed subsequent therapy, venetoclax or R-BAC) were meta-analysed and compared with unadjusted KTE-X19 data. The hazard ratio (HR) for death is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19.

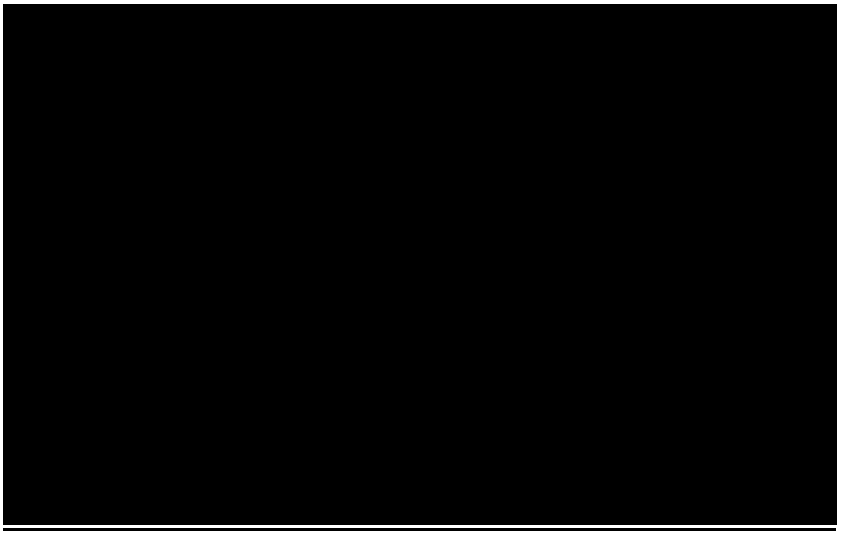
Figure 21 shows the parametric survival curves for OS when all included studies (mixed subsequent therapy, venetoclax or R-BAC) were meta-analysed and compared with matching-adjusted KTE-X19 data. The HR for death is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19.

Figure 22 shows the parametric survival curves for OS when mixed subsequent therapy studies were meta-analysed and compared with unadjusted KTE-X19 data. The HR for death is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19.

Figure 23 shows the parametric survival curves for OS when mixed subsequent therapy studies were meta-analysed and compared with matching-adjusted KTE-X19 data. The HR for death is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19.

Parametric survival curves for additional OS scenarios are provided in Appendix D, as are the unadjusted and matching-adjusted Kaplan–Meier curves for KTE-X19.

Figure 20: Pairwise indirect comparison of naïve (unadjusted) comparison of overall survival – all included studies (mixed subsequent therapy, venetoclax or R-BAC) versus KTE-X19 (Cohort 1; mITT), parametric survival curves



Key: CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat; R-BAC, rituximab, bendamustine and cytarabine.
Notes: log normal model fitted to both arms; dotted lines represent 95% CI.

Figure 21: Pairwise indirect comparison of matching-adjusted comparison of overall survival – all included studies (mixed subsequent therapy, venetoclax or R-BAC) versus KTE-X19 (Cohort 1; mITT), parametric survival curves

Key: CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat; R-BAC, rituximab, bendamustine and cytarabine.
Notes: Gompertz model fitted to KTE-X19 arm, log normal model fitted to standard of care arm; dotted lines represent 95% CI.

Figure 22: Pairwise indirect comparison of naïve (unadjusted) comparison of overall survival – mixed subsequent therapy studies versus KTE-X19 (Cohort 1; mITT), parametric survival curves

Key: CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat.
Notes: log normal model fitted to both arms; dotted lines represent 95% CI.

Figure 23: Pairwise indirect comparison of matching-adjusted comparison of overall survival – mixed subsequent therapy studies versus KTE-X19 (Cohort 1; mITT), parametric survival curves

Key: CI, confidence interval; HR, hazard ratio; mITT, modified intent-to-treat.
Notes: Gompertz model fitted to KTE-X19 arm, log normal model fitted to standard of care arm; dotted lines represent 95% CI.

Table 19: Comparative survival estimate summary of KTE-X19 (Cohort 1; modified intent-to-treat) versus 'standard of care'

OS scenario	Naïve (unadjusted) comparison				Matching-adjusted comparison			
	KTE-X19		SOC (pooled)	KTE-X19 vs SOC	KTE-X19		SOC (pooled)	KTE-X19 vs SOC
	N	Mean OS, months (95% CI)	Mean OS, months (95% CI)	OS HR (95% CI)[a]	ESS	Mean OS, months (95% CI)	Mean OS, months (95% CI)	OS HR (95% CI)[a]
All included studies (mixed ST, venetoclax or R-BAC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] *Log normal*	0.17 (0.04, 0.77)
All included studies with Time 0 set at time of ST	68	25.1 (19.9, 29.8) *Log normal*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed ST studies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed ST or R-BAC studies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed ST or R-BAC studies with Time 0 set at time of ST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; OS, overall survival; R-BAC, rituximab, bendamustine and cytarabine; SOC, standard of care; ST, subsequent therapy.
Notes: [a], average HRs are reported based on survival functions from 0-33 months.

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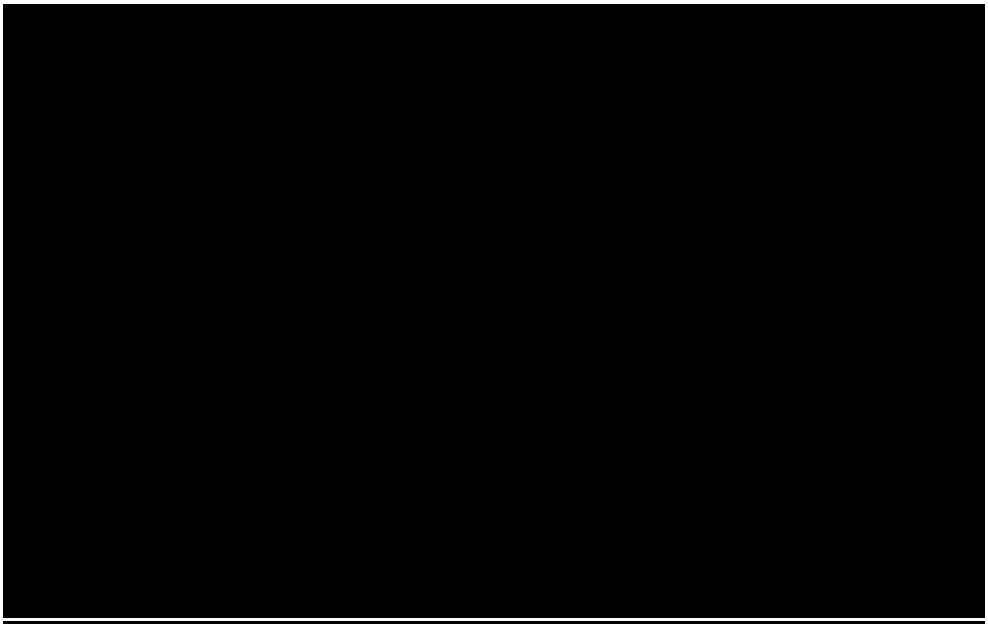
B.2.9.2.3. Progression-free survival

According to the model selection process, the best-fitting survival distributions for KTE-X19 PFS varied between Gompertz and log normal. Alternative survival distributions and AIC scores for all distributions are provided in Appendix D, as are the unadjusted and matching-adjusted Kaplan–Meier curves for KTE-X19.

Figure 24 shows the parametric survival curves for PFS when all included studies (venetoclax or R-BAC) were meta-analysed and compared with unadjusted KTE-X19 data. The HR for disease progression or death is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19.

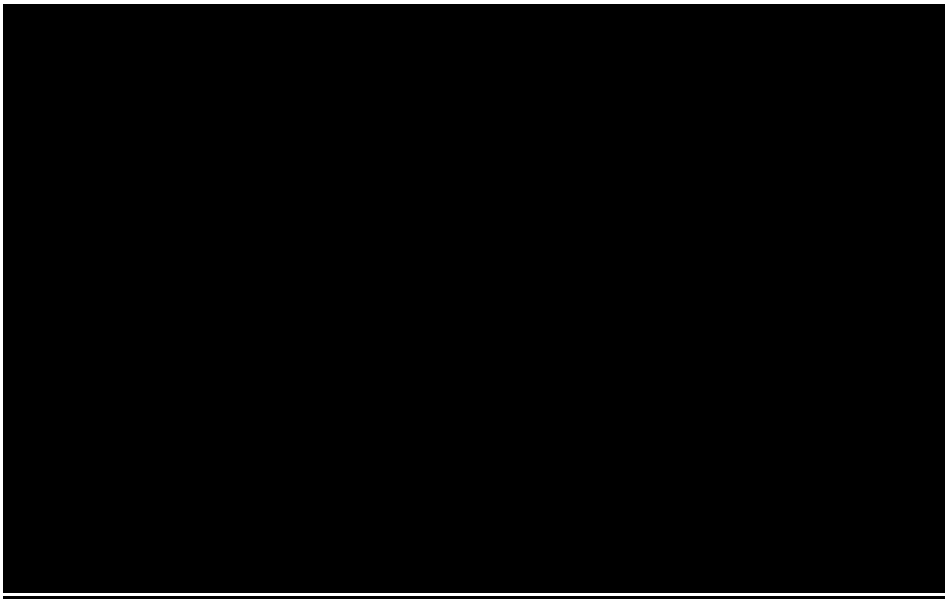
Figure 25 shows the parametric survival curves for PFS when all included studies (venetoclax or R-BAC) were meta-analysed and compared with matching-adjusted KTE-X19 data. The HR for disease progression or death is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19.

Figure 24: Pairwise indirect comparison of naïve (unadjusted) comparison of progression-free survival – all included studies (venetoclax or R-BAC) versus KTE-X19 (Cohort 1; modified intent-to-treat), parametric survival curves



Key: CI, confidence interval; HR, hazard ratio; R-BAC, rituximab, bendamustine and cytarabine.
Notes: Gompertz model fitted to KTE-X19 arm, log normal model fitted to standard of care arm; dotted lines represent 95% CI.

Figure 25: Pairwise indirect comparison of matching-adjusted comparison of progression-free survival – all included studies (venetoclax or R-BAC) versus KTE-X19 (Cohort 1; modified intent-to-treat), parametric survival curves



Key: CI, confidence interval; HR, hazard ratio; R-BAC, rituximab, bendamustine and cytarabine.
Notes: log normal model fitted to both arms; dotted lines represent 95% CI.

Table 20 summarises the indirect comparison results, including outcomes of the naïve (unadjusted) comparison and the MAIC for KTE-X19 versus a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes.

Table 20: Comparative progression-free survival estimate summary of KTE-X19 (Cohort 1; modified intent-to-treat) versus 'standard of care' (all included studies: venetoclax or R-BAC)

		N / ESS	Mean PFS, months (95% CI)	PFS HR (95% CI)[a]
Naïve (unadjusted) comparison	KTE-X19	[redacted]	[redacted]	[redacted]
	SOC (pooled)	[redacted]	[redacted]	
Matching-adjusted comparison	KTE-X19	[redacted]	[redacted]	[redacted]
	SOC (pooled)	[redacted]	[redacted]	

Key: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; mITT, modified intent-to-treat; PFS, progression-free survival; R-BAC, rituximab, bendamustine and cytarabine; SOC, standard of care.
Notes: [a], average HRs are reported based on survival functions from 0-33 months.

B.2.9.2.4. Response

Table 21 summarises the indirect comparison results, including outcomes of the naïve (unadjusted) comparison and the MAIC for KTE-X19 versus a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes.

When all included studies (mixed subsequent therapy, venetoclax, R-BAC, RiBVD or lenalidomide based) were meta-analysed and compared with unadjusted KTE-X19 data, the odds ratio (OR) for response is estimated at [redacted] in favour of KTE-X19. When all included studies (mixed subsequent therapy, venetoclax, R-BAC, RiBVD or lenalidomide based) were meta-analysed and compared with adjusted KTE-X19 data, the OR for response is estimated at [redacted] in favour of KTE-X19.

When mixed subsequent therapy studies were meta-analysed and compared with unadjusted KTE-X19 data, the OR for response is estimated at [redacted] in favour of KTE-X19. When mixed subsequent therapy studies were meta-analysed and compared with adjusted KTE-X19 data, the OR for response is estimated at [redacted] in favour of KTE-X19.

When all included studies providing OS and ORR data (mixed subsequent therapy, venetoclax or R-BAC) were meta-analysed and compared with unadjusted KTE-X19 data, the OR for response is estimated at [redacted] in favour of KTE-X19. When all included studies providing OS and ORR data (mixed subsequent therapy, venetoclax or R-BAC) were meta-analysed and compared with adjusted KTE-X19 data, the OR for response is estimated at [redacted] in favour of KTE-X19.

When mixed subsequent therapy studies providing OS and ORR data were meta-analysed and compared with unadjusted KTE-X19 data, the OR for response is estimated at [redacted] in favour of KTE-X19. When mixed subsequent therapy studies providing OS and ORR data were meta-analysed and compared with adjusted KTE-X19 data, the OR for response is estimated at [redacted] in favour of KTE-X19.

Response estimates informing these comparisons are provided in Appendix D. In the unadjusted analyses, KTE-X19 showed ORR and CR rates of 93% and 65%, compared with ORR and CR rates of [redacted]% and [redacted]% when all included studies were pooled for the ‘standard of care’ comparator, and of [redacted]% and [redacted]% when mixed subsequent treatment studies are pooled for the ‘standard of care’ comparator.

Table 21: Comparative response estimate summary of KTE-X19 (Cohort 1; modified intent-to-treat) versus 'standard of care'

	Naïve (unadjusted) comparison			Matching-adjusted comparison		
	KTE-X19 vs SOC OR (95% CI)			KTE-X19 vs SOC OR (95% CI)		
	ORR	CR	PR	ORR	CR	PR
All included studies (mixed ST, venetoclax, R-BAC, RiBVD or LEN-based)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed ST studies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All included studies with OS and ORR data (mixed ST, venetoclax or R-BAC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed ST studies with OS and ORR data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; LEN, lenalidomide; mITT, modified intent-to-treat; OR, odds ratio; ORR, overall response rate; OS, overall survival; PR, partial response; R-BAC, rituximab, bendamustine and cytarabine; RiBVD, rituximab, bendamustine, bortezomib and dexamethasone; SOC, standard of care; ST, subsequent therapy.

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B.2.9.3. Indirect comparison conclusions

Outcomes of the naïve (unadjusted) comparison and the MAIC for KTE-X19 versus a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes, demonstrated:

- KTE-X19 is associated with a [redacted]% reduction in risk of death versus 'standard of care' (HR range: [redacted])
- KTE-X19 is associated with a [redacted]% reduction in risk of disease progression or death versus 'standard of care' (HR range: [redacted])
- KTE-X19 is at least ten times and up to [redacted] times more likely to induce a response than 'standard of care' (OR range: [redacted])

These conclusions should be made with appropriate caution, in consideration of the uncertainties in the indirect comparisons (see Section B.2.9.4) and general limitations of estimating relative effectiveness outside of a controlled clinical trial setting, but are nevertheless highly promising.

B.2.9.4. Uncertainties in the indirect comparisons

There are several limitations across the meta-analysis and indirect comparisons needed to estimate the relative effect of KTE-X19, and several challenges, not least the fact that there is no true 'standard of care' in the post-BTKi setting. In the absence of a single intervention standard of care and the associated paucity of evidence in the post-BTKi setting, a blended comparator approach that aims to utilise studies providing post-BTKi treatment outcomes is necessitated. However, not all treatments investigated across these studies could be considered established clinical management in NHS England. Scenario analyses around the studies included in the meta-analysis and indirect comparisons aim to address any uncertainty resulting from this limitation.

Within the evidence that is available in the post-BTKi setting, further limitations are observed in the study design (the evidence base is made up of small, retrospective, non-comparative, observational studies), data availability (several studies were only reported at conference), and sample sizes (reflecting the rare nature of the r/r MCL post-BTKi patient population). There was also heterogeneity observed in study baseline definitions (Time 0 for outcome analyses at the time of BTKi treatment

versus subsequent therapy). Of note, one study included in the meta-analysis and subsequent ITC based on data presented at conference (McCulloch 2019[57]) has since been published in full with additional data[40] but analyses were not updated as outcomes were similar across datasets.

Heterogeneity was also observed both within and across study populations with a broad range of baseline characteristics reported and again, differences were observed in baseline definitions (at diagnosis, at start of BTKi treatment, and at start of subsequent therapy). The biggest differences when comparing the ZUMA-2 population to comparator study populations were observed in the proportion of patients with MIPI high-risk disease (13% vs 22-64%) and the proportion of patients with Ki-67 proliferation index ≥50% (69% vs 45-50%) (although as noted above, study baseline definitions differed such that these data could relate to patient characteristics at diagnosis, at start of BTKi treatment, or at start of subsequent therapy). All patients had however relapsed or demonstrated refractoriness to BTKi therapy and therefore represent the overarching target population for KTE-X19 in clinical practice. Similarity in naïve and matching-adjusted comparisons suggest these differences had little impact on trial outcomes. For some studies, only a subgroup of the study population were of interest to this analysis, but data on baseline characteristics were only available for the total group. An assumption was thus needed that these were representative of the subgroup of interest. Baseline characteristics data were also not routinely reported, meaning that the MAIC could not control for those not reported or reported in only one study without making strong assumptions. In the meta-analysis, an assumption was made that the weighted average for the arms reporting the baseline characteristic of interest was representative of those that did not. There is uncertainty around if and how these assumptions may influence the MAIC results.

Additional challenges arose when trying to adjust for a complete list of baseline characteristics of interest. The ESSs for KTE-X19 were as low as 13% of the original sample size when such an adjustment was conducted, and the resulting shift in the weighted OS curve lacked face validity: an upward shift was observed despite a smaller proportion of patients in ZUMA-2 having a high MIPI risk (18% versus 57%). A restricted list of baseline characteristics were subsequently included in the

adjustment, but the ESSs were still low after matching. As a result of the reductions, the weighted PFS curve beyond 15 months was represented by an ESS of 2. Consequently, when fitting any given parametric survival function to this weighted data, the function is fitting to data in the first 15 months; data beyond that have insignificant weight to the model fit.

Little can be done about the general paucity of evidence in this patient group and the associated uncertainties, but the consistency in positive outcomes is encouraging and suggests superiority of KTE-X19 over 'standard of care' across the various analyses conducted in line with NICE guidance (technical support document 18[61]). This is despite the 'standard of care' survival estimates from meta-analyses potentially being over-optimistic compared with real-world practice (see Section B.2.8.4). In consideration of the substantially low ESS for the adjusted comparisons, the naïve (unadjusted) comparisons that preserve the original sample size will have less uncertainty and are preferred in subsequent economic analysis (see Section B.3).

In terms of the approach taken, a significant limitation of Step three is that none of the parametric survival distributions tested allowed for potential plateau (flattening in the tail end of the survival curve) representing long-term survivorship. While we would not expect this with conventional treatment for which such a plateau is not observed in MCL, there is the potential for long-term survivorship with KTE-X19 (discussed further in Section B.2.13.2). For the economic analysis, mixture cure modelling approaches that do account for potential plateau were tested and validated for use in the cost-effectiveness base case, as detailed in Section B.3.6.

A final limitation of the MAIC is that it only provides comparative efficacy estimates and does not extend to comparative safety. A safety analyses was not possible due to a paucity of comparable safety data reported across studies (see Appendix D).

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B.2.10. Adverse reactions

The population from Cohort 1 for which data are presented throughout the rest of this section are:

- **The safety analysis set:** The 68 patients in Cohort 1 that received KTE-X19 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 for efficacy outcomes.

B.2.10.1. Safety summary

All patients treated experienced at least one adverse event (AE). Table 22 presents an overview of AEs for the safety analysis set of Cohort 1; comparable data for Cohort 2 are provided in Appendix F.

Nearly all patients treated at target dose experienced an AE of Grade 3 or higher [redacted] (Table 22). Approximately two thirds of patients experienced a serious adverse event (SAE), and [redacted] of patients experienced an SAE deemed related to KTE-X19 (Table 22). There were two deaths observed due to AEs: 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 KTE-X19.[4]

Table 22: Safety summary (Cohort 1; safety analysis set)

	KTE-X19 (n = 68)
Any adverse event, n (%)	68 (100)
Worst Grade 3	11 (16)
Worst Grade 4	52 (76)
Worst Grade 5	2 (3)
Any serious adverse event, n (%)	46 (68)
Worst Grade 3	20 (29)
Worst Grade 4	13 (19)
Worst Grade 5	2 (3)
Any KTE-X19-related adverse event, n (%)	[redacted]
Worst Grade 3	[redacted]
Worst Grade 4	[redacted]
Worst Grade 5	[redacted]

	KTE-X19 (n = 68)
Any KTE-X19-related serious adverse event, n (%) Worst Grade 3 Worst Grade 4 Worst Grade 5	[redacted] [redacted] [redacted] [redacted]
Key: CSR, clinical study report. **Source:** Wang et al. 2020[4]; ZUMA-2 CSR.[48]	

B.2.10.2. Common adverse events

Table 23 summarises AEs that occurred in ≥ 30% of patients treated at target dose . These included pyrexia (94%), neutropenia (87%), thrombocytopenia (74%), anaemia (68%) and hypotension (51%).[4]

Table 23: Common adverse events (AEs that occurred in ≥ 30% of patients) (Cohort 1; safety analysis set)

n (%)	KTE-X19 (n=68)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any adverse event	68 (100)	0	1 (1)	11 (16)	54 (79)	2 (3)
Pyrexia	64 (94)	14 (21)	41 (60)	9 (13)	0	0
Neutropenia	59 (87)	0	1 (1)	11 (16)	47 (69)	0
Thrombocytopenia	50 (74)	9 (13)	6 (9)	11 (16)	24 (35)	0
Anaemia	46 (68)	0	12 (18)	34 (50)	0	0
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

n (%)	KTE-X19 (n=68)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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]						

SAEs that occurred in at least three patients are provided in Appendix F. The most common SAEs in patients treated at target dose were pyrexia and encephalopathy (22% each) .[4]

Common adverse events observed are reflective of cytokine release syndrome (CRS), neurological events and B-cell aplasia that are typical of the CAR T-cell therapy class and discussed in further detail below.

B.2.10.2.1. 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.[62] 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 other organ toxicity in more severe cases. 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 but CAR T delivery centres are now well experienced in how to manage these toxicities in a way that, generally, keeps them from becoming severe (see Section B.2.10.3). 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.

Of patients treated in Cohort 1 of ZUMA-2, 91% experienced a CRS event. Most of these events were Grade 1–2, and all CRS events resolved after a median duration of 11 days, as summarised in Table 24. CRS events by Grade are detailed in Appendix F. No Grade 5 (fatal) CRS events occurred.

Table 24: Summary of CRS events (Cohort 1; safety analysis set)

	KTE-X19 (n = 68)
Any CRS event, n (%)	62 (91)
Grade ≥ 3	10 (15)
Symptom of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
Chills	21 (31)
Tachycardia	16 (24)
Headache	15 (22)
Alanine aminotransferase increased	10 (15)
Aspartate aminotransferase increased	9 (13)
Fatigue	9 (13)
Nausea	9 (13)
CRS management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Vasopressors	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.2.10.2.2. Neurological events

Neurotoxicity that typically manifests as a toxic encephalopathy (brain disease, damage or malfunction) is frequently observed with CAR T-cell therapy, but the mechanism underlying such CAR T-cell associated neurotoxicity is unknown. [62] Symptoms can therefore be hard to predict, and neurological evaluation, including an evaluation of mental status, headache and abnormal movements 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 necessitate 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.[63]

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 25. Neurological events by Grade are detailed in Appendix F. Nearly all neurological events resolved after a median duration of 12 days (Table 25). At the time of analysis, four patients had ongoing symptoms, including Grade 1 tremor (in three patients), Grade 2 concentration impairment (in one patient) and Grade 1 dysaesthesia (in one patient).[4] Two further patients died from unrelated AEs (organising pneumonia and staphylococcal bacteraemia) prior to the resolution of neurological events.[52]

No Grade 5 (fatal) neurological events occurred. One patient had Grade 4 cerebral oedema but fully recovered with aggressive multimodality therapy including tocilizumab, siltuximab, high-dose steroids, intrathecal cytarabine plus dexamethasone, mannitol, ventriculostomy, and intravenous anti-thymocyte immunoglobulin (ATG) (rabbit).[52] This is the first reported use of ATG in treating CAR T-cell therapy-related toxicities. The neurotoxicities fully resolved, with the patient remaining in CR 24 months later.

Table 25: Summary of neurological events (Cohort 1; safety analysis set)

	KTE-X19 (n = 68)
Any neurological event, n (%)	43 (63)
Grade ≥ 3	21 (31)
Symptom of neurological event, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
Aphasia	10 (15)
Neurological event management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	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

	KTE-X19 (n = 68)
Patients with resolved neurological events, n/N (%)	37/43 (86)
Key: CRS, cytokine release syndrome. **Source:** Wang et al., 2020.[4]	

B.2.10.2.3. 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 as a result of their disease and exacerbated in r/r MCL patients as a result of previous treatment that can destruct healthy B-cells alongside cancerous B-cells. Conditioning chemotherapy and subsequent CAR T-cell therapy can also result in such destruction, although the exact mechanisms are unclear.

Grade 3 or higher cytopenias included neutropenia (85% in Cohort 1), thrombocytopenia (51% in Cohort 1) and anaemia (50% in Cohort 1).[4] A total of 26% of treated patients in Cohort 1 had cytopenias of Grade 3 or higher more than 90 days after the infusion of KTE-X19, including neutropenia (16%), thrombocytopenia (16%) and anaemia (12%).

Infection of Grade 3 or higher occurred in 32% of patients in Cohort 1, with the most common being pneumonia (9%).[4] Two cases of Grade 2 cytomegalovirus infection occurred. Grade 3 hypogammaglobulinaemia and Grade 3 tumour lysis syndrome occurred in one patient each. A total of 22 patients (32%) received intravenous immunoglobulin therapy. Infection events by Grade are detailed in Appendix F.

No cases of replication-competent retrovirus, Epstein–Barr virus–associated lymphoproliferation, haemophagocytic lymphohistiocytosis, or KTE-X19–related secondary cancers were reported.

B.2.10.3. Safety overview

The safety profile observed in ZUMA-2 is similar to that observed with other CAR T-cell therapies, typified by CRS, neurological events and B-cell aplasia that are the most prominent toxicities of cellular immunotherapy. Importantly, HRQL data from ZUMA-2 suggest no long-term impact on patient quality of life resulting from the

short-term toxicity associated with CAR T-cell therapy and start of B-cell recovery was observed by flow cytometry in the majority of patients who had an ongoing response at 6 months (21 of 34 patients [62%]).[4]

Since the approved access of tisagenlecleucel and axicabtagene ciloleucel through the Cancer Drugs Fund (CDF) in NHS England, clinicians are increasingly comfortable with toxicity management for CAR T-cell therapy.[47] Indeed, real-world data of high-grade lymphoma patients treated with CD19 CAR T-cell therapy in NHS England showed lower rates of Grade ≥ 3 CRS and Grade ≥ 3 neurological events with increased use of tocilizumab and steroid use than reported across the pivotal clinical trials of tisagenlecleucel-T (JULIET) and axicabtagene ciloleucel (ZUMA-1).[64] We may therefore expect a similar translation of ZUMA-2 safety data to clinical practice, with respect to a lowering of AE rates with increased familiarity to their management. However. we should acknowledge that data available to date across the MCL and DLBCL patient groups suggest a slightly higher rate of AEs in the former; this could be due to the typically higher disease burden observed in MCL patients and higher prevalence of circulating tumour cells.

As recommended in the summary of product characteristics for KTE-X19 (see Appendix C), patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities. Physicians should consider hospitalisation for this period or at the first signs or symptoms of CRS and/or neurological events. After the first 10 days following infusion, patients should be monitored at the physicians discretion but instructed to remain within proximity of a qualified clinical facility for at least 4 weeks. Prior to infusion, CAR T-cell therapy centres should also ensure that a minimum of four doses of tocilizumab are available for each patient.

Blood counts should be monitored after KTE-X19 infusion and patients should also be monitored for signs and symptoms of infection, before, during and after KTE-X19 infusion (and treated appropriately). Prophylactic anti-microbials should be administered according to standard institutional guidelines. Immunoglobulin levels should also be monitored after treatment with KTE-X19 and managed using infection precautions, antibiotic prophylaxis and immunoglobulin replacement in case of recurrent infections.

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B.2.11. Ongoing studies

ZUMA-2 is ongoing and will provide additional evidence of KTE-X19 for the treatment of patients with r/r MCL who have previously received a BTKi in the next 12 months, including longer survival follow-up with [redacted]. An expanded access study for KTE-X19 in r/r MCL (ZUMA-18) is also planned, but data from this study will not be available in the next 12 months.

Comparator data collection is also ongoing, which we hope will provide additional evidence of 'standard of care' for the treatment of patients with r/r MCL who have previously received a BTKi in the next 12 months.

B.2.12. Innovation

KTE-X19 is a personalised medicine in which the patient's own T-cells are collected and engineered ex vivo to express a CAR that programs them to target and kill cancer cells, upon return to the patient via a single infusion. Unique to the production of KTE-X19 compared with axicabtagene ciloleucel is a manufacturing process step designed to remove tumour cells from the leukapheresis harvest and thus increase the chance of successfully producing the CAR T-cell therapy product (see Section B.1.2). KTE-X19 was successfully manufactured for 96% of patients enrolled to Cohort 1 in ZUMA-2 (71/74).[4]

KTE-X19 represents a breakthrough treatment in the post-BTKi r/r MCL setting, offering the potential of long-term survivorship to patients with an extremely poor life expectancy and for whom there is no current standard of care (see Section B.1.3.5). There have been no major advancements in r/r MCL therapeutics since the introduction of ibrutinib back in 2013 (KTE-X19 is the first treatment to be prospectively assessed in the post-BTKi setting), let alone the introduction of a personalised medicine with long-term survivorship potential from a single treatment infusion. The hope KTE-X19 could offer to patients, carers and healthcare professionals should not be undervalued. There are also clear administration benefits of a single treatment infusion versus the recurrent cyclic nature of conventional immunochemotherapy.

While the main health-related benefits will have been captured in the QALYs for KTE-X19, it is difficult to capture true innovation in such a calculation, and the significant difference this treatment choice could make to patients, carers and healthcare services is such that KTE-X19 access would represent a step change in management of MCL. This potential is reflected in the EMA granting KTE-X19 access to the PRIME scheme which provides enhanced support for priority medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options.[65]

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Principal findings from the clinical evidence

The ZUMA-2 trial demonstrates that KTE-X19 provides an effective treatment option for patients with r/r MCL who have previously received a BTKi: a patient group with significant unmet medical need and a poor prognosis; patients are unlikely to achieve sustainable response with further treatment and most are not expected to survive beyond a year (see Section B.1.3).

Over 90% of patients treated with KTE-X19 in ZUMA-2 achieved an objective response, with two thirds of patients achieving a CR. Such high responses are unprecedented in the post-BTKi setting, with pooling of observational studies reporting post-BTKi treatment outcomes estimating an ORR of [redacted]% and a CR rate of [redacted]% (depending on included studies). Of patients with ≥ 24 months follow-up at the time of analysis, almost half of responding patients remained in response and the longest DOR observed to date is [redacted] months, far exceeding the typical life expectancy of patients with r/r MCL who have previously received a BTKi (see Section B.2.13.4).

After a median follow-up of just over 12 months, median PFS and median OS have not been reached in ZUMA-2. Over 80% of patients treated with KTE-X19 are estimated to live for at least 12 months, and over 60% of patients treated are estimated to live progression-free for at least 12 months. Such high survival rates are similarly unprecedented in the post-BTKi setting, with pooling of observational studies reporting post-BTKi treatment outcomes estimating a 12-month OS rate of [redacted]% (depending on included studies) and a 12-month PFS rate of [redacted]%.

B.2.13.2. Strengths and limitations of the evidence base

ZUMA-2 is the only prospective clinical trial in the r/r MCL post-BTKi setting and provides high-quality evidence of ground-breaking treatment effect in a patient group with no current 'standard of care' due to a lack of effective treatment options.

Without a true 'standard of care', an appropriate control arm for KTE-X19 could not be pre-defined. Patients enrolled to ZUMA-2 had failed multiple prior therapies, and given their poor prognosis, a placebo control arm would be deemed unethical. To address the evidence gap regarding comparative effectiveness, a series of indirect treatment comparisons have been conducted. Across these analyses, a consistent trend of KTE-X19 superiority is observed when comparing to a 'standard of care' comparator based on studies providing post-BTKi treatment outcomes. KTE-X19 was associated with a [redacted]% reduction in risk of death, a [redacted]% reduction in risk of disease progression or death, and a [redacted] times increased chance of response. As noted above, after a median follow-up of just over 12 months, median PFS and median OS have not been reached in ZUMA-2, and while this indicates an improved PFS and OS compared with current practice, the precise magnitude of benefit is uncertain. Considering the immunotherapeutic nature of CAR T-cell therapy, it is expected that at least a proportion of patients will experience long-term survivorship following KTE-X19 treatment. In the broader NHL setting, CAR T-cell therapy survival curves are starting to show an observed plateau with no downward tail, representing long-term survivorship.[66] In recently reported 3-year survival data from ZUMA-1, only four deaths were observed since the 2-year follow-up (patients at risk, n=51).[66] No such survival curve plateau is observed with conventional immunochemotherapy treatment.

The depth of response in ZUMA-2 further supports an expectation of longer-term treatment benefit from KTE-X19. Of the two-thirds of patients achieving a CR, over three quarters remain in response at the time of primary analysis (maximum DOR follow-up = [redacted] months) and the majority ([redacted]%) are still alive; over [redacted]% of patients with CR to KTE-X19 treatment are estimated to live for at least 12 months, and over [redacted]% are estimated to live progression-free for at least 12 months. The high level of MRD observed in patients treated with KTE-X19 (83% MRD negativity at 4 weeks) is also considered a further positive sign of the potential for long-term survivorship with

KTE-X19 treatment, as MRD-negative status has previously been shown to correlate to longer PFS and OS in the MCL setting.[67, 68]

To address the evidence gap regarding longer-term benefit, a series of survival scenarios have been modelled within the cost-effectiveness analyses presented in Section B.3.3.3. We are also open to KTE-X19 being a CDF candidate to accommodate patient access alongside longer-term data collection.

B.2.13.3. Applicability of clinical evidence to practice

B.2.13.3.1. Patient characteristics

The trial population of ZUMA-2 represents a heavily pre-treated patient group who had failed all standard treatment options, including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, and ibrutinib or acalabrutinib. The median number of prior therapies was three, with 81% of patients receiving three or more therapies prior to trial enrolment. KTE-X19 is intended for use post-BTKi in clinical practice, which is optimally in the third-line setting according to the current pathway of care (see Section B.1.3.4). These patients would be less heavily pre-treated than the ZUMA-2 population and may be expected to have improved outcomes with KTE-X19 compared with those observed in ZUMA-2 as the typical trend in MCL is a worsening prognosis with each subsequent treatment line.[21-23]

In addition, a high proportion of the ZUMA-2 population were refractory to BTKi therapy (68%), whereas less than a fifth of patients are expected to be refractory to ibrutinib in clinical practice.[47] Although there is no conclusive evidence that BTKi refractory status is a prognostic factor in the third- or later-line r/r MCL setting, clinical expectation is that such patients would have a worse prognosis as early treatment failure is generally associated with more aggressive disease and reduced survival.[22, 42] Indeed, clinical experts consulted during development of the submission stated “patients who are refractory to ibrutinib tend to do particularly badly” when asked to comment on important prognostic factors.[47] A less refractory patient population (as expected in clinical practice) may therefore be expected to have improved outcomes with KTE-X19 than observed in ZUMA-2.

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Demographically, patients enrolled to ZUMA-2 may appear younger than the 'average' patient in clinical practice with the HMRN reporting a median age at diagnosis of 72.9 years for MCL[15] (compared with a median age of 65 in ZUMA-2). Patients in the studies used for ITC were also generally younger (median age at time of subsequent therapy: 66–69 years), and on consultation, clinical experts surmised that patients enrolled to ZUMA-2 were slightly younger and fitter than patients being considered for third-line treatment in clinical practice.[47] However, it is expected that it would be patients slightly younger than the 'average' patient who would be considered for KTE-X19 treatment, specifically those free of significant co-morbidities and end-organ dysfunction in line with the ZUMA-2 eligibility criteria and therefore the trial population is considered representative of patients expected to receive KTE-X10 treatment in clinical practice.

B.2.13.3.2. Prior and subsequent therapy

The types of previous therapies received by ZUMA-2 participants are considered generally reflective of clinical practice. The main exception to this is that patients enrolled to ZUMA-2 could have received prior ibrutinib or acalabrutinib, the latter of 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 that should impact the applicability of ZUMA-2 data to patients in the UK, and sub-group analyses show no clear differences in response to KTE-X19 based on type of prior BTKi (Appendix E).

Ibrutinib was also the most common bridging therapy used in ZUMA-2 which would not be routinely reimbursed in NHS England (it is only reimbursed for second-line use). The more likely bridging therapy in clinical practice is expected to be chemotherapy or steroids. It is important to recognise that bridging therapy is used without expectation of tumour regression but in the hope of slowing progression enough to allow CAR T-cell therapy to be manufactured and administered. Patients receiving bridging therapy in the trial continued to show advancing disease (note a high proportion of the population were refractory to BTKi at enrolment), and sub-group analyses show no clear differences in response to KTE-X19 based on bridging therapy receipt (Appendix E). The impact of this difference on trial outcomes vs anticipated outcomes in the real-world is thus expected to be minimal.

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Subsequent therapies received by the trial population of ZUMA-2 are similarly reflective of clinical practice in that a 'mixed bag' of treatments was adopted, given the lack of 'standard of care' in the later-line r/r MCL setting. Although venetoclax, the most commonly adopted subsequent treatment in ZUMA-2, is not indicated for MCL and is not widely adopted due to a lack of durable response, it has previously been made available for off-label use in UK patients via a compassionate use program supported by the manufacturer.[45] Moreover, ibrutinib, the second most commonly adopted subsequent treatment in ZUMA-2, is only reimbursed for use at second-line in England. The potential impact of the use of these treatments post-KTE-X19 on the trial survival data is unclear, though the limited impact of these agents as salvage treatments makes it unlikely that they will have added much to the OS in KTE-X19 recipients.

It should also be acknowledged that [redacted] with a KTE-X19-induced remission went onto receive allo-SCT in ZUMA-2. This would not be expected in clinical practice with KTE-X19 offering the potential of long-term survivorship without the need for allo-SCT consolidation. In addition, two patients in ZUMA-2 were retreated (as permitted by the ZUMA-2 protocol), but this is not expected to form part of the marketing authorisation. The impact of these patients on the overarching conclusions taken from ZUMA-2 are considered negligible; both demonstrated reduced response compared with the overall population. The impact of allo-SCT is difficult to disaggregate and therefore this is modelled as observed (with appropriate costing) in the cost effectiveness base case (see Section B.3.7).

B.2.13.3.3. Analysis sets

In consideration of the most appropriate analysis set for decision making, KTE-X19 Cohort 1 mITT data are presented alongside the primary IAS data and used in subsequent cost-effectiveness analysis (see Section B.3). This group provides data for KTE-X19 dosing as per the anticipated dosing terms of the EU marketing authorisation (as compared with Cohort 2), and the mITT analysis set provides data for all treated patients, irrespective of follow-up. Treated patients align to the costing framework proposed for KTE-X19 where only patients treated are paid for by the NHS, and the lack of restriction to follow-up avoids any potential selection bias.

B.2.13.3.4. Service provision

The manufacturing process of KTE-X19 has a unique step whereby tumour cells are removed from the leukapheresis harvest prior to ex vivo expansion of patient T-cells. This should help KTE-X19 manufacturing attempts to be successful first-time and facilitate prompt delivery of KTE-X19 to the patient. That said, there was an observed time lapse from leukapheresis to delivery of KTE-X19 to study site and to the patient in ZUMA-2: this was related to a patient for whom the shipment of KTE-X19 was intentionally delayed. The patients' disease progressed soon after leukapheresis and they were treated with rituximab-bendamustine that resulted in CR, deeming them ineligible for the trial. Approximately three months later, the patients' disease progressed again, and they were rescreened and deemed to be eligible. The patients' original product was subsequently shipped from the manufacturing facility, 127 days after the initial leukapheresis date.

Despite this difference in manufacturing, importantly, KTE-X19 does not have additional or different infrastructure and personnel needs compared with other CAR T-cell therapies and therefore would fit into current service provisions for such treatment, already set up in NHS England.

B.2.13.4. KTE-X19 as an end-of-life therapy

KTE-X19 satisfies the criteria to be considered an effective end-of-life therapy. Based on meta-analyses of studies providing post-BTKi treatment survival outcomes and real-world outcomes in UK studies, the life expectancy of adult patients with r/r MCL who have previously received a BTKi is estimated to be much less than 24 months typically. KTE-X19 is expected to extend this life expectancy by far more than the requisite 3 months, as demonstrated in a series of ITCs and subsequent cost-effectiveness modelling. Table 26 summarises these data.

It should also be noted that ibrutinib, which is used at an earlier treatment line, was considered an end-of-life therapy for r/r MCL patients in TA502[38] and CAR T-cell treatments have previously been considered end-of-life therapies in DLBCL indications.[69, 70]

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Table 26: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Current 'standard of care' survival estimates from MAIC: Restricted mean survival[a]: [redacted] months 24-month survival rate: [redacted]%	Section B.2.9.2 Page 70
	Reported survival post-BTKi: Median survival: 3.6 to 12.5 months	Section B.1.3.5 Page 19
	Current 'standard of care' survival estimates from economic modelling: Mean survival[b]: [redacted]months 24-month survival rate: [redacted]	Section B.3.3.3 Page 136
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	KTE-X19 survival estimates from MAIC modelling: Restricted mean survival[a]: [redacted] months	Section B.2.9.2 Page 70
	KTE-X19 survival estimates from ZUMA-2: 24-month survival rate: [redacted]% Median survival: not reached Longest observed survival to date: [redacted] months	Section B.2.6.3 Page 43
	KTE-X19 survival estimates from economic modelling: Mean survival[c]: [redacted] months 24-month survival rate: [redacted] Life years gained with KTE-X19 vs standard of care: [redacted]	Section B.3.3.3 Page 129 Section B.3.7 Page 178

Key: AUC, area under the curve.
Notes: [a], based on AUC of the survival function from 0 to 33 months, log-normal model; [b], based on AUC of the survival function over a lifetime horizon, log-normal model; [c], based on AUC of the survival function over a lifetime horizon, mixture cure log-normal model.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic search for existing economic evaluations in previously treated MCL did not identify any previous cost-effectiveness studies for KTE-X19 for MCL patients with relapsed or refractory disease. The search strategy, originally run on 13 February 2019, was adapted and updated on 10 January 2020. Full details of these searches and the findings are reported in Appendix G. The only published NICE single technology appraisal of treatment for relapsed or refractory MCL is TA502; *Ibrutinib for treating relapsed or refractory mantle cell lymphoma*; this guidance was published on 31 January 2018.[38] Table 27 summarises key components of the TA502 cost-effectiveness analysis. Throughout the remainder of Section B.3, we draw lessons from TA502, in the spirit of incremental evidence development and consistency across NICE evaluations.

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Table 27: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA502[38]	2018	The company submitted a de novo cohort-level cost-effectiveness model described by the company as a '*standard three health-state model*'. These three health states were: progression-free survival; post-progression survival; and death.[71] A 15-year time horizon was specified, and a 4-week cycle length was applied. The perspective was consistent with the NICE reference case.[71] The NICE final scope comparator was established clinical management without ibrutinib, including R-CHOP, R-CVP, FCR, RC. The company submission assumed R-CHOP as the most widely used comparison, presenting base case model results vs R-CHOP and scenario comparisons to other R-chemotherapy options.[72, 73]	The company submission targeted the licensed population: 'Adults with relapsed or refractory MCL'.[71] The clinical data used by the company to represent the effectiveness in this group was pooled from the pivotal Phase III RAY study, an RCT of ibrutinib vs temsirolimus; and supportive Phase II 'SPARK' and 'PCYC1104' studies. The median baseline age in this pooled dataset, assumed to be the mean age at the start of the economic model, was 68 years.[71] The company base case used an indirect treatment comparison to the 'Physician's choice' arm of the OPTIMAL study, an RCT of temsirolimus vs 'Physician's choice' in patients with r/r MCL after 2 to 7 prior therapies, supplemented with registry data for the effect of rituximab. The final recommendation was restricted to relapsed or refractory MCL patients who have had only one previous line of therapy.[74]	Total QALYs: Ibrutinib: Redacted information R-CHOP (base case comparator): Redacted information Incremental QALYs (ibrutinib vs R-CHOP, for the one prior therapy group): 0.82 to 1.87 using the Committee's preferred model, depending on the scenario.[38]	Total Costs: Ibrutinib: Redacted information R-CHOP (base case comparator): Redacted information Incremental costs (ibrutinib with PAS vs R-CHOP): £93,196 in the scenario with incremental QALYs 1.87, ICER £49,849	Ibrutinib with PAS vs R-CHOP: Plausible estimates ranging from £49,849/QALY gained to at least £69,142/QALY gained.[38, 71]

Key: FCR, fludarabine cyclophosphamide and rituximab; ICER, incremental cost-effectiveness ratio; MCL, mantle cell lymphoma; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; QALY, quality-adjusted life year; RC, rituximab and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; RCT, randomised controlled trial; R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone; r/r, relapsed or refractory; TA, Technology Appraisal.

B.3.2. Economic analysis

B.3.2.1. Patient population

The patient population considered in this analysis is adults with r/r MCL who have previously received a BTKi, in accordance with the anticipated EMA licence and reflective of the pivotal ZUMA-2 trial population. As discussed in Section B.1.1, the wording issued in the final NICE scope differs slightly in that it does not specify that patients will have previously received a BTKi; rather, it states that patients must have received at least two previous lines of therapy. Ibrutinib is the only BTKi recommended for use in MCL patients in NHS England clinical practice, and its NICE recommendation is specific to patients who have received one prior line of therapy (i.e. it is given at second line).[38] As such, the final NICE scope population wording is consistent with the patient group considered in this analysis.

As described in Section B.2.3, ZUMA-2 investigated the safety and efficacy of KTE-X19 in patients with r/r MCL. Specifically, in these patients the disease had progressed on (i) anthracycline- or bendamustine-containing chemotherapy, (ii) an anti-CD20 antibody, and (iii) a BTKi (ibrutinib and/or acalabrutinib). As discussed in Section B.2.13.3, compared with patients expected to receive KTE-X19 in clinical practice, ZUMA-2 patients were generally more heavily pre-treated (the median number of prior therapies was three; according to the current pathway of care, KTE-X19 is intended for use after two prior lines) and more refractory to BTKi treatment.

Two practising NHS England Consultants; Dr Sunil Iyengar (Royal Marsden NHS Foundation Trust) and Dr Jonathan Lambert (University College London Hospitals NHS Foundation Trust); were interviewed on 3 April 2020, to ensure our economic approach was consistent with expert clinical expectations, as described in Section B.3.10. In consideration of how ZUMA-2 baseline characteristics compare to the average patient in NHS England who is on post-ibrutinib third-line treatment, these Consultants surmised that the ZUMA-2 mITT group overall are slightly younger and fitter than the typical UK 3rd-line patient but comparable to groups in other published studies in 3rd line MCL.[47] Focusing on the proportion who were BTKi-refractory (62%, versus less than 20% in practice) however, the group can be categorised as high risk.[47] On balance, these experts considered ZUMA-2 patients to be broadly reflective of those who would receive KTE-X19 in NHS England clinical practice.[47]

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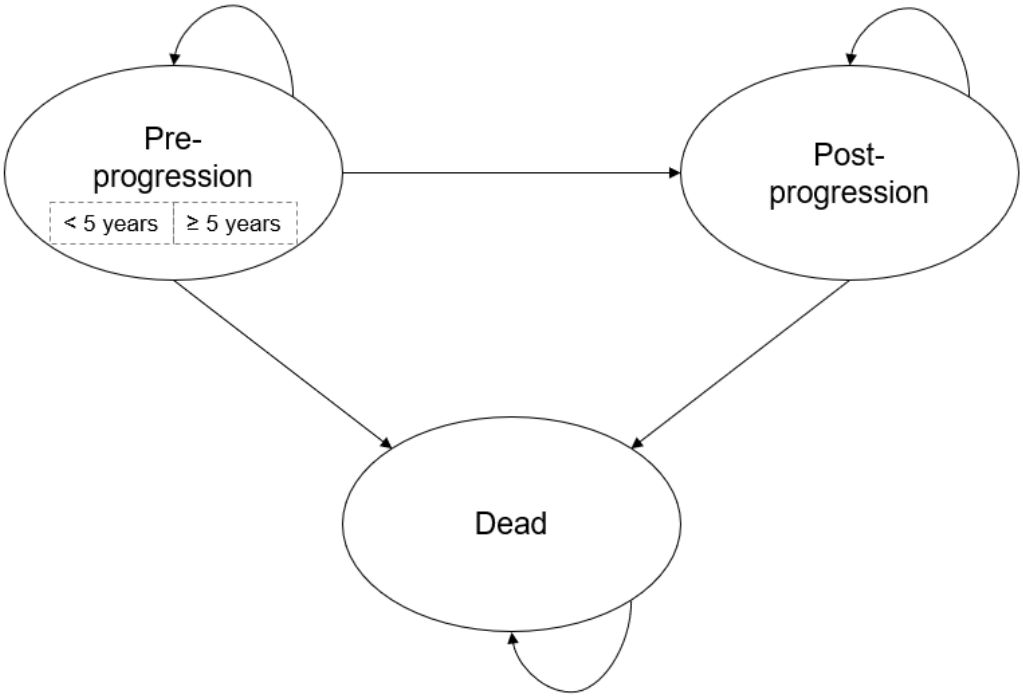
B.3.2.2. Model structure

A de novo cost-effectiveness model was developed in Microsoft Excel®. A partitioned survival approach with three health states (pre-progression, post-progression and death) was specified. Figure 26 presents the model's structure.

Figure 26: Model structure schematic



As shown in Figure 26, the partitioned survival model has three mutually exclusive health states:

- Pre-progression (< 5 years and ≥ 5 years)
- Post-progression
- Dead

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 up to 5 years, and those who remain in pre-progression for 5 years or more. This was done to explicitly capture the proportion of patients who remain in pre-progression for 5 years as 'long-term survivors'. In previous NICE appraisals of CAR T-cell therapies

in DLBCL, TAs 559 and 567[69, 70], it was assumed that these patients, though having heightened risk of death versus age-equivalent general population, do not incur further resource use and have improved HRQL, but from an earlier timepoint of 2 years post CAR-T-cell therapy. We broadly follow these assumptions for consistency, as detailed in Sections B.3.5.3 and B.3.4.5, but incorporate a 6-monthly cost of ongoing GP visits (Section B.3.5.3) based on NHS Consultant expectations.[47] 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 'dead' state; an absorbing health state. At any time point in the model, a patient can be alive with non-progressed disease (pre-progression), 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; zero.

The partitioned survival model structure is both simple and flexible enough to extrapolate survival using various methods and can incorporate relative efficacy in numerous ways. It allows for key trial endpoints such as OS and PFS to be modelled directly, and reflects the clinical pathway of disease in that, once progressed, patients cannot return to the pre-progression state. The approach is also 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.

Partitioned survival modelling is a widely used and accepted approach in oncology appraisals, particularly for end-stage cancer treatments. It is also consistent with the model structure used in the mock appraisal of regenerative therapies and cell therapy products (such as CAR T-cell therapies) published by Hettle et al., 2017.[75] Moreover, decision-making analysis in each of the previous NICE appraisals of CAR

T-cell therapies has used a partitioned survival model structure.[38, 76, 77] In each of these appraisals, the committee accepted this structure as appropriate for decision making (TA554, final appraisal determination [FAD], p.16, paragraph 3.15; TA559, FAD, p. 16, paragraph 3.16; TA567, FAD, p.11, paragraph 3.11). The model developed for the appraisal of ibrutinib in r/r MCL (TA502) also adopted a 'standard three-health-state model' with health states of progression-free survival, post-progression survival, and death.[38]

Of specific note, in TA554 and TA567, an initial decision tree was used to account for the costs and outcomes of patients who receive leukapheresis but do not go on to have the tisagenlecleucel-T infusion. In the de novo model, for the patients in the KTE-X19 arm who underwent leukapheresis but did not go on to receive KTE-X19 infusion in ZUMA-2, rather than modelling this as an initial decision tree, this was instead accounted for by using cost multipliers. This is consistent with the approach used in TA559.[76] Details are reported in Section B.3.5.2.1.

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.[78]

The model uses a 1-month cycle length (30.44 days). KTE-X19 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 KTE-X19, 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 allo-SCTs 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

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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 also specified by the NICE reference case.[78] 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 and the hope that KTE-X19 will offer long-term survivorship for some.

Table 28 compares the features of the current economic appraisal to previous NICE appraisals.

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Table 28: Features of the current economic analysis versus previous appraisals

Factor	Previous appraisals	Current appraisal	
	TA502	Chosen values	Justification
Time horizon	Lifetime	Lifetime	Long enough to reflect all important differences in costs or outcomes between the technologies being compared, in line with the reference case.[78] Survival benefits for patients treated with KTE-X19 are only fully captured if a lifetime horizon is used
Treatment waning effect?	Not applied	Not applied	Not appropriate as CAR T-cell therapies are given as a single dose
Source of utilities	EQ-5D-3L data from pooled Phase III RCT (RAY/MCL3001) and Phase II study (SPARK/MCL2001) data. Impact of R-chemo toxicity on HRQL taken from expert clinical advice and compared with available published literature.	EQ-5D-5L data from Phase II study, ZUMA-2. Mapped to EQ-5D-3L equivalent utility estimates, using the van Hout algorithm (pre-progression values only)[79], in line with the October 2019 NICE position statement on this issue.[80] Post-progression utility estimated using the data used for Committee decision-making and in ERG exploratory analyses to derive the relative difference between pre-progression and post-progression values. Alternative scenarios explored using published literature.	EQ-5D data reported directly from patients with utilities based on public preferences is considered the preferred method by NICE[78] Where post-progression EQ-5D-3L data was not available from ZUMA-2 (due to very small patient number), literature-based assumptions were used.

Factor	Previous appraisals	Current appraisal	
	TA502	Chosen values	Justification
Source of costs	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: CAR T-cell, chimeric antigen receptor T-cell; eMIT, electronic Market Information Tool; EQ-5L, EuroQol 5 dimensions; HRQL, health-related quality of life; MCL, mantle cell lymphoma; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; TA, technology appraisal.			

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B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention

The intervention, KTE-X19, is implemented in the model as per the expected marketing authorisation, anticipated [redacted], and is reflective of the decision problem described in Section B.1.1.

KTE-X19 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.

KTE-X19 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

As detailed in Section B.1.3.4, although the treatment options at first line and at first relapse (second line) are well established, treatment options at higher relapse (third and later line) are not. Following second-line BTKi (ibrutinib) failure, there is no true standard of care and treatment is chosen on an individual basis from the limited options available. Typically, patients receive an alternative immunochemotherapy strategy to that adopted at first-line, but responses are almost always inferior at later lines and rapid progression is expected.[37]

Guidelines from the BSH recommend that for patients who have higher relapse following a BTKi, the treatment options are an alternative immunochemotherapy, BTKi or other targeted therapy.[34] The BSH guidelines, published in 2018, were deemed representative of the current treatment pathway in England by practising NHS Consultants.[47] At third line, no novel treatments are routinely available. Instead,

patients are usually given a regimen of chemotherapy they have not previously received.[81]

As stated in Section B.1.1, allo-SCT is not considered a relevant comparator and would not be used as an alternative treatment to KTE-X19 for patients who have relapsed/demonstrated refractoriness after receiving a BTKi. Rather, it may be used to consolidate a response to BTKi treatment (before KTE-X19 in the pathway), but, importantly, it is 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).[34, 37]

With the above in mind, the comparator considered in the economic model is standard of care (SoC) as a blended comparator of several limited therapy options. Specifically, the SoC arm consists of regimens recommended at first line in the BSH guidelines and those included in the final scope for TA502. These are the following:

- R-bendamustine
- R-CHOP
- R-BAC
- Rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP)
- Fludarabine, cyclophosphamide and rituximab (FCR)

Treatment-related costs associated with SoC are captured by the expected distribution of these treatment options across the patient group, informed by NHS Consultant reflections[47], as described in Section B.3.5.2.2. The clinical effectiveness assumed for these treatments is modelled based on systematic review and meta-analysis of available published data, as introduced in Section B.2.9, described in Section B.2.3, and further harnessed in Section B.3.3.

B.3.3. Clinical parameters and variables

The clinical parameters used to inform the KTE-X19 and SoC arms in the economic model, and their respective sources, are summarised in Table 29 and discussed in more detail throughout this section and, in the case of AE rates, Section B.3.4.

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The ZUMA-2 primary endpoint, ORR, is not explicitly captured within the cost-effectiveness analysis, yet is indirectly captured. For patients who respond well to CAR T-cell therapy, there is hope – data for this population exist, as well as science-driven anticipation of long-term healthy survivorship. The more flexible survival analyses described in this section, and incorporated into the cost-effectiveness analysis, are sufficient to capture this data-driven expectation.

Table 29: Data sources of clinical parameters used in the model

Component	Application with the model	Source(s) for KTE-X19	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[82] • Literature (Maurer et al., 2014)[83]	• Meta-analyses of published literature • UK lifetables[82] • Literature (Maurer et al., 2014)[83]
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 cost and disutility associated with each AE	• ZUMA-2 Cohort 1, mITT population	• TA502
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[84] • Wider literature (AE utility effects)	• ZUMA-2 Cohort 1, mITT population (pre-progression) • TA502 for post-progression • Ara and Brazier 2010[84] • TA502 (AE utility effects)
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

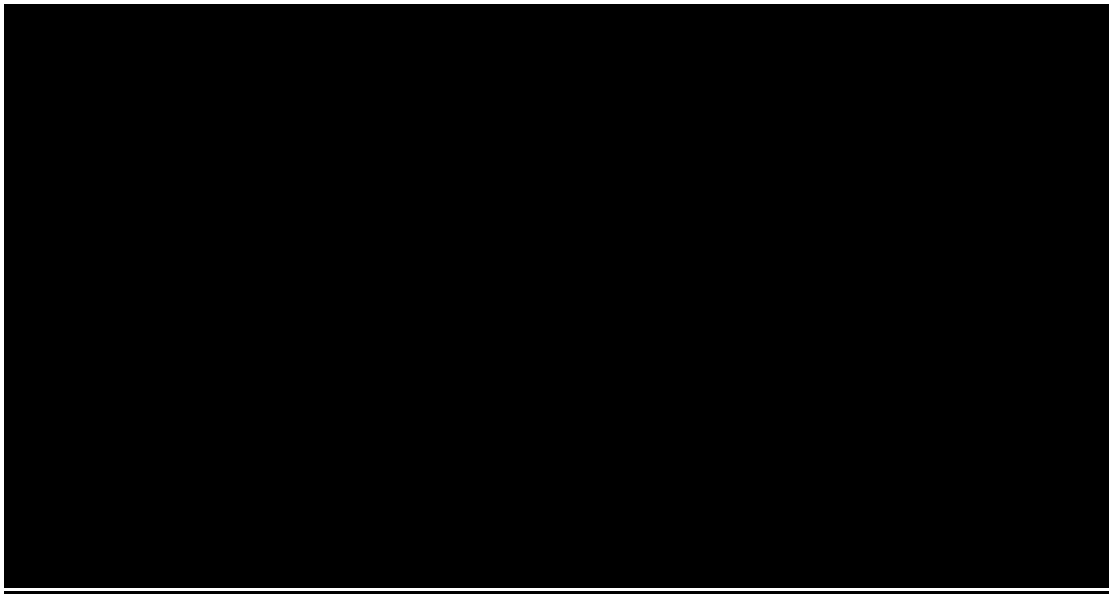
B.3.3.1.1. KTE-X19

KTE-X19 OS and PFS expectations are driven by ZUMA-2 patient data. Survival analyses for KTE-X19 were conducted using the mITT analysis set as described in Section B.2.4 (all patients treated with any dose of KTE-X19; N = 68).

Latest available (24 July 2019 database lock) KTE-X19 PFS and OS Kaplan–Meier data are presented in Figure 27 and Figure 28, respectively. As the latest OS and PFS Kaplan–Meier data are incomplete (i.e. there were patients still alive and/or progression-free at point of database lock), extrapolation was required to capture lifetime OS and PFS. The approach used to capture lifetime outcomes, and its alignment to guidance in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14, is described across B.3.3.2.1 and B.3.3.3.1.[85]

Despite the relatively short follow-up period and small number of patients at risk, the flat tails observed in the PFS and OS data suggest a remarkable proportion of relapsed or refractory MCL patients experiencing long-term remission and survival. Sections B.3.3.1.1 and B.3.3.2.1 illustrate how, in comparison to standard parametric survival approaches described in TSD 14 and shown in Section B.2.9, more flexible 'mixture cure' methodologies better fit both these data and expectation of long-term prospects for patients responding to CAR T-cell therapy.

Figure 27: Progression-free survival in ZUMA-2 mITT population



Key: mITT, modified intent to treat.

Figure 28: Overall survival in ZUMA-2 mITT population

Key: mITT, modified intent to treat.

B.3.3.1.2. Standard of care

As ZUMA-2 is a single-arm trial, efficacy estimates for SoC were sourced from the published literature. The comparator literature sources used to estimate the efficacy of SoC are summarised in Table 30. As discussed in Section B.2.9, a criterion for being included in the final analysis was whether the study reported Kaplan–Meier data. Four studies met this criterion for OS, and two for PFS.

Table 30: Literature sources included in the analysis of standard of care efficacy

Source	N	PFS KMs/IPD available	OS KMs/IPD available	Subsequent treatment post-BTK inhibitor
Jain (2018)[43]	41	×	✓	Salvage treatments (n = 36) Subsequent treatment included R-HyperCVAD (n=6), radiochemotherapy (n=6), bendamustine-based (n=5), lenalidomide-based (n=4), bortezomib-based (n=3), R-CHOP (n=3), radiation alone (n=3), R-ESHAP with allo-SCT (n=1), lenalidomide + rituximab + proteasome inhibitor (n=2), phosphoinositide 3-kinase inhibitor (n=1), miscellaneous (n=2)

Source	N	PFS KMs/IPD available	OS KMs/IPD available	Subsequent treatment post-BTK inhibitor
Martin (2016)[44]	114	×	✓	Subsequent treatments (n = 73) Rituximab, 53%; lenalidomide, 26%; cytarabine, 18%; bendamustine, 16%; bortezomib, 10%; anthracycline, 7%; phosphoinositide 3-kinase inhibitor, 5%
Eyre (2019)[45]	20	✓	✓	Venetoclax (n = 20)
McCulloch (2019)[57]	29	✓	✓	R-BAC (n = 29)
Key: allo-SCT, allogenic stem cell transplant; BTK, Bruton tyrosine kinase; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisolone; IPD, individual patient data; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; R-BAC, rituximab bendamustine cytarabine; R-ESHAP, rituximab etoposide methylprednisolone cytarabine cisplatin; R-HyperCVAD rituximab vincristine doxorubicin dexamethasone.				

Guidance from NICE DSU TSD 18 was followed when deriving estimates of comparative efficacy from unanchored datasets.[61] As discussed in Section B.2.9, an unanchored indirect treatment comparison was performed as (i) a naïve (unadjusted) comparison and (ii) an MAIC (adjusted). Although the MAIC attempts to adjust for the observable differences between the ZUMA-2 individual patient-level data and the SoC aggregate data study populations, this is reliant on strong assumptions, inherent uncertainty and an unknown direction of bias. In particular, a notable challenge was the extreme reduction in ESS after adjusting ZUMA-2 for the baseline characteristics of interest (for OS, the ESS was reduced to 19.4; for PFS, the ESS was reduced to 15.5 [from N = 68]).

Reassuringly, MAIC-adjusted and naïve comparisons did not differ greatly in their survival projections (Section B.2.9, Table 19). In view of the limitations of MAIC-adjusted comparisons, the naïve comparisons that use the ZUMA-2 mITT sample data in full are used for cost-effectiveness analysis.

For the cost-effectiveness base case, summarised in B.3.6.1, to use the maximum amount of available data for the SoC arm while being mindful of the validity and applicability of each study, a meta-analysis of all the identified relevant studies in Table 30 was used; i.e. four studies for OS, two for PFS. Meta-analyses for OS and PFS were performed using both fixed- and random-effects models; however, for the

random-effects model, the 95% confidence interval (CI) around the survival curve had a lower and higher bound of 0 and 1, respectively, which was not interpretable. Therefore, only the results of the fixed-effects model were used.

In addition to the preferred base case, the flexibility and functionality for the user to explore various study combinations as scenario analyses is incorporated into the cost-effectiveness model. These various options are summarised in Table 31.

Table 31: Standard of care data source scenarios

Dataset	Description	Included studies
SoC OS		
OS all included studies (base case)	The base case includes all four studies	Jain 2018b, Martin 2016, Eyre 2019, McCulloch 2019
OS mixed ST only	Includes studies with mixed treatments only	Jain 2018b, Martin 2016
OS mixed ST or R-BAC	Includes studies with mixed treatment or R-BAC	Jain 2018b, Martin 2016, McCulloch 2019
OS t = 0 at start of ST	Includes studies where time 0 is start of ST	Martin 2016, Eyre 2019, McCulloch 2019
OS t = 0 at start of ST, excluding venetoclax	Includes studies where time 0 is start of ST, excluding venetoclax	Martin 2016, McCulloch 2019
OS Jain only	Includes only Jain 2018b	Jain 2018b
OS Martin only	Includes only Martin 2016	Martin 2016
OS Eyre only	Includes only Eyre 2019	Eyre 2019
OS McCulloch only	Includes only McCulloch 2019	McCulloch 2019
SoC PFS		
PFS pooled (base case)	Includes both studies for PFS	Eyre 2019, McCulloch 2019
PFS Eyre only	Includes only Eyre 2019	Eyre 2019
PFS McCulloch only	Includes only McCulloch 2019	McCulloch 2019
Key: OS, overall survival; PFS, progression-free survival; R-BAC, rituximab, bendamustine and cytarabine; SoC, standard of care; ST, subsequent therapy.		

The PFS and OS Kaplan–Meier data available for SoC are shown in Figure 29 and Figure 30, respectively. Note, for ease of interpretation of overlain data from various sources, numbers at risk are not presented.

Figure 29: Standard of care progression-free survival Kaplan–Meier plots: all included studies

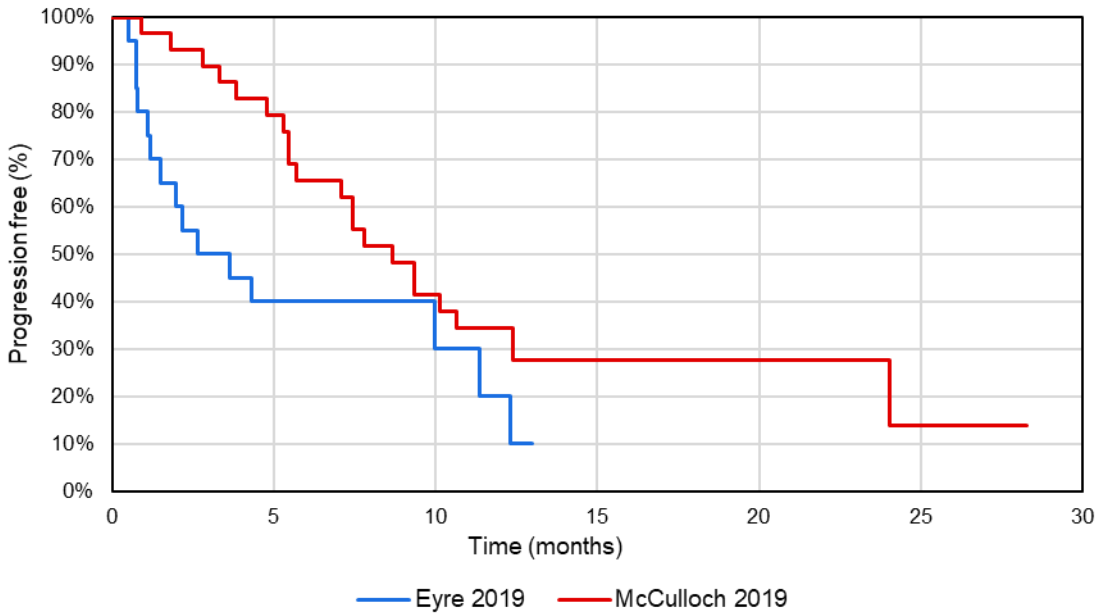
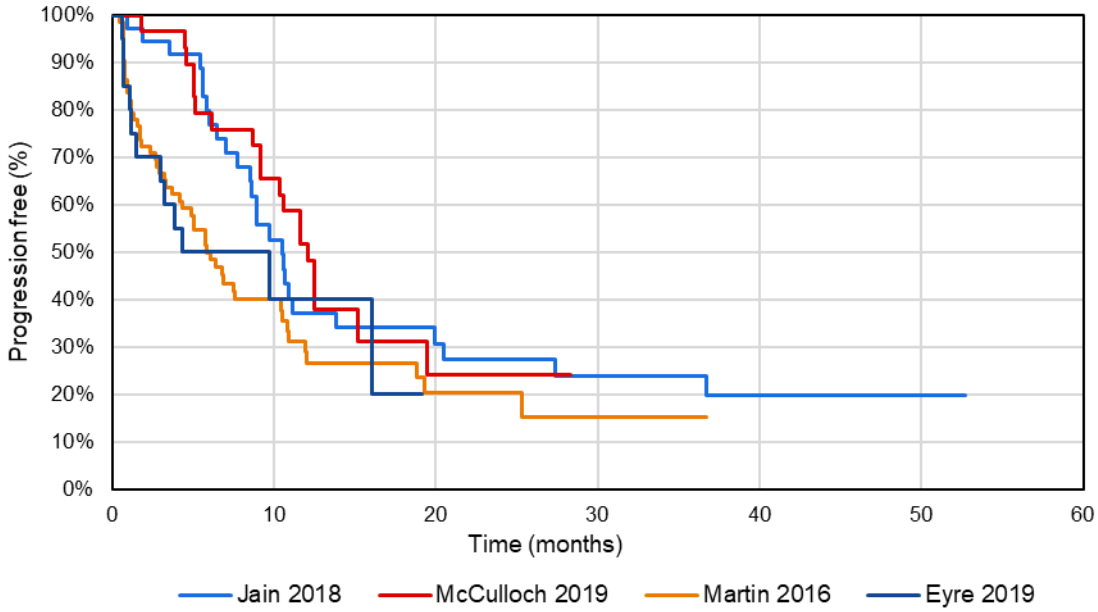


Figure 30: Standard of care overall survival Kaplan–Meier plots: all included studies



As with KTE-X19, OS and PFS data from literature sources were incomplete. As such, NICE TSD 14 guidance was followed to capture lifetime outcomes, as described in Sections B.3.3.2.2 and B.3.3.3.2.[85]

B.3.3.2. Progression-free survival analysis

This section details the approaches to modelling PFS for the KTE-X19 and SoC treatment arms. A summary of the base case approaches used is provided in Table 32.

Table 32: Summary of base case approach used to model PFS, by treatment arm

	KTE-X19	SoC
Clinical data source(s) to inform the modelling of PFS	• ZUMA-2 mITT PFS data • UK life table data to inform age- and gender-matched background mortality • SMR to adjust age- and gender-matched background mortality	• PFS data from Eyre et al., and McCulloch et al. • UK life table data to inform age- and gender-matched background mortality • SMR to adjust age- and gender-matched background mortality
Survival modelling approach	• Mixture cure model (ZUMA-2 PFS data)	• Meta-analysis of standard parametric survival models (Eyre et al., and McCulloch et al., PFS data)
Key: mITT, modified intent to treat; PFS, progression-free survival; SMR, standardised mortality ratio; SoC, standard of care.		

B.3.3.2.1. KTE-X19

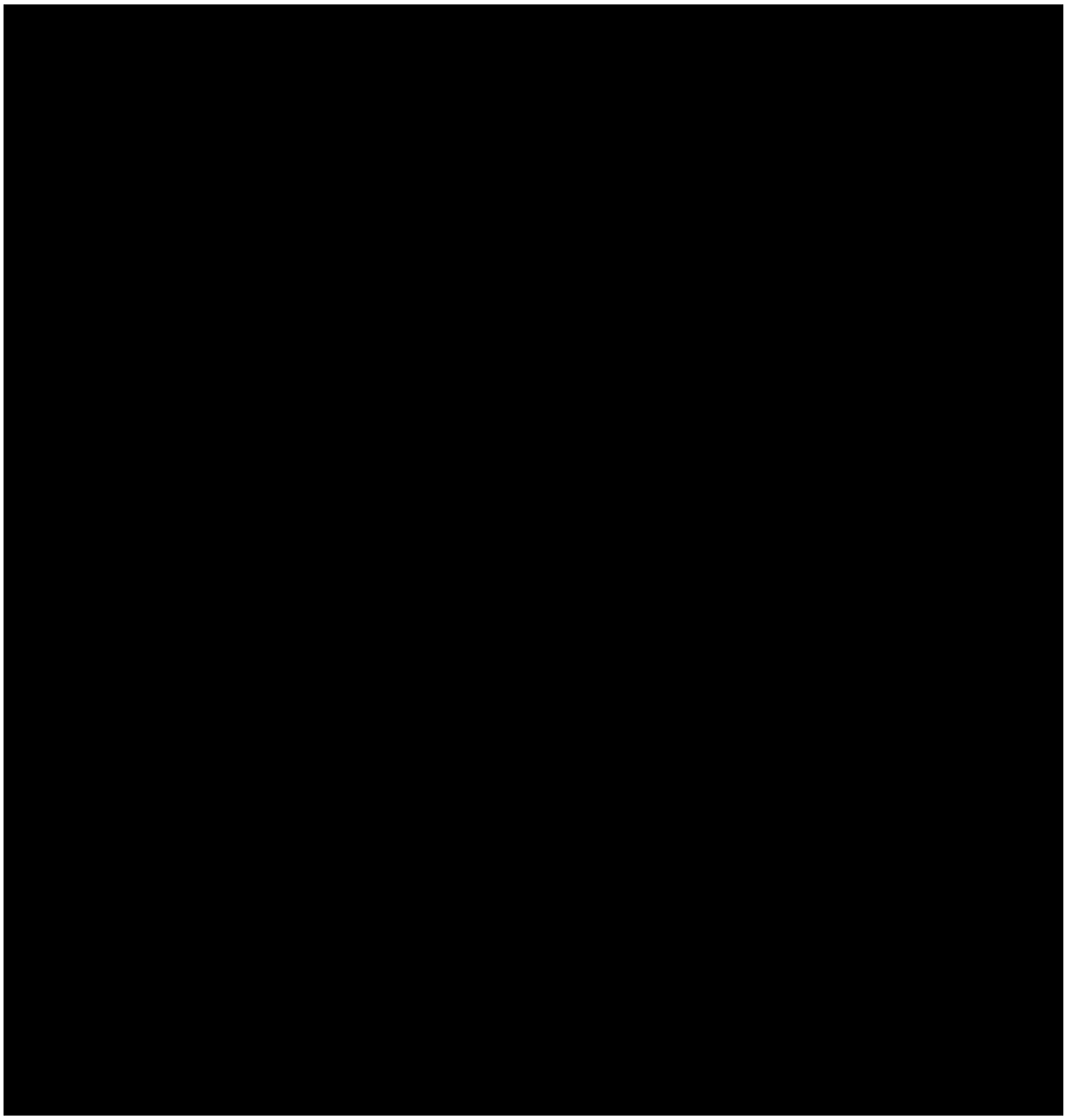
Standard parametric curves

A range of standard parametric survival models were fitted to KTE-X19 PFS data. 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 31, with corresponding smoothed hazard plots presented in Figure 32. AIC and Bayesian information criterion (BIC) statistics and landmark estimates are presented in Table 33.

Figure 31: KTE-X19 progression-free survival: standard parametric curves



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

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Figure 32: KTE-X19 progression-free survival: standard parametric model smoothed hazard plots

[redacted]

Key: KM, Kaplan–Meier.

Table 33: KTE-X19: progression-free survival: standard parametric curve AIC and BIC statistics and landmark survival estimates

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

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

Based on the goodness-of-fit statistics and visual interpretation of trends, the generalised gamma and Gompertz models provide the best fit to the Kaplan–Meier data. Based on the mechanism of action of KTE-X19 and precedent from previous studies of CAR T-cell therapies, it is expected that a proportion of patients will experience long-term survivorship; the generalised gamma and Gompertz models depicted in Figure 31 both reflect this, to varying extents. Additionally, these models were also shown in Figure 32 to better reflect the observed hazards of progression compared with the other models.

However, although the generalised gamma and Gompertz models provide the best visual fit, neither model appears to provide a good visual fit to the observed data from approximately 10 months onwards. The Gompertz model estimates highly optimistic long-term projections (prior to correction for background mortality). Given these limitations, which can be largely attributed to the limited flexibility of the standard parametric models for these data, 'mixture cure' models were also tested.

Mixture cure models

NICE TSD 14 discusses the potential benefits of using more flexible models when standard parametric curves do not provide a good fit to the observed data. Mixture cure models represent an alternative, more flexible approach to modelling PFS for KTE-X19 that can potentially account for more complex hazard functions. The use of these models can be beneficial over standard parametric models where there is evidence to support that a proportion of patients have more favourable outcomes (i.e. experience long-term survivorship) following treatment, and a proportion do not. Furthermore, these models have been used for decision making in the previous CAR T-cell therapy appraisals TA554, TA559 and TA567, where, similar to this appraisal, the observed data were immature and where there was clinical expectation of a plateau in progression-free/overall survival.[76, 77, 86]

Mixture cure models were estimated using the ZUMA-2 patient-level data, for which a logistic regression was used to model the probability that patients experienced long-term survivorship. This is termed the 'implied long-term survivor fraction', as presented in Table 34. Applying this survivor fraction splits the ZUMA-2 population into two underlying groups: patients who experience long-term survival and those

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who do not. Long-term survivor mortality is captured by standardised mortality ratio (SMR)-adjusted age- and gender-matched general population mortality data (derived from UK lifetable data)[82]; for those less fortunate, risk of progression was defined by the standard parametric survival model fits to ZUMA-2 data.

Table 34: KTE-X19 Progression-free survival: implied long-term survivor fractions

Model	Implied long-term survivor fraction
Exponential	[redacted]
Generalised gamma	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Weibull	[redacted]

Overall PFS projections are a blended average of the two 'mixture cure' subpopulations. These are graphically represented alongside ZUMA-2 PFS Kaplan–Meier data in Figure 33 with corresponding smoothed hazard plots presented in Figure 34. AIC and BIC statistics and landmark estimates are presented in Table 35.

Figure 33: KTE-X19 progression-free survival: mixture cure models

[redacted]

Key: KM, Kaplan–Meier.

Figure 34: KTE-X19 progression-free survival: mixture cure model smoothed hazard plots

[redacted]

Key: KM, Kaplan–Meier.

Table 35: KTE-X19 progression-free survival: mean, median and landmark values and AIC and BIC statistics for mixture cure model curves

Model	AIC	BIC	Mean PFS	Median PFS	Proportion pre-progression at each landmark value			
					6 months	1 year	2 years	5 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

By assessing the visual fit of the mixture cure models, all but the generalised gamma model appear to provide a good fit to the observed data, and all models produce

similar long-term projections. These projections capture the observed, and anticipated, plateau in the PFS Kaplan–Meier plot. Given the visual similarities of the models, the base case model was selected based on providing the best statistical goodness of fit; this was the log-normal model.

The mixture cure model was used as the base case approach, rather than the standard parametric models, given the strong biomedical rationale for believing that a proportion of those patients treated with KTE-X19 will have a durable long-term survivorship. Furthermore, the mixture cure extrapolations were considered consistent with both the data and hopes and expectations for CAR T-cell therapy in MCL at NHS Consultant review.[47] However, general population mortality rates may be inappropriate given the impact of prior treatments on survival in these patients; an appropriate value for disease-adjusted mortality from DLBCL is available and may be appropriate for responders. An SMR of 1.09, derived from a publication by Maurer et al., (2014)[83] and used in NICE TA559, which assessed the mortality of DLBCL patients who maintained event-free at 2 years, is used in the model base case to adjust for excess mortality in long-term survivors.

To explore the impact of the SMR on the model outcomes, a scenario (Section B.3.8.3) assuming unadjusted general population mortality for long-term survivorship PFS. Additionally, due to the uncertainty around this parameter estimate, the SMR parameter is also varied within one-way and probabilistic sensitivity analyses (Section B.3.8.1).

B.3.3.2.2. Standard of care

As described previously in Section B.3.3.1.2, SoC efficacy is based on the literature-based meta-analysis. Specifically, SoC PFS consists of the meta-analysed data from Eyre et al. and McCulloch et al.[24, 45] As detailed in Section B.2.8, a two-step approach to meta-analysis was taken:

- Step one – various parametric survival distributions were fitted to digitised data, and the most appropriate distribution chosen based on AIC and visual inspection
- Step two – parameter estimates were synthesised with a multivariate meta-analysis model, as proposed by Achana et al.[59], to provide a time-varying treatment effect

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Step one

The standard six parametric models were fitted to the digitised PFS data (using digitiser software: DigitizeIt[87]) from Eyre et al. and McCulloch et al. separately; these models are presented graphically in Figure 35 and Figure 36, respectively. Corresponding smoothed hazard plots for the models fitted to the Eyre et al. and McCulloch et al. PFS data are presented in Figure 37 and Figure 38, respectively. Statistical goodness-of-fit statistics, in the form of AIC only, are reported in Table 36.

Figure 35: Eyre et al. progression-free survival: standard parametric curves

Key: KM, Kaplan–Meier.

Figure 36: McCulloch et al. progression-free survival: standard parametric curves

[redacted]

Key: KM, Kaplan–Meier.

Figure 37: Eyre et al. progression-free survival: standard parametric model smoothed hazard plots

[redacted]

Key: KM, Kaplan–Meier.

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Figure 38: McCulloch et al. progression-free survival: standard parametric model smoothed hazard plots

[redacted]

Key: KM, Kaplan–Meier.
Note: Gompertz and exponential models are overlapping.

Table 36: Eyre et al. and McCulloch et al. progression-free survival: standard parametric curve AIC statistics

Model	AIC: Eyre et al.	AIC: McCulloch et al.	Sum
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Key: AIC, Akaike information criterion.			

By assessing the visual fit of the models fitted to Eyre et al., PFS, all models appear to provide a similar fit to the observed data and start to differ more greatly after the study period. After this point, the generalised gamma provides the most optimistic long-term projections, while the exponential model provides the most pessimistic. Of the models fitted to PFS from McCulloch et al., visually all six models are similar,

both to the observed data and the projected PFS. The AIC indicated that the log-logistic model provides the best statistical fit to observed data. To select the best fitting model overall (across both studies), a sum of the AIC values was taken; this indicated the log-normal to be the best fitting model to the observed data, overall. This is also consistent with base case structural assumption for the group who receive KTE-X19 but are not predicted to achieve long-term survivorship, as described in Section B.3.3.1.1.

Step two

The shape and scale parameters and correlation between the parameters from the models that were fitted individually for each study were then synthesised in a multivariate meta-analysis model. The resulting pooled curves are presented in Figure 39. Additionally, the landmark survival estimates for each pooled parametric model are presented in Table 37.

Figure 39: Standard of care progression-free survival: standard parametric curves

[redacted]

Table 37: Standard of care progression-free survival: standard parametric curve landmark survival estimates

Model	Mean PFS	Median PFS	Proportion pre-progression at each landmark value			
			6 months	1 year	2 years	5 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: PFS, progression-free survival
Notes: Mean and median values are provided in units of months.

By assessing the visual fit of the pooled models, all six appear to be similar, particularly for the first 12 months. After this time point, again, the generalised gamma provides the most optimistic PFS projections and the exponential provides the most pessimistic, based on mean PFS.

As discussed in Section B.1.3.4, a recently reported observational study of R-BAC use post-BTKi failure across UK and Italian centres (n = 36) reported a median PFS of 10.1 months.[57] This study is an update of the n = 29 McCulloch et al. study included in the analysis. With the maturity of the data in mind, the best fitting (log-normal) model is used in the base case. If the McCulloch et al. data better reflect current NHS England outcomes than the Eyre et al. data, the meta-analysed log-normal model may be a slight underestimate. NHS Consultants were asked to consider and advise on the plausibility of these extrapolations.[47] After considering that less than 15% to 30% could plausibly achieve allo-SCT from third-line treatment, expectation was of 2–3% PFS at 5 years.[47] Use of the most optimistic (generalised gamma) projection is tested in a scenario in Section B.3.8.3.

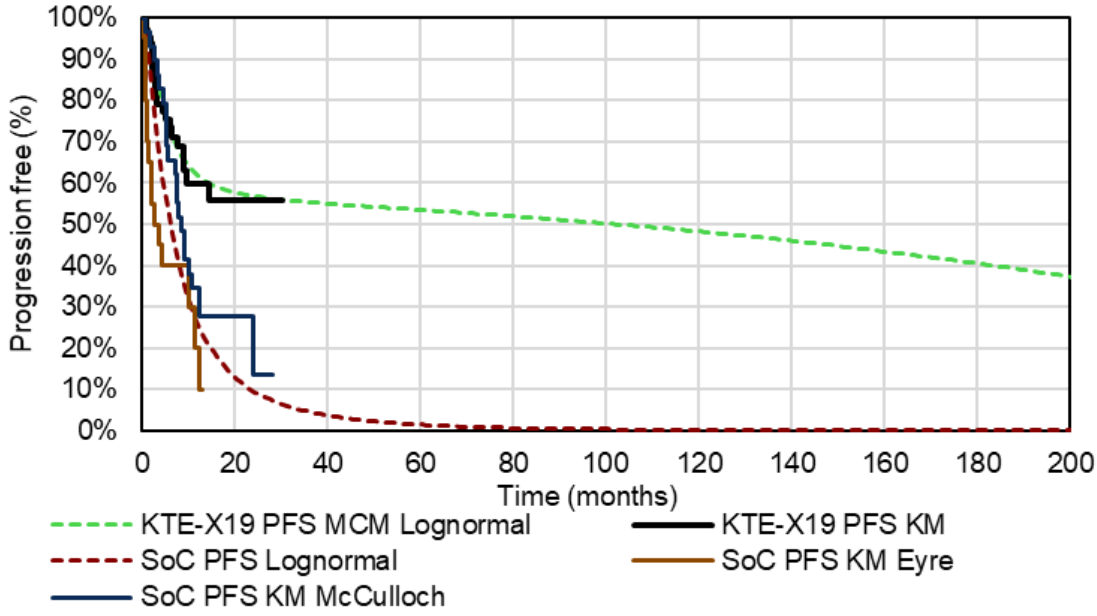
In contrast to the mixture cure model methodology, background mortality was not used directly to model PFS for the SoC arm; rather, it was used to ensure that the hazard of progression for the SoC-treated patient population exceeded (or was equal

to) the age- and gender-matched general population hazard of death. Therefore, to be consistent with the assumptions used to model efficacy for the KTE-X19 arm, the 1.09 SMR-adjusted general population mortality rate was also applied to the SoC arm.

B.3.3.2.3. Comparison of base case progression-free survival for KTE-X19 and standard of care

Following model selection, Figure 40 presents the selected base case models used for estimating PFS in the KTE-X19 and SoC treatment arms. These were the log-normal mixture cure model for KTE-X10 PFS and the log-normal model for SoC PFS. This figure indicates the expected relative benefit of KTE-X19 over SoC – a far greater proportion of patients remaining progression-free over time.

Figure 40: Comparison of selected models for KTE-X19 and standard of care progression-free survival



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

B.3.3.3. Overall survival analysis

This section details the approaches to modelling OS for the KTE-X19 and SoC treatment arms. A summary of the base case approach and data is provided in Table 38.

Table 38: Summary of base case approach and data used to model overall survival, by treatment arm

	KTE-X19	SoC
Clinical data source(s) to inform the modelling of OS	• ZUMA-2 mITT OS data • UK life table data to inform age- and gender-matched background mortality • SMR to adjust age- and gender-matched background	• OS data from Jain et al., Martin et al., Eyre et al., and McCulloch et al. • UK life table data to inform age- and gender-matched background mortality • SMR to adjust age- and gender-matched background
Modelling approach taken	• Mixture cure model (ZUMA-2 OS data)	• Meta-analysis of standard parametric survival model (Jain et al., Martin et al., Eyre et al., and McCulloch et al., OS data)
Key: mITT, modified intent to treat; OS, overall survival; PFS, progression-free survival; SMR, standardised mortality ratio; SoC, standard of care.		

B.3.3.3.1. KTE-X19

Standard parametric curves

Adopting the procedure used to model PFS, a variety of standard parametric curves were used to model KTE-X19 OS. These models are graphically represented alongside ZUMA-2 OS Kaplan–Meier data in Figure 41, with corresponding smoothed hazard plots presented in Figure 42. AIC and BIC statistics and landmark estimates are presented in Table 39.

Figure 41: KTE-X19 overall survival: standard parametric curves

Key: KM, Kaplan–Meier.

Note: Standard parametric curves presented here have not been corrected for background mortality

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Figure 42: KTE-X19 overall survival: standard parametric model smoothed hazard plots

[redacted]

Table 39: KTE-X19: overall survival standard parametric curve AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Mean OS	Median OS	Proportion surviving at each landmark value			
					6 months	1 year	2 years	5 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Based on goodness-of-fit statistics, the generalised gamma and exponential models provide the best fit to the KM data. Similar to the respective observation for the KTE-X19 PFS data, generalised gamma and Gompertz models appear to capture the expectation that a proportion of patients will experience long-term survivorship; again, to varying extents. However, from Figure 42, of the six models considered, only the Gompertz model appears to reflect the observed hazards.

Given the short-term follow-up of OS from ZUMA-2, the generally poor visual fit overall of the Gompertz model to the observed OS, what appears to be an overly optimistic long-term survival projection with the Gompertz model, and for consistency with PFS modelling, mixture cure models were again considered.

Mixture cure models

Combining the estimated long-term survivor fraction (Table 40), age- and gender-matched mortality for the proportion of patients who experienced long-term survivorship, and the fitted parametric patients for the proportion of patients who did not, Figure 43 presents the overall estimated OS for each mixture cure model compared with the ZUMA-2 OS KM data. Additionally, corresponding smoothed hazard plots are presented in Figure 44, while AIC and BIC statistics and landmark estimates are presented in Table 41.

By assessing the visual fit of the mixture cure models, all appear to provide a good fit to the observed data, and all models produce similar long-term survival projections. These projections capture the observed and anticipated plateau in the OS KM plot. The generalised gamma model failed to converge and is therefore not considered for the analysis. Due to the visual similarities of the models, the base case model was selected based on providing the best statistical goodness of fit; those most relevant based on this criterion were the log-normal and exponential models. Given that the log-normal model was selected for KTE-X19 PFS, this was deemed most appropriate to capture the same underlying trends across the two endpoints. This was explained at NHS Consultant review, with little constructive feedback given the visual similarity across extrapolations.[47] Therefore, the log-normal model was selected for the base case. The most optimistic and pessimistic models based on

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mean OS (Weibull and exponential, respectively) were tested in scenario analyses, the results of which are presented in Section B.3.8.3.

Table 40: KTE-X19 progression-free survival: implied long-term survivor fractions

Model	Implied long-term survivor fraction
Exponential	[redacted]
Generalised gamma*	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Weibull	[redacted]
Key: NA, not applicable **Notes:** * The generalised gamma model did not converge and was therefore omitted from the model base case selection.	

Figure 43: KTE-X19 overall survival: mixture cure models

[redacted]

Key: KM, Kaplan–Meier.

Figure 44: KTE-X19 overall survival: mixture cure model smoothed hazard plots

[redacted]

Key: KM, Kaplan–Meier.

Table 41: KTE-X19 overall survival, mean, median and landmark values and AIC and BIC statistics for mixture cure model curves

Model	AIC	BIC	Mean OS	Median OS	Proportion surviving at each landmark value			
					6 months	1 year	2 years	5 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; NA, not applicable; OS, overall survival.
Notes: Mean and median values are provided in units of months. Best fitting model in bold. The generalised gamma model was omitted from the model base case selection.

As discussed in Section B.3.3.2.1, it may be considered an optimistic approach to assume that the proportion of patients experiencing long-term survivorship (i.e. the cure fraction) have survival equal to that of the age- and gender matched population. As such, the SMR of 1.09 applied to PFS is also applied to OS in the model base case to adjust for excess mortality.[83]

The scenario in Section B.3.8.3 explores the use of unadjusted general population mortality in mixture cure OS extrapolations. As for PFS, uncertainty around the base case SMR parameter is tested in one-way (Section B.3.8.1) and probabilistic (Section B.3.8.2) sensitivity analyses. exploring the use of unadjusted general population mortality in mixture-cure PFS projections, noted in Section B.3.3.2.1, also assumes unadjusted general population mortality in mixture-cure OS extrapolations.

B.3.3.3.2. Standard of care

As described in Section B.3.3.1.2, SoC efficacy is based on the literature-sourced meta-analysis. Specifically, SoC OS consists of the meta-analysed data from Jain et al., Martin et al., Eyre et al. and McCulloch et al. As for PFS, the same two-step approach was taken.

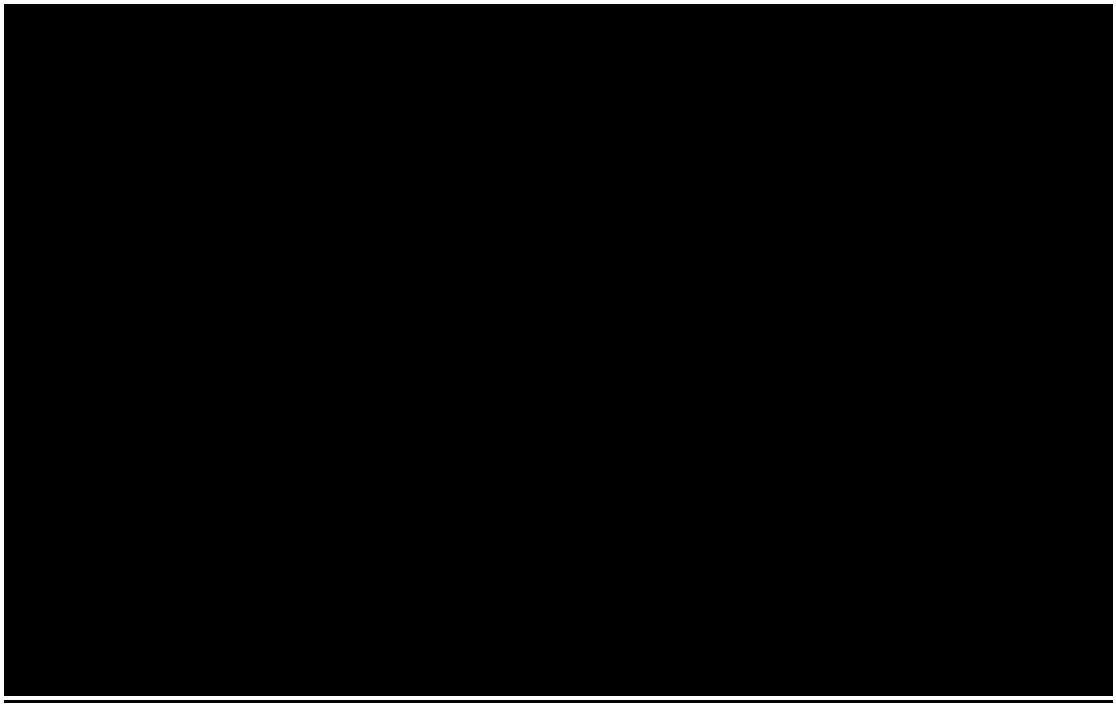
Step one

The standard six parametric models were fitted to the digitised OS data from Jain et al., Martin et al., Eyre et al. and McCulloch et al., separately; in order, these models are presented graphically in Figure 45 to Figure 48. Corresponding smoothed hazard plots are presented in Figure 49 to Figure 52. Statistical goodness of fit measures, in the form of AIC only, are reported in Table 42.

Figure 45: Jain et al. overall survival, standard parametric curves

Key: KM, Kaplan–Meier.

Figure 46: Martin et al. overall survival, standard parametric curves



Key: KM, Kaplan–Meier.

Figure 47: Eyre et al. overall survival, standard parametric curves

Key: KM, Kaplan–Meier.

Figure 48: McCulloch et al. overall survival, standard parametric curves

Key: KM, Kaplan–Meier.

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Figure 49: Jain et al. overall survival, standard parametric model smoothed hazard plots

[redacted]

Key: KM, Kaplan–Meier.

Figure 50: Martin et al. overall survival, standard parametric model smoothed hazard plots

[redacted]

Key: KM, Kaplan–Meier.

Figure 51: Eyre et al. overall survival, standard parametric model smoothed hazard plots

Key: KM, Kaplan–Meier.

Figure 52: McCulloch et al. overall survival, standard parametric model smoothed hazard plots

Key: KM, Kaplan–Meier.

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Table 42: Jain et al., Martin et al., Eyre et al. and McCulloch et al. overall survival, standard parametric curve AIC statistics

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

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

Based on the summed AICs across the OS studies, the generalised gamma model provides the best statistical fit. However, as can be seen in Figure 45, this model provided a good fit to the observed data period in Eyre et al., but convergence issues caused the curve to fall to zero after this point. Additionally, the generalised gamma models fitted to the other study data resulted in long tails and, alongside the Gompertz model, generally resulted in the most optimistic survival projections.

The second-best fitting model, based on AIC, was the log-normal model. For all four studies, the log-normal resulted in survival estimates at some point between the most optimistic and most pessimistic models. Furthermore, based on the smoothed hazard plots, the log-normal hazards generally appeared to reflect the observed hazards, for each study.

Step two

The shape and scale parameters and correlation between the parameters from the models that were fitted individually for each study were then synthesised in a multivariate meta-analysis model. The resulting pooled curves are presented below in Figure 53. Additionally, Table 43 presents the landmark survival estimates for each pooled parametric model.

Figure 53: Standard of care overall survival, standard parametric curves

[redacted]

Key: KM, Kaplan–Meier.

Table 43: Standard of care, overall survival, standard parametric curve landmark survival estimates

Model	Mean OS	Median OS	Proportion pre-progression at each landmark value			
			6 months	1 year	2 years	5 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: OS, overall survival.
Notes: Mean and median values are provided in units of months. Projected OS values here are not accounting for background mortality correction, meaning that there are slight differences between the figures presented here and in Table 26 and Section B.3.10.1, which are corrected for background mortality.
* Due to convergence issues this model was omitted from the model base case selection.

By assessing the visual fit of the pooled models, all five models (barring generalised gamma, which was omitted from the model selection process due to convergence issues) appear to be similar, particularly for the first 24 months. After this time point, the Gompertz model results in a long tail and plateauing of the survival curve. The exponential model resulted in the most pessimistic survival projections.

NHS Consultants were asked to advise on SoC expectations, with view of these extrapolations.[47] As for the PFS projections in Section B.3.3.2.2, it was felt that the range of models is consistent with the broad expectations of 10–20% surviving to 2 years and 5–10% surviving to 5 years, given allo-SCT expectations.[47]

The log-normal model was chosen for use in the base case as it provided good visual and statistical fit to the individual studies, aligns with clinical expectations and importantly, the log-normal is used for SoC PFS. This selection therefore ensures consistent distributional assumptions across SoC PFS and OS endpoints.

Use of the most optimistic (Gompertz) model is tested in a scenario in Section B.3.8.3.

Background mortality was applied to ensure that the hazard of death for the SoC-treated patient population exceeded (or was equal to) the age- and gender-matched general population hazard of death. To be consistent with the assumptions used to model efficacy for the KTE-X19 arm, the 1.09 SMR-adjusted general population mortality rate was also applied to the SoC arm.

B.3.3.3.3. Comparison of base case overall survival for KTE-X19 and standard of care

Following model selection, Figure 54 presents the selected base case models used for estimating OS in the KTE-X19 and SoC treatment arms; these were the log-normal mixture cure model for KTE-X19 OS, and the log-normal model for SoC OS.

Figure 55 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 KTE-X19 versus current NHS care for post-ibrutinib MCL patients.

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Base case projections imply a possibility of long-term survivorship beyond disease progression for a minority of the cohort, as illustrated by Figure 55. A scenario in which no long-term PPS is assumed is tested in Section B.3.8.3.

Figure 54: Comparison of selected models for KTE-X19 and SoC OS

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

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Figure 55: Base case lifetime OS and PFS projections across model arms, alongside ZUMA-2 KTE-X19 KM data

[redacted]

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

B.3.3.4. Time on treatment

As detailed in Section B.1.2, KTE-X19 is a single-infusion product (i.e. it is given as a one-off infusion). For SoC, time on treatment is determined for each of the considered regimens using guidelines reported in London Cancer North and East (2015), NHS England Cheshire and Merseyside (2017) and Pan Birmingham Cancer Network (2010).[88-90] 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[91], but active disease, in the absence of effective treatment,

affects multiple domains of their quality of life – from mobility through to anxiety and depression.[92]

In common with other lymphomas, duration of response to available treatments typically shortens with each line of therapy. Knowledge of this, paired with the terminal nature of the disease and absence of effective, tolerable MCL treatments beyond the BTKi ibrutinib, can naturally cause anxiety and depression. In this context, access to ibrutinib has had a transformative effect on MCL patient HRQL in those who have received and responded to it. Yet when ibrutinib fails, MCL symptoms return and prognosis is poor. Fatigue and propensity to infections are typical problems in absence of active treatment. R-immunochemotherapy and steroids can alleviate these in eligible patients, but bring different problems, most commonly hair loss and nausea.[47] Many patients also have ascites and are transfusion dependent, often ending up spending time in hospital for intravenous antibiotics.[47] There is real hope, based on the promise of the ZUMA-2 data to read out so far, that KTE-X19 can have a step-change effect on the HRQL of this patient group – an effect that transforms the long-term outlook for NHS MCL patients, both in terms of survival and health-related quality of life.

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

EQ-5D-5L data were collected in ZUMA-2 within 28 days of enrolment, 4 weeks (+/- 3 days) after KTE-X19 infusion, 3 months (+/- 1 week) after KT-X19 infusion and 6 months (+/- 1 week) after KTE-X19 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,[80] the crosswalk algorithm developed by van Hout et al. (2012)[79] was used to convert EQ-5D-5L scores into EQ-5D-3L utility values. Table 44 shows summary EQ-5D-3L utility data over scheduled collections.

Table 44: 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]

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	Screening	Week 4	Month 3	Month 6
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 KTE-X19 also collected.

Only three EQ-5D observations were collected from patients who had progressed. As such, the data are considered informative for the PFS utility assumptions, but not directly informative for PPS 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 utility is estimated to be [redacted], with standard error (SE) [redacted].

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 on this matter[93], the van Hout et al. algorithm was used to estimate EQ-5D-3L equivalent utility values from the EQ-5D-5L questionnaire data.[79]

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 10 January 2020, and is reported in full in Appendix H.

The most relevant utility data and assumptions of those identified, for the purposes of this appraisal, are arguably those from the NICE TA502 ibrutinib appraisal. In this case, the manufacturer's 2015 search and review of HRQL evidence identified two studies reporting data in the form of utility estimates from MCL patients.[94, 95] These studies were also identified by our search. In addition, our review improves on TA502 work in capturing post-first-line utility data in the NICE TA370 documentation for bortezomib in previously untreated MCL. It is also an advance in terms of data from HTA documents published since, relating to various treatment options for relapsed or refractory MCL, including ibrutinib HTA documentation across different geographies. The review and summary of evidence includes tabulation of reported patient utility estimates, and is documented in full, alongside the search strategy in Appendix H.

In the NICE TA502 submission, the company applied a mixed model regression analysis to EQ-5D-5L patient data from their chosen ibrutinib effectiveness dataset: pooled ibrutinib patient data from the Phase III RAY study and Phase II SPARK Study, as described in Table 27 in Section B.3.1. From this, the company estimated utility values of 0.780 (SE 0.010) and 0.680 (SE 0.024) for progression-free and post-progression disease states, respectively.[96] These values were applied to alive disease states in the company's three-state model, with the caveat of a toxicity decrement of 0.200 for the proportion of the comparator arm cohort actively receiving R-chemotherapy (implied utility 0.580), based on clinical opinion.[96] The company

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also applied adjustments to utility over time, assuming it declines in relapsed or refractory MCL patients with age in line with general population trends,[96] as represented by Health Survey for England data modelled by Ara and Brazier.[84]

The TA502 ERG questioned aspects of the company's approach to capture HRQL in their cost-effectiveness model, and explored alternative utility values from the company's systematic review of MCL cost-effectiveness literature[96] – specifically, those from LaChaine et al. (progression-free utility = 0.805; post-progression utility = 0.618) and Yoong et al. (progression-free utility = 0.81; post-progression utility = 0.60).[97, 98] In the absence of MCL-specific utility data, these studies used estimates from FL patients specifically,[97] and NHL patients generally.[98] Results from these exploratory analyses did not lead to further substantial concerns from the Committee; the company submission approach to utility informed the eventual recommendation.

Owing to the innovative nature of CAR T-cell therapy in this disease area, the relapsed or refractory MCL HRQL literature cannot inform appropriate utility assumptions for relapse-free long-term survivorship. For this, we refer to the decision-informing assumptions from the only CAR T-cell therapy NICE TAs of similarly aged patients to date, both in previously treated DLBCL: TA559 and TA567. In TA559, EQ-5D-5L data from the pivotal ZUMA-1 study informed pre- and post-progression health state utility assumptions, until 2 years of relapse-free disease post-treatment – a pivotal remission milestone in DLBCL.[99] At this point, age-equivalent general population utility was assumed.[99] In TA567, a similar approach was taken: pivotal JULIET study SF-36 data were used to inform pre- and post-progression health state assumptions up to 2 years, at which point long-term survivorship, and pre-progression-equivalent utility, was assumed.[100] The ERG critiqued these company utility approaches in each submission[99, 100], but decision-making utility assumptions only differed marginally from those submitted;[69, 70] in TA567, the ERG prompted the incorporation of ageing effects upon utility.[100]

Importantly, the landmark of 2 years progression-free survival indicating long-term, relapse-free survivorship is specific to DLBCL. Following the approach for OS extrapolation in Section B.3.3, a more cautious landmark of 5 years is used here, reflecting the differing natures of r/r DLBCL and r/r MCL.

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B.3.4.4. Adverse events

As discussed in Section B.2.10, since the approved access of tisagenlecleucel-T and axicabtagene ciloleucel through the CDF in NHS England, clinicians have become increasingly comfortable with toxicity management for CAR T-cell therapy. [47] However, it is acknowledged that there are still short-term impactful AEs for many following KTE-X19 therapy. Therefore, a comprehensive approach to capturing these in the model for the KTE-X19 arm has been taken.

For the SoC arm, a more simplistic approach based on precedent has been taken.

B.3.4.4.1. Adverse event rates

The analysis attempts to capture KTE-X19 AE consequences based on the rates reported in the ZUMA-2 mITT analysis set underpinning multiple aspects of the cost-effectiveness analysis. The cost-effectiveness model includes all Grade 3 and 4 AEs occurring in ≥ 10% of the ZUMA-2 cohort; consistent with the limits of the CSR reporting. For AEs of particular clinical importance for CAR T-cell therapies (CRS requiring tocilizumab treatment, and B-cell aplasia [hypogammaglobulinaemia]), AEs of all grades were included in the model, in line with previous CAR T-cell therapy NICE appraisals.[69, 70, 86]

Specifically, the following AEs were modelled:

- Grade 3 or higher KTE-X19-related AEs occurring in ≥ 10% of subjects in ZUMA-2
- Grade 3 or higher conditioning chemotherapy-related AEs occurring in ≥ 10% of subjects in ZUMA-2
- Grade 3 or higher treatment-emergent CRS occurring in ZUMA-2 ([redacted] of patients) and any grade CRS requiring treatment with tocilizumab ([redacted] of patients)
- The proportion of patients who received immunoglobulin treatment ([redacted]

No Grade 3 or higher leukapheresis-related AEs occurred in ≥ 10% of subjects in ZUMA-2. Grade 3 or higher leukapheresis-related AEs that occurred in < 10% of patients include dehydration, febrile neutropenia, neutropenia, neutrophil count decrease and sepsis.

The incidence of modelled Grade 3 or higher KTE-X19 related AEs by type are presented in Table 45, while the incidence of AEs due to conditional chemotherapy are presented in Table 46.

Table 45: Incidence of Grade 3+ KTE-X19-related adverse events occurring in ≥ 10% subjects (N = 68)

Adverse event	Number (%)
Pyrexia	8 (12%)
Hypotension	15 (22%)
Anaemia	19 (28%)
Hypoxia	13 (19%)
White blood cell count decreased	21 (31%)
Encephalopathy	13 (19%)
Fatigue	1 (1%)
Neutrophil count decreased	18 (26%)
Platelet count decreased	10 (15%)
Alanine aminotransferase increased	6 (9%)
Headache	1 (1%)
Hypophosphataemia	12 (18%)
Hyponatraemia	4 (6%)
Confusional state	8 (12%)
Aspartate aminotransferase increased	7 (10%)
Diarrhoea	2 (3%)
Dyspnoea	1 (1%)
Hypocalcaemia	2 (3%)
Neutropenia	10 (15%)
Asthenia	1 (1%)
Aphasia	3 (4%)
Hypogammaglobulinaemia	1 (1%)
Hypertension	6 (9%)
Thrombocytopenia	4 (6%)
Acute kidney injury	3 (4%)
Dizziness	1 (1%)
Pleural effusion	1 (1%)
Somnolence	2 (3%)
Upper respiratory tract infection	1 (1%)

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Table 46: Incidence of Grade 3+ conditioning chemotherapy-related adverse events occurring in ≥ 10% subjects (N=68)

Adverse event	Number (%)
Anaemia	31 (46%)
Nausea	1 (1%)
Neutrophil count decreased	33 (49%)
Platelet count decreased	22 (32%)
Pyrexia	3 (4%)
White blood cell count decreased	27 (40%)
Neutropenia	24 (35%)
Fatigue	1 (1%)
Hypophosphataemia	10 (15%)
Diarrhoea	2 (3%)
Alanine aminotransferase increased	4 (5%)
Hyponatraemia	3 (4%)
Asthenia	1 (1%)
Hypotension	5 (7%)
Thrombocytopenia	7 (10%)
Hypocalcaemia	2 (2%)
Dizziness	1 (1%)
Hypokalaemia	3 (4%)
Hypoxia	2 (2%)
Aspartate aminotransferase increased	4 (6%)
Encephalopathy	3 (4%)
Leukopenia	8 (11%)
Lymphocyte count decreased	8 (12%)
Hypertension	6 (9%)
Muscular weakness	2 (3%)

For the SoC arm, of the studies used to capture SoC effectiveness, Grade 3–4 AEs were only reported by Eyre et al. As such, decision making assumptions from TA502 are borrowed, as is described in Section B.3.4.4.2.

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B.3.4.4.2. Adverse event utility decrements

Consistent with the approach used by Hettle et al., and the base case approach used in TA559, it is assumed that those experiencing CRS have a quality of life of zero (i.e. the utility decrement is set to be the negative of the utility value in the progression-free health state).[75] Also, in line with the methods used by Hettle et al., a disutility for hypogammaglobulinaemia was not applied as it is not thought to result in a reduction of health-related quality of life.[75] For all other AEs, a utility decrement of 0.15 was applied. This approach was used in TA567[70] and was originally derived from a cost-effectiveness analysis by Guadagnolo et al. (2006) in patients after primary treatment for Hodgkin's disease.[101]

AE utility decrements are applied in the model for the expected duration of each AE. Table 47 shows the average duration estimate for each Grade 3/4 AE considered and its source. In the first instance, AE durations were sourced from ZUMA-2; if this was not reported, AEs from ZUMA-1 (as reported in TA559[69]) were used. Where an expected duration estimate could not be sourced from ZUMA-2 or ZUMA-1, mean duration was assumed to be the average of the available duration estimates.

Table 47: Duration of adverse event

Adverse event	Duration (days)	Source
Acute kidney injury	26	Assumed to be the average of all Grade 3/4 AEs
Alanine aminotransferase increased	26	Assumed to be the average of all Grade 3/4 AEs
Anaemia	14	ZUMA-1 CSR, as reported in NICE TA559[69]
Aphasia	12	ZUMA-2 CSR[48]
Aspartate aminotransferase increased	26	Assumed to be the average of all Grade 3/4 AEs
Asthenia	26	Assumed to be the average of all Grade 3/4 AEs
Confusional state	12	ZUMA-2 CSR[48]
CRS	11	ZUMA-2 CSR[48]
Diarrhoea	26	Assumed to be the average of all Grade 3/4 AEs
Dizziness	26	Assumed to be the average of all Grade 3/4 AEs
Dyspnoea	26	Assumed to be the average of all Grade 3/4 AEs
Encephalopathy	12	ZUMA-2 CSR[48]

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Adverse event	Duration (days)	Source
Fatigue	26	Assumed to be the average of all Grade 3/4 AEs
Headache	26	Assumed to be the average of all Grade 3/4 AEs
Hypertension	5	ZUMA-1 CSR, as reported in NICE TA559[69]
Hypocalcaemia	26	Assumed to be the average of all Grade 3/4 AEs
Hypogammaglobulinaemia	26	Assumed to be the average of all Grade 3/4 AEs
Hypokalaemia	26	Assumed to be the average of all Grade 3/4 AEs
Hyponatraemia	26	Assumed to be the average of all Grade 3/4 AEs
Hypophosphataemia	16	ZUMA-1 CSR, as reported in NICE TA559[69]
Hypotension	26	Assumed to be the average of all Grade 3/4 AEs
Hypoxia	26	Assumed to be the average of all Grade 3/4 AEs
Leukopenia	21	ZUMA-1 CSR, as reported in NICE TA559[69]
Lymphocyte count decreased	64	ZUMA-1 CSR, as reported in NICE TA559[69]
Muscular weakness	26	Assumed to be the average of all Grade 3/4 AEs
Nausea	26	Assumed to be the average of all Grade 3/4 AEs
Neutropenia	47	ZUMA-1 CSR, as reported in NICE TA559[69]
Neutrophil count decreased	17	ZUMA-1 CSR, as reported in NICE TA559[69]
Platelet count decreased	50	ZUMA-1 CSR, as reported in NICE TA559[69]
Pleural effusion	26	Assumed to be the average of all Grade 3/4 AEs
Pyrexia	2	ZUMA-1 CSR, as reported in NICE TA559[69]
Somnolence	26	Assumed to be the average of all Grade 3/4 AEs
Thrombocytopenia	63	ZUMA-1 CSR, as reported in NICE TA559[69]
Upper respiratory tract infection	26	Assumed to be the average of all Grade 3/4 AEs
White blood cell count decreased	40	ZUMA-1 CSR, as reported in NICE TA559[69]
Key: CRS, cytokine release syndrome; CSR, clinical study report; NICE, National Institute for Health and Care Excellence		

AEs related to the KTE-X19 arm are expected to occur in the short term after the initial treatment of KTE-X19; therefore, a one-off QALY decrement is applied in the first model cycle.

In line with TA502 decision-making, for the SoC arm, a utility decrement of 0.2 is assumed for patients actively receiving R-chemotherapy.[96] This decrement is

therefore applied over the SoC treatment duration. Treatment duration differs depending on the regimen given; this is further detailed in Section B.3.5.2.2.

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

Table 48 summarises the utility values used in the base case cost effectiveness analysis, signposting the reader to further description and justification of each estimate.

Table 48: Summary of utility values for cost-effectiveness analysis

Health state	Utility value	Uncertainty	Reference in submission
Model health state			
Pre-progression	[redacted]	Section B.3.6.1	Section B.3.4.3
Post-progression	[redacted]		Section B.3.4.5
Pre-progression, after 5 years	0.797		Section B.3.4.5
Grade 3-4 adverse event			
CRS	-0.780	Section B.3.6.1	Section B.3.4.4
Hypogammaglobulinaemia	0.000		
Other KTE-X19 adverse events	-0.150		
R-chemo toxicity	-0.200		

Key: CRS, cytokine release syndrome.
Notes: Health state utility values reported are those applied in the initial cost-effectiveness model cycle. Utility changes over time in the cost-effectiveness model, in line with trends observed in published analysis of Health Survey for England EQ-5D-3L data, as described in Section B.3.4.5

The pre-progression utility estimate, [redacted], is that 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 absence of sufficient post-progression ZUMA-2 EQ-5D-5L patient data, the post-progression utility estimate, [redacted], is derived from previously published estimates. Specifically, the range of estimates considered by the company and ERG in TA502, selected here for consistency across appraisals. [redacted]

Table 49: TA502 company and ERG PFS and PPS utility values

TA502 source	PFS utility value	PPS utility value	
Company-preferred SPARK and RAY patient EQ-5D estimate	0.78	0.68	
ERG exploratory analysis, LaChaine et al., 2013	0.81	0.62	
ERG exploratory analysis, Yoong et al., 2009	0.81	0.60	

Key: ERG, Evidence Review Group; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal.

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, from 5 years from baseline onwards. To do this, supplementary materials from Ara and Brazier's analysis of Health Survey for England data were used.[84] Specifically, linear regression results capturing general population EQ-5D utility as a function of age and gender. Baseline mean age in ZUMA-2 was 63.2; 83.8% of the group were male. The 0.797 utility estimate in Table 48 corresponds to a 68.2-year old 83.8% male individual; the assumed makeup of the alive cohort after 5 years.

Ara and Brazier data are also used to capture ageing trends in utility, for those health states with otherwise time-insensitive utility estimates.[84]

Various scenarios in Section B.3.8.3 explore the effect of alternative assumptions around patient utility. A down-weighting of long-term survivorship general-population-

equivalent utility is explored, while individual sources considered in TA502, summarised in Table 49, are also tested, in turn.

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

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

A systematic search for published 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 10 January 2020. HTA documentation identified and included in the economic evaluation and HRQL reviews across Appendices G and H also met inclusion criteria for this review. Again, arguably the most relevant of these for this appraisal is the most recent NICE single technology appraisal in r/r MCL: TA502. Cost and resource use data from this appraisal is tabulated alongside data from other inclusions in Appendix I, and used to inform assumptions in this analysis, as described in Section B.3.5.3.

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. Again, TA559 and TA567 are useful here. The assumptions used for resource use in disease-free long-term survivorship in these appraisals was consistent with that used for HRQL in each case. In TA559, general population-equivalent resource use was assumed[99, 102]; in TA567, progression-free survival-equivalence was assumed.[100, 103]

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

B.3.5.2.1. KTE-X19 costs and resource use

For KTE-X19, the treatment-related costs included in the model are:

- Leukapheresis costs
- Bridging therapy costs

- Conditioning chemotherapy costs
- KTE-X19 acquisition costs
- KTE-X19 infusion and monitoring costs (including hospitalisation)

As discussed in Section B.2.3.1, two patients in Cohort 1 were retreated with KTE-X19. These patients underwent a second course of conditioning chemotherapy and KTE-X19. In practice, retreatment is not anticipated. For consistency with ZUMA-2 outcomes, we nevertheless account for additional costs of these retreated patients in the cost-effectiveness analysis. Additional costs for conditioning chemotherapy and cell infusion and monitoring (hospitalisation) are applied to the account for the 2.9% (i.e. 2/68) of patients receiving retreatment. As the quantity of KTE-X19 initially manufactured is sufficient for the delivery of up to two treatments, no additional leukapheresis or KTE-X19 acquisition costs are applied to the retreated patients.

For simplicity, all costs associated with KTE-X19 treatment are assumed to be incurred at the start of the first model cycle as treatment is given as a single infusion.

Leukapheresis costs

As described in Section B.2.3, in the ZUMA-2 Cohort 1 population, 74 patients were enrolled and underwent leukapheresis, 69 patients received conditioning chemotherapy and 68 patients (the mITT group) received KTE-X19. Of the six patients not treated with KTE-X19:

- Manufacturing failed for three patients
- Two patients died due to disease progression
- One patient received conditioning chemotherapy but was subsequently deemed ineligible for KTE-X19 treatment

The cost of leukapheresis was calculated as the weighted average of all healthcare resource groups (HRGs) for stem cell and bone marrow harvest in the latest NHS national schedule of reference costs (2018–2019),[104] aligned with previous CAR T-cell therapy appraisals.[76] Table 50 details the unit costs of leukapheresis.

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Table 50: Unit costs of leukapheresis

Currency code	Currency description	Number of cases	Unit cost
SA34Z	Peripheral Blood Stem Cell Harvest	3,293	£1,481.09
SA18Z	Bone Marrow Harvest	156	£2,365.97

The weighted average cost of leukapheresis was calculated to be £1,521.11. An uplifting factor of 1.088 (74/68) was used to adjust the unit leukapheresis cost for use in the model, to account for patients who undergo leukapheresis but do not proceed to receive KTE-X19. Therefore, the assumed total cost of leukapheresis is £1,655.33.

Bridging therapy costs

It is necessary for some patients to receive bridging therapy after leukapheresis. In ZUMA-2, patients could receive bridging therapy after leukapheresis and up to 5 days prior to the initiation of conditioning chemotherapy. Bridging therapy was considered for any patient but particularly for those with high disease burden at screening, to maintain stable disease during the manufacturing of KTE-X19.

The BTKi ibrutinib was permitted as a bridging therapy in ZUMA-2 but would not be routinely reimbursed for this purpose in NHS England. The more likely bridging therapy in clinical practice is expected to be chemotherapy, specifically cytarabine-containing regimens. For costing purposes, it is therefore assumed that patients requiring bridging therapy would receive a single cycle of R-BAC. A scenario investigating bridging therapy as per ZUMA-2 is presented in Section B.3.8.3.

A single cycle of R-BAC is associated with drug costs of £1292.87 and administration costs of £852.53 resulting in a total bridging therapy cost of £2145.40 per patient. Further details of R-BAC costs are presented in Section B.3.5.2.2.

Of the 68 patients in the ZUMA-2 mITT population, 25 patients received bridging therapy (37%). The total cost per patient was multiplied by the proportion of patients receiving bridging therapy, resulting in a weighted cost of £788.75. Of the 74 patients who were enrolled and underwent leukapheresis, [redacted] patients received bridging therapy. To account for patients who receive bridging therapy but do not proceed to

receive KTE-X19, a multiplier of [redacted] was applied. Therefore, the assumed cost of bridging therapy is [redacted]

Conditioning chemotherapy costs

Of the 74 patients who underwent leukapheresis, 69 patients received 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 anticipated licence for KTE-X19. Unit costs for cyclophosphamide and fludarabine were taken from eMIT and are presented in Table 51.[105]

Table 51: Unit costs of conditioning chemotherapy

Conditioning chemotherapy	Formulation	Measure (mg)	Unit cost	Pack size	Source
Fludarabine	Solution for injection vials	50	£99.88	1	eMIT national database, March 2020[105]
Cyclophosphamide	Powder for solution for injection vials	1000	£13.19	1	eMIT national database, March 2020[105]
	Powder for solution for injection vials	2000	£27.50	1	
	Powder for solution for injection vials	500	£8.16	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 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 using the method of moments. Mean BSA was estimated based on mean height and weight data from the mITT population of ZUMA-2 using the Du Bois formula[106], and a standard deviation of 20% of the mean BSA was assumed. A normal distribution was fitted to the BSA parameters 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 52 shows the combination of vials on average required per patient per dose.

Table 52: 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	1.78
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 £194.41. Conditioning chemotherapy is given over the course of 3 days, therefore, the total assumed cost of conditioning chemotherapy was £583.23.

During NHS Consultant validation, clinicians explained that patients receiving conditioning chemotherapy would be required to stay in a hotel close to the hospital site.[47] Therefore, conditioning chemotherapy administration is conservatively costed as an elective inpatient stay, as per KTE-X19 hospitalisation. The total administration cost for conditioning chemotherapy was assumed to be the daily cost of hospitalisation, £460.99 (see the below Section “KTE-X19 infusion and monitoring hospitalisation costs”.) multiplied by 3, for the number of days receiving conditioning chemotherapy. This results in a total administration cost for conditioning chemotherapy of £1382.97.

A multiplier of 1.015 (69/68) was used to adjust both the conditioning chemotherapy cost and the hospitalisation cost for conditioning chemotherapy to account for the one patient in ZUMA-2 who was treated with conditional chemotherapy but not KTE-X19, resulting in a total conditioning chemotherapy cost of £1995.12. (£2052.95 after considering the proportion of patients requiring retreatment)

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KTE-X19 acquisition costs

As detailed in Section B.1.2, KTE-X19 is administered as a one-off infusion. The acquisition cost of KTE-X19 is assumed to be a one-off cost of [redacted] including shipping, engineering and generation of the CAR T-cells.

For the two patients in Cohort 1 who were retreated with KTE-X19, the costs for the additional KTE-X19 infusion is not included as the quantity of KTE-X19 initially manufactured is sufficient for the delivery of up to two treatments. It is not anticipated that patients would be retreated in clinical practice.

KTE-X19 infusion and monitoring hospitalisation costs

The infusion of KTE-X19 and subsequent monitoring is assumed to incur the cost of an elective hospitalisation, in line with the assumptions used in TA559.

The mean length of stay observed in the ZUMA-2 trial following KTE-X19 infusion was [redacted] days, which is longer than that reported for malignant neoplasms of lymphoid, haematopoietic and related tissue inpatient admissions in the Hospital Episode Statistics[107] (i.e. a mean duration of 9.4 days). To cost this in the model, firstly, the weighted average of elective inpatient HRGs for malignant lymphoma, including Hodgkin's lymphoma and NHL, from the latest NHS reference costs (2018-2019)[104], was used (Table 53).

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Table 53: Malignant lymphoma elective inpatient healthcare resource groups

Currency code	Currency description	Number of cases	Unit cost
SA31A	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 15+	224	£13,851.04
SA31B	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 10–14	509	£8,347.18
SA31C	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 6–9	1,011	£5,122.96
SA31D	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 4–5	988	£4,156.24
SA31E	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 2–3	1,562	£3,457.39
SA31F	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 0–1	1,978	£2,599.09
Key: CC, complication and comorbidity.			

The weighted average cost of elective inpatient HRGs was calculated to be £4,333.30.

Secondly, a per day cost was calculated using the weighted average elective inpatient stay cost; this was calculated to be £460.99 (£4,333.30/9.4 days). The daily cost was subsequently multiplied by [redacted] days to obtain a final cost for hospitalisation of [redacted]

Finally, the additional costs of hospitalisation during KTE-X19 infusion and monitoring for the 2.9% retreated patients were also accounted for. The total cost of KTE-X19 infusion and monitoring hospitalisation used in the model was [redacted]

B.3.5.2.2. SoC costs and resource use

The SoC arm is applied as a blended comparator, which is comprised of five different regimens, as detailed in Section B.3.2.3.2. The model applies costs for each regimen, multiplied by their expected distribution of use in NHS England. Clinical expert opinion was sought to determine the distribution over SoC chemotherapy regimens in clinical practice. Based on clinical opinion; it is assumed that 65% patients would receive R-BAC, 30% of patients would use R-benda and 5% of patients would use R-CHOP.[47]

Drug acquisition

The treatments included in each regimen are a mixture of both orally administered and intravenously administered drugs. Table 54 summarises the unit, measure, pack size and cost per mg, for each SoC therapy. For sourcing these costs, the drugs and pharmaceutical electronic market information tool (eMIT) was used in the first instance as this better reflects the prices paid by hospitals; where eMIT costs were not available, or were not available for the formulation indicated in the SmPC, the Monthly Index of Medical Specialities (MIMS) was 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.

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Table 54: SoC individual drugs, cost per mg

SoC drug	Formulation	Measure (mg)	Unit cost	Pack size	Cost per mg	Source	Assumptions
Rituximab	Concentrate for solution for infusion vials	100 mg	£314.33	2	£1.57	MIMS UK, March 2020[108]	Rixathon brand used - cheapest cost per mg
	Concentrate for solution for infusion vials	500 mg	£785.84	1	£1.57	MIMS UK, March 2020[108]	
	Concentrate for solution for infusion vials	500 mg	£1,571.67	2	£1.57	MIMS UK, March 2020[108]	
Cyclophosphamide	Powder for solution for injection vials	1000 mg	£13.19	1	£0.01	eMIT national database, March 2020[105]	NA
	Powder for solution for injection vials	2000 mg	£27.50	1	£0.01		
	Powder for solution for injection vials	500 mg	£8.16	1	£0.02		
Doxorubicin	Solution for injection vials	10 mg	£3.30	1	£0.33	eMIT national database, March 2020[105]	Given as IV bolus injection as per chemotherapy protocols
	Solution for injection vials	50 mg	£12.38	1	£0.25		

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SoC drug	Formulation	Measure (mg)	Unit cost	Pack size	Cost per mg	Source	Assumptions
Vincristine	Solution for injection vials	1 mg	£11.56	5	£2.31	eMIT national database, March 2020[105]	NA
	Solution for injection vials	2 mg	£16.82	5	£1.68		
	Solution for injection vials	5 mg	£99.00	5	£3.96		
Prednisolone	Tablets	5 mg	£0.28	28	£0.00	eMIT national database, March 2020[105]	Cheapest cost per mg of all oral formulations
Bendamustine	Powder for solution for infusion vials	100 mg	£56.31	5	£0.11	eMIT national database, March 2020[105]	Cheapest cost per mg of all pack sizes
	Powder for solution for infusion vials	25 mg	£2.91	1	£0.12		
Cytarabine	Solution for injection vials	100 mg	£13.20	5	£0.03	eMIT national database, March 2020[105]	Cheapest cost per mg of all 100mg vials
	Solution for injection vials	1000 mg	£6.65	1	£0.01		NA
	Solution for injection vials	2000 mg	£7.05	1	£0.00		NA
	Solution for injection vials	500 mg	£17.50	5	£0.01		NA
Fludarabine	Solution for injection vials	50 mg	£99.88	1	£2.00	eMIT national database, March 2020[105]	Cheapest cost per mg of all 50mg vials
Key: IV, intravenous; NA, not applicable.							

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All SoC chemotherapy drugs except for prednisolone were dosed variably according to patient BSA. For both the R-CHOP and R-CVP regimens, prednisolone is given at a dose of 100mg orally daily for 5 days, as reported in the London Cancer North and East Guidelines for the management of non-Hodgkin's and Hodgkin's lymphoma in adults (2015).[88]

Consistent with the approach used for costing the conditioning chemotherapies in the KTE-X19 arm, using the mean 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 using the method of moments.

Table 55 shows the combination of vials on average required per patient per dose based upon the BSA of patients from the ZUMA-2 trial.

Table 55: Average number of vials required per administration of conditioning chemotherapies

SoC drug	Dose needed (mg/m^2)	Source	Vial size (mg)	Mean number of vials per patient per day per administration
Rituximab (all regimens)	375	London Cancer North and East (2015); NHS England Cheshire and Merseyside (2017); Pan Birmingham Cancer Network (2010)[88-90]	100	7.87
Cyclophosphamide (R-CHOP, R-CVP regimens)	750	London Cancer North and East (2015)[88]	500	0.52
			1,000	1.46
Cyclophosphamide (FCR regimen)	150	Pan Birmingham Cancer Network (2010)[89]	500	1.00
			1,000	0.00
Doxorubicin (R-CHOP regimen)	50	London Cancer North and East (2015)[88]	10	1.14
			50	1.88
Vincristine (R-CHOP, R-CVP regimens)*	1.4	London Cancer North and East (2015)[88]	1	0.00
			2	1.00
Bendamustine (R-BAC regimen)	70	London Cancer North and East (2015)	25	1.70
			100	1.08
Bendamustine (R-benda regimen)	90	NHS England Cheshire and Merseyside (2017)	25	1.49
			100	1.52

SoC drug	Dose needed (mg/m^2)	Source	Vial size (mg)	Mean number of vials per patient per day per administration
Cytarabine (R-BAC regimen)	800	London Cancer North and East (2015)	100	0.04
			500	0.05
			1,000	0.03
			2,000	0.97
Fludarabine (FCR regimen)	24	Pan Birmingham Cancer Network (2010)	50	1.38

Key: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-BAC, rituximab, bendamustine and cytarabine; R-benda, rituximab and bendamustine; R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone; FCR, fludarabine, cyclophosphamide and rituximab; SoC, standard of care.

Once the cost per dose was established for each individual drug, the cost per regimen per cycle was calculated, as presented in Table 56. In addition, Table 56 shows the treatment duration for each regimen, reported as the number of cycles that make up a complete course.

Given the regimens were administered over different length treatment cycles (either 21- or 28-day cycles), the number of administrations for each regimen was calculated per monthly model cycle. Taking into account the proportions of patients receiving each regimen, this was then used to calculate a total weighted average cost of SoC per month. This is presented in Table 57.

Table 56: SoC regimen drug acquisition costs per treatment cycle

Regimen	Individual drugs schedule	Day of chemotherapy cycle					Total drug acquisition cost per treatment cycle	Cycle frequency	Source
		Day 1	Day 2	Day 3	Day 4	Day 5			
R-CHOP	Rituximab, Day 1	£1,236.82	£0.00	£0.00	£0.00	£0.00	£1,291.73	Every 3 weeks (6 cycles assumed)	London Cancer North and East (2015)[88]
	Cyclophosphamide, Day 1	£23.55	£0.00	£0.00	£0.00	£0.00			
	Doxorubicin, Day 1	£27.00	£0.00	£0.00	£0.00	£0.00			
	Vincristine, Day 1	£3.36	£0.00	£0.00	£0.00	£0.00			
	Prednisolone, Days 1-5	£0.20	£0.20	£0.20	£0.20	£0.20			
R-BAC	Rituximab, Day 1	£1,236.82	£0.00	£0.00	£0.00	£0.00	£1,292.87	Every 4 weeks (6 cycles assumed)	London Cancer North and East (2015)[88]
	Bendamustine, Days 2-3	£0.00	£17.07	£17.07	£0.00	£0.00			
	Cytarabine, Days 2-4	£0.00	£7.30	£7.30	£7.30	£0.00			
R-Benda	Rituximab, Day 1	£1,236.82	£0.00	£0.00	£0.00	£0.00	£1,279.77	Every 4 weeks (6 cycles assumed)	NHS England Cheshire and Merseyside (2017)[90]
	Bendamustine, Days 1-2	£21.47	£21.47	£0.00	£0.00	£0.00			

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Regimen	Individual drugs schedule	Day of chemotherapy cycle					Total drug acquisition cost per treatment cycle	Cycle frequency	Source
		Day 1	Day 2	Day 3	Day 4	Day 5			
R-CVP	Rituximab, Day 1	£1,236.82	£0.00	£0.00	£0.00	£0.00	£1,264.73	Every 3 weeks (6 cycles assumed)	London Cancer North and East (2015)[88]
	Cyclophosphamide, Day 1	£23.55	£0.00	£0.00	£0.00	£0.00			
	Vincristine, Day 1	£3.36	£0.00	£0.00	£0.00	£0.00			
	Prednisolone, Days 1-5	£0.20	£0.20	£0.20	£0.20	£0.20			
FCR	Fludarabine, Days 1-5	£138.03	£138.03	£138.03	£138.03	£138.03	£1,967.77	Every 4 weeks for 6 cycles	Pan Birmingham Cancer Network (2010)[89]
	Cyclophosphamide, Days 1-5	£8.16	£8.16	£8.16	£8.16	£8.16			
	Rituximab, Day 1	£1,236.82	£0.00	£0.00	£0.00	£0.00			

Key: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-BAC, rituximab, bendamustine and cytarabine; R-benda, rituximab and bendamustine; R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone; FCR, fludarabine, cyclophosphamide and rituximab; SoC, standard of care.

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Table 57: Number of regimen administrations and calculated total SoC drug cost per model cycle

Regimen	Model cycle 1	Model cycle 2	Model cycle 3	Model cycle 4	Model cycle 5
R-CHOP	2.00	1.00	1.00	1.00	1.00
R-BAC	2.00	1.00	1.00	1.00	1.00
R-benda	2.00	1.00	1.00	1.00	1.00
R-CVP	2.00	1.00	1.00	1.00	1.00
FCR	2.00	1.00	1.00	1.00	1.00
Total SoC drug cost per model cycle (weighted)	£2,577.76	£1,288.88	£1,288.88	£1,288.88	£1,288.88

Key: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-BAC, rituximab, bendamustine and cytarabine; R-benda, rituximab and bendamustine; R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone; FCR, fludarabine, cyclophosphamide and rituximab; SoC, standard of care.

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Drug administration

It was assumed that SoC regimens are administered in an outpatient setting. It is also assumed that if a patient requires more than one IV chemotherapy per day, only a single administration cost applies. It is assumed that oral drugs incur no administration cost. The costs used for an IV administration are presented in Table 58.

Table 58: IV chemotherapy administration costs

Description / code / setting	Cost	Reference
Deliver Simple Parenteral Chemotherapy at First Attendance / SB12Z / Outpatient	£183.54	NHS reference costs (2018-2019)[104]
Deliver Subsequent Elements of a Chemotherapy Cycle / SB15Z / Outpatient	£223.00	NHS reference costs (2018-2019)[104]
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 59 presents the administration cost per regimen per treatment cycle and Table 60 presents the calculated total weighted average cost of SoC administration per model cycle.

The total SoC cost per month, considering both drug acquisition and administration, is shown in Table 61.

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Table 59: 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	Day 4	Day 5	
R-CHOP	Rituximab, Day 1	£183.54	£0.00	£0.00	£0.00	£0.00	£183.54
	Cyclophosphamide, Day 1	£0.00	£0.00	£0.00	£0.00	£0.00	
	Doxorubicin, Day 1	£0.00	£0.00	£0.00	£0.00	£0.00	
	Vincristine, Day 1	£0.00	£0.00	£0.00	£0.00	£0.00	
	Prednisolone, Days 1-5	£0.00	£0.00	£0.00	£0.00	£0.00	
R-BAC	Rituximab, Day 1	£183.54	£0.00	£0.00	£0.00	£0.00	£852.53
	Bendamustine, Days 2-3	£0.00	£223.00	£223.00	£0.00	£0.00	
	Cytarabine, Days 2-4	£0.00	£0.00	£0.00	£223.00	£0.00	
R-Benda	Rituximab, Day 1	£183.54	£0.00	£0.00	£0.00	£0.00	£406.54
	Bendamustine, Days 1-2	£0.00	£223.00	£0.00	£0.00	£0.00	
R-CVP	Rituximab, Day 1	£183.54	£0.00	£0.00	£0.00	£0.00	£183.54
	Cyclophosphamide, Day 1	£0.00	£0.00	£0.00	£0.00	£0.00	
	Vincristine, Day 1	£0.00	£0.00	£0.00	£0.00	£0.00	
	Prednisolone, Days 1-5	£0.00	£0.00	£0.00	£0.00	£0.00	
FCR	Fludarabine, Days 1-5	£183.54	£223.00	£223.00	£223.00	£223.00	£1,075.52
	Cyclophosphamide, Days 1-5	£0.00	£0.00	£0.00	£0.00	£0.00	
	Rituximab, Day 1	£0.00	£0.00	£0.00	£0.00	£0.00	

Key: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-BAC, rituximab, bendamustine and cytarabine; R-benda, rituximab and bendamustine; R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone; FCR, fludarabine, cyclophosphamide and rituximab; SoC, standard of care.

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Table 60: Number of regimen administrations and calculated total SoC administration cost per model cycle

Regimen	Model cycle 1	Model cycle 2	Model cycle 3	Model cycle 4	Model cycle 5
R-CHOP	2.00	1.00	1.00	1.00	1.00
R-BAC	2.00	1.00	1.00	1.00	1.00
R-benda	2.00	1.00	1.00	1.00	1.00
R-CVP	2.00	1.00	1.00	1.00	1.00
FCR	2.00	1.00	1.00	1.00	1.00
Total SoC administration cost per model cycle (weighted)	£1,370.56	£685.28	£685.28	£685.28	£685.28

Key: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-BAC, rituximab, bendamustine and cytarabine; R-benda, rituximab and bendamustine; R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone; FCR, fludarabine, cyclophosphamide and rituximab; SoC, standard of care.

Table 61: Total SoC cost

Treatment	Model cycle 1	Model cycle 2	Model cycle 3	Model cycle 4	Model cycle 5
SoC	£3,948.33	£1,974.16	£1,974.16	£1,974.16	£1,974.16

Key: SoC, standard of care

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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. Consistent with the assumption used to model utility values, a time point of 5 years is used to determine when patients remaining progression-free are assumed to be long-term survivors and thus experience reduced resource use needs.

Resource use in each health state was derived from TA502[38], where a survey was designed to obtain the types and frequency of medical resource use (including visits, procedures, and tests) for an average 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 62. 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 62: Total monthly resource use by health state as reported in TA502 and applied in the model

Resource type	Stable disease*		Post-progression	
	Description	Per month	Description	Per month
Full blood count	Every 2 months	0.50	Every 1.5 months	0.75
X-ray	Once per year	0.08	Once per year	0.08
Blood glucose	N/A	0.00	N/A	0.00
Lactate dehydrogenase	Every 3 months	0.33	Five times per year	0.42
Lymphocyte count	Every 2 months	0.50	Every 1.5 months	0.75
Bone marrow exam	Once per year	0.08	N/A	0.00
Haematologist visit	Every 2 months	0.50	Every 1.5 months	0.75
Inpatient visit (medical)	Once per year	0.08	Every 6 months	0.17
Biopsy	Once per year	0.08	N/A	0.00
Blood transfusion	Once per year	0.08	Every 3 months	0.33
Platelet transfusion	N/A	0.00	Every 6 months	0.17

Key: TA, technology appraisal.
Notes: *Assumed resource use for stable disease in TA502 applies to pre-progression patients in model.

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For use in the economic model, the most recent NHS reference costs (2018–2019)[104] were used to derive costs for each of the resource use components, as presented in Table 63.

Table 63: Resource use unit costs

Resource use type	Unit cost	Description / code / setting
Full blood count	£2.79	Haematology / DAPS05 / Directly accessed pathology services (DAPS)
X-ray	£30.59	Directly accessed plain film / DAPF / Directly accessed diagnostic services (DADS)
Blood glucose	£1.10	Clinical Biochemistry / DAPS04 / Directly accessed pathology services (DAPS)
Lactate dehydrogenase	£1.10	Clinical Biochemistry / DAPS04 / Directly accessed pathology services (DAPS)
Lymphocyte count	£2.79	Haematology / DAPS05 / Directly accessed pathology services (DAPS)
Bone marrow exam	£287.14	Diagnostic Bone Marrow Extraction / SA33Z (Service code 303) / Outpatient procedures, clinical haematology
Haematologist visit	£703.61	Non-Admitted Face-to-Face Attendance, Follow-up / WF01A (Service code 303) / Outpatient procedures, clinical haematology
Inpatient visit (medical)	£4,333.30	Weighted average cost of Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's codes SA31A-F / elective inpatient
Biopsy	£410.28	Core Needle Biopsy of Axillary Lymph Nodes / YJ04Z (Service code 100) / Outpatient procedures, general surgery
Blood transfusion	£253.13	Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over / SA44A (Service code 303) / Outpatient procedures, clinical haematology
Platelet transfusion	£253.13	Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over / SA44A (Service code 303) / Outpatient procedures, clinical haematology
Key: DADS, directly accessed diagnostic services; DAPF, directly accessed plain film; DAPS, directly accessed pathology services.		

The resulting costs per cycle for the pre-progression (< 5 years) and post-progression health states were £797.83 and £1,383.68, respectively.

Pre-progression patients surviving for longer than 5 years, are assumed to incur costs for regular GP appointments. The cost of a GP visit is applied every 6 months,

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based on clinical expert opinion.[47] The cost of a GP visit was taken from on the Unit Costs of Health and Social Care (2019) and is £39 per surgery consultation lasting 9.22 minutes (including direct care staff costs and qualification costs).[109]

B.3.5.4. Adverse event costs

As AE costs are only applied to the KTE-X19 treatment arm, these were applied as a one-off cost in the first model cycle, with the exception of hypogammaglobulinaemia, which is associated with ongoing treatment costs. This is aligned with TA559 and Hettle et al.[75] Also, consistent with TA559 and Hettle et al., all AEs, barring CRS and hypogammaglobulinaemia, assume the cost of one additional inpatient day (£460.99). It is assumed that the costs of AEs are covered in hospitalisation period during cell infusion and monitoring, and costing each AE individually would result in double counting.

The approaches to account for the NHS costs of hypogammaglobulinaemia and CRS care are detailed below.

B.3.5.4.1. Hypogammaglobulinaemia

As described in Section B.3.4.4.1, hypogammaglobulinaemia occurred in [redacted] patients ([redacted] in the mITT population of ZUMA-2 ([redacted] patients [redacted] with hypogammaglobulinaemia, and [redacted] patients [redacted] with blood immunoglobulin G decreased). 22 patients (32%) were treated with IVIG therapy.

Hypogammaglobulinaemia has not been applied as a one-off cost because it requires ongoing treatment over a relatively long period of time.

The cost for administration of a simple parenteral chemotherapy regimen in an outpatient setting (as per the SoC chemotherapy regimens described in Section B.3.5.2) was used for IVIG administration, in line with TA567 and TA554.[77, 110] For the IVIG treatment costs, the immunoglobulin drug costs reported in MIMS were used; specifically, it was assumed that the immunoglobulin with the cheapest cost per mg, Gammaplex 5% solution for infusion, would be used in practice. Only Normal Human Immunoglobulins licensed for hypogammaglobulinaemia or IgG level < 4 g/l were included. Table 64 summarises the IVIG unit, measure, pack size and cost per mg used in the model.

Table 64: IVIG cost per mg

IVIG therapy	Formulation	Measure (mg)	Unit cost	Pack size	Cost per mg	Source
Gammaplex	1 vial, 5% soln for inf in bottle (5g/100ml)	5	£209.00	1	£0.04	MIMS UK, March 2020[108]
	1 vial, 5% soln for inf in bottle (10g/200ml)	10	£418.00	1	£0.04	
	1 vial, 5% soln for inf in bottle (20g/400ml)	20	£836.00	1	£0.04	
Key: IVIG, intravenous immunoglobulin; MIMS, Monthly Index of Medical Specialities; soln, solution.						

In line with the assumptions used in TA559 (which were based on Hettle et al.,[75]) a dose of 0.5g/kg every 4 weeks was assumed. Furthermore, IVIG is assumed to be administered to pre-progression patients for a duration of 12 months, consistent with the assumption used in TA559.[69]. During validation, 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,[47] therefore, no wastage is assumed when costing IVIG.

Table 65: IVIG dosing parameters

IVIG therapy	Dose (g/kg)	Frequency	Duration	Source
Gammaplex 5g vial	0.5	Every 4 weeks	12 months	TA559, Hettle et al., Clinical expert opinion[47, 75, 76]
Key: IVIG, intravenous immunoglobulin **Notes:** *Smallest vial size selected for greater flexibility of dosing as all vials have same cost per g.				

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 requiring IVIG therapy (32%) and the cost of treatment administration and acquisition, the weighted average monthly cost of IVIG treatment is £667.28.

B.3.5.4.2. CRS

As described in Section B.2.10, 91% of patients in the mITT analysis set of ZUMA-2 experienced a CRS event but most were Grade 1-2 and all CRS events resolved after a median duration of 11 days. The method for costing CRS was taken from previous CAR T-cell appraisals and Hettle et al.[75] It is assumed that patients with Grade 3/4 CRS event (15% of patients) accrue the cost of an intensive care unit (ICU) hospitalisation. The cost of an ICU hospitalisation was calculated based on non-specific, general adult critical care costs from NHS reference costs 2018-2019.[104]

A weighted average of the costs for supporting 1 and 2 organs was assumed based on feedback from clinicians during validation, equating to an daily ICU cost of £1329.86. A duration of 4 days was assumed for the ICU stay, based on assumptions in the final appraisal determination for TA559.[69] The final ICU cost for all patients with Grade 3/4 CRS is £5319.43.

Table 66: Adult critical care costs

Currency code	Currency description	Number of cases	Unit cost
XC05Z	Adult Critical Care, 2 Organs Supported	245,822	£1,575
XC06Z	Adult Critical Care, 1 Organ Supported	338,820	£1,152

Furthermore, [redacted] patients ([redacted] of patients in ZUMA-2 were treated with a cytokine inhibitor drug – tocilizumab. The modelled cost of cytokine inhibitor drugs is £623.14, taken from NHS reference costs 2018-2019 (currency code HICD0375, cytokine inhibitor drugs, band 1).[104] It is assumed that this cost is the average cost per tocilizumab administration and covers both drug and administration costs. It is further assumed that only one administration of tocilizumab would be required. The total cost for CRS management including hospitalisation and tocilizumab treatment, applied upfront in the model is [redacted]

B.3.5.5. Miscellaneous unit costs and resource use

B.3.5.5.1. Allogeneic stem cell transplant

As described in Section B.2.6, [redacted] in the mITT analysis set had an allo-SCT, while in a KTE-X19 induced remission. The costs of allo-SCT is therefore applied to [redacted]% of patients in the KTE-X19 arm of the model.

During validation, clinical experts explained that the proportion of third-line patients receiving consolidation with allo-SCT is low. Based on clinical input, it is assumed that 20% of patients on the SoC arm would receive allo-SCT.[47] A range of alternative assumptions are explored in the scenario analysis in Section B.3.8.3.

A weighted average of allo-SCT HRGs, taken from the NHS reference costs (2018-2019)[104], was used to estimate the initial transplant cost, as presented in Table 57.

Table 67: Allogeneic stem cell transplant costs

Currency code	Currency description	Number of cases	Unit cost
SA38A	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 19 years and over	227	£27,590
SA39A	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 19 years and over	491	£31,163
SA40Z	Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified)	274	£47,031

The weighted average cost of allo-SCT was calculated to be £34,728. 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.

Costs based on the admission period do not capture the full cost of allo-SCT over the patient's lifetime. Therefore, consistent with the costing approach used in TA559[69] (originally specified in Hettle et al.) the estimate of post-transplant costs was based on the UK Stem Cell Strategy Oversight Committee Report.[111] The cost per transplant patient in each follow-up period is reported in Table 68. These costs were inflated from 2014 to a 2019 cost year, based on inflation indices reported in the Unit Costs for Health and Social Care.[109, 112]

Table 68: Costs of allogeneic stem cell transplant follow-up

Follow-up period	Cost per transplant patient	Inflated cost
Discharge to 6 months after transplant	£25,551	£27,519
6 to 12 months after transplant	£9,361	£10,082
12 to 24 months after transplant	£4,363	£4,699

B.3.5.6. End-of-life care

Patients with end-stage cancer typically incur costs at the end of life for palliative and hospice care. The publication by Round et al. is a standard source used for such costs in submissions to NICE.[113] Costs were taken from this publication and inflated to 2019 prices.[109, 112] As the publication does not specifically report an end-of-life care cost for patients with MCL (or any form of haematological malignancy), the average cost for all cancer types reported was assumed. End-of-life care costs are applied as a lump sum upon death. Costs are detailed in Table 69.

Table 69: End-of-life care costs

	Cost	Cost year	Inflated cost (2019)	Reference
Mean cost (during last period of life)	£4,254.00	2015	£4,540.95	Round et al. (2015)[113]

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

B.3.6.1. Summary of base case analysis inputs

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

B.3.6.2. Assumptions

The approach to modelling has been designed to make the best use of the available data to inform the decision problem, in line with the NICE reference case and

guidance on methods of appraisal. In the absence of key data, key assumptions have been necessary, and have been made true to the appraisal history of the disease are and therapy type at hand, with NHS Consultant validation of each assumption central to the approach. With this approach at heart, care has been taken to describe and justify necessary assumptions throughout Sections B.3.2 to B.3.5. A selection of these; those assumptions perceived to be key and most central to the economic analysis; are described in Table 70.

Table 70: 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 previous CAR-T TAs (TA554, TA559 and TA567), as well as the mock appraisal of regenerative therapies and cell therapy products published by Hettle et al., 2017.[75]
2	The expected absolute clinical effectiveness of KTE-X19 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 mixture-cure survival modelling model in which the data for "uncured" patients follow a lognormal distribution fitted to the KM data and long-term survivors follow age-adjusted ONS general population survival data, adjusted by a standardised mortality ratio of 1.09	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 [85] 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.[47]
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 the	None	Sections B.2.9 and 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 [85] and previous NICE appraisals. Projections for SoC PFS

#	Assumption	Likely bias direction	Justification
	published literature, captured and extrapolated over a lifetime perspective using lognormal survival modelling.		and OS over time are consistent with NHS Consultant expectations.[47]
4	The expected relative clinical effectiveness of KTE-X19 versus SoC, in terms of disease delay and survival, is the lifetime difference between #2 and #3	None	Sections B.2.9 and B.3.3.1 to B.3.3.3 Following NICE DSU TSD guidance, indirect treatment comparison methods were tested in Section B.2.9; a naïve unadjusted comparison is considered to be more useful than a matching-adjusted comparison, given the limitations and differences in data reporting and collection and patient characteristics across ZUMA-2 mITT and available comparator data sources. Similar "naïve" comparisons were used to inform decision-making in previous CAR-T appraisals (TA554, TA559 and TA567).
5	The patient utility associated with PFS after KTE-X19 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	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 [78] and the October 2019 Position Statement on the use of EQ-5D-5L data.[80]
6	The patient utility associated with PFS with SoC is similar to observed in patient EQ-5D data from ZUMA-2, with the HRQL impact rituximab-chemotherapy toxicity separately accounted for	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; the estimate is higher than that used in TA502. The use of a rituximab-chemotherapy toxicity decrement is consistent with TA502.
7	Patient utility and health care resource use for patients who are predicted to be progression-free 5 years after KTE-X19 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 TA559, where long-term survivors were assumed to have utility and NHS resources similar to age-matched general population estimates. In MCL, 5 years is considered the cut-off for long-term survivorship, as opposed to 2 years for DLBCL in TA559, given the different underlying mechanisms of the two diseases.

#	Assumption	Likely bias direction	Justification
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	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 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.3.7. Base case results

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

Table 71 displays base case cost-effectiveness results. All cost-effectiveness results presented, here and throughout the dossier, reflect the list price of [redacted] for KTE-X19. Figure 56 and Figure 57 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.

Consistent with the outlook for post-ibrutinib patients in absence of KTE-X19 therapy and the hope and expectation of the transformative effect KTE-X19 CAR-T therapy may offer this group, KTE-X19 is estimated to offer a high per-patient incremental health benefit, providing [redacted] additional years of life, or an additional [redacted] discounted QALYs, versus current standard of care. The estimated deterministic incremental cost-effectiveness ratio (ICER) for KTE-X19 is close to the NICE decision-making threshold limit, given end-of-life weighting.

Table 71: Base-case deterministic cost-effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[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.

Figure 56: Lifetime Markov trace for KTE-X19

[redacted]

Figure 57: Lifetime Markov trace for SoC

[redacted]

Key: SoC, standard of care

Estimates of clinical outcomes compared with trial results and disaggregated results are presented in Appendix J, and summarised and interpreted in B.3.10.

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B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

PSA results for the base case analysis are summarised across Table 72, Figure 58 and Figure 59. Figure 60 shows a PSA scatterplot where survival analysis parameters have been excluded from the PSA, to illustrate the independent importance of uncertainty around these parameters for the shape and size of the PSA scatterplot. The cost-effectiveness model allows the user to generate probabilistic results for any of the programmed settings options, including all scenarios analyses reported in Section B.3.8.3. The PSA results shown are based on 1000 random draws from uncertain input parameter distributions; the mean PSA ICER appears robust to additional PSA draws, as illustrated within the cost-effectiveness model.

Every PSA iteration indicates that KTE-X19 offers an incremental QALY benefit versus SoC at a positive incremental cost, as shown in Figure 39. In comparison to equivalent deterministic results, KTE-X19 mean PSA total costs are slightly higher and mean PSA total QALYs slightly lower, leading to a slightly higher mean PSA ICER. Comparison of Figure 59 and Figure 60 illustrates how this partly due to the asymmetrical uncertainty distributions of interrelated survival analysis parameters. However, mean deterministic results in Table 71 are a reasonable approximation of mean PSA results in Table 72, suggesting deterministic results are generally robust to uncertainty from parameter distributions.

As illustrated in Figure 58, the estimated probability that KTE-X19 is a cost-effective alternative to current SoC is [redacted] at an end-of-life willingness to pay threshold of £50,000 for an additional QALY, rising sharply to [redacted] at a threshold of £60,000 and [redacted] at a threshold of £70,000.

Table 72: Mean PSA base case results

Technologies	Mean costs	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[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 58: Cost-effectiveness acceptability curve, from base case probabilistic results

[redacted]

Key: SoC, Standard of Care

Figure 59: PSA Scatterplot, KTE-X19 vs SoC, from base case PSA results

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

Figure 60: PSA Scatterplot, KTE-X19 vs SoC, excluding survival analysis parameters

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

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B.3.8.2. Deterministic sensitivity analysis

Figure 61 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 PFS 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.

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Figure 61: 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.

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B.3.8.3. Scenario analysis

The scenario analyses reported here together test the sensitivity of cost-effectiveness results to methodological, parameter and structural uncertainties in the cost-effectiveness analysis, and form an important element of this submission. Table 73 describes different scenarios tested, the rationale behind each, and documents the ICER associated with each scenario in turn. Summary results are generally robust to changes tested across the broad range of scenarios. The most impactful scenarios are those associated with annual time-preference discount rate assumptions.

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Table 73: Scenario analyses impact summary

Base case equivalent	Scenario detail	Brief rationale	ICER
Base case			[redacted]
Time horizon: 50 years	Time horizon: 20 years	Alternative time horizons	[redacted]
	Time horizon: 30 years		[redacted]
	Time horizon: 40 years		[redacted]
Discount rate 3.5%	Annual discount rate for costs 1.5%; QALYs 1.5%	Alternative time discounting assumptions	[redacted]
	Annual discount rate for costs 6.0%; QALYs 6.0%		[redacted]
Mixture cure using log-normal PSM for KTE-X19 OS	KTE-X19, OS; most optimistic MCM; Weibull	Alternative structural survival models	[redacted]
	KTE-X19, OS; most pessimistic MCM Exponential		[redacted]
Assume long-term post-progression survival following KTE-X19 is plausible	Assume long-term post-progression survival following KTE-X19 is implausible		[redacted]

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Meta-analysis of log-normal OS PSMs based on published KM data	SoC, OS; OS McCulloch only; Lognormal		[redacted]
	SoC, OS; OS Eyre only; Lognormal		[redacted]
	SoC, OS; OS Martin only; Lognormal		[redacted]
	SoC, OS; OS Jain only; Lognormal		[redacted]
	SoC, OS Pooled all studies, most optimistic projection; Gompertz		[redacted]
	SoC, PFS Pooled all studies, most optimistic projection; Generalised gamma		[redacted]
SMR of 1.09 applied to general population survival data for long-term survivors	SMR for long-term survivors: 1	Alternative log-term survivorship assumptions	[redacted]
Long-term survivor point for cost and utility assumptions: 60 months	Time point at which patients are assumed to be long-term survivors: Costs, 24 months; Utility, 24 months		[redacted]
Bridging therapy regimen: RBAC	Bridging therapy regimen: as per ZUMA-2	Alternative cost assumptions	[redacted]
Assumed SoC regimen split: 65% RBAC, 30% R-bendamustine, 5% RCHOP	Assumed SoC regimen split: even across RBAC, R-bendamustine, RCHOP, RCVP, FCR		[redacted]
Duration of IVIG: 1 year	Duration of IVIG: 2 years		[redacted]
	Duration of IVIG: 3 years		[redacted]
Number of tocilizumab doses: 1	Number of tocilizumab doses: 4		[redacted]

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Proportion of patients receiving subsequent alloSCT, SoC: 20.0%	Proportion of patients receiving allo-SCT, SoC: 15.0%	Alternative SoC subsequent allo-SCT and related data source assumptions	[redacted]
	Proportion of patients receiving allo-SCT, SoC: 30.0%		[redacted]
	Proportion of patients receiving allo-SCT, SoC: 21%, McCulloch SoC efficacy, all SoC patients receive RBAC		[redacted]
Utility for long-term survivors: general-population equivalent, capturing aging effect	Utility for long-term survivors: multiplier of 0.92 applied	Alternative utility assumptions	[redacted]
Primary health state patient utility source: ZUMA-2 mapping	Primary health state patient utility source: NICE TA502 base case		[redacted]
	Primary health state patient utility source: LaChaine (2013)		[redacted]
	Primary health state patient utility source: Yoong (2009)		[redacted]
Health state utility adjusted for aging	Remove utility aging adjustment		[redacted]

Key: allo-SCT, allogeneic stem cell transplant; R-BAC, rituximab, bendamustine, cytarabine; BGM, background mortality; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; FCR, fludarabine, cyclophosphamide, rituximab; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; IVIG, intravenous immunoglobulin; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; PSM, parametric survival modelling; QALY, quality-adjusted life year; SMR, standardised mortality ratio; SoC, standard of care.

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B.3.8.4. Summary of sensitivity analyses results

While there is inherent uncertainty around the precise clinical- and cost-effectiveness of KTE-X19 for relapsed or refractory MCL patients, the expected incremental benefit of this treatment remains substantial across plausible scenarios. Overall, the sensitivity and scenario analyses explored indicate that under a range of assumptions and across different datasets, the estimated cost-effectiveness of KTE-X19 is close to the decision-making threshold for end-of-life medicines. Key areas of uncertainty; in particular, uncertainty around expected absolute overall survival following KYE-X19 therapy in NHS post-ibrutinib MCL patients, and uncertainty around IVIG therapy use; could be plausibly addressed through CDF data collection.

B.3.9. Subgroup analysis

As described in Section B.2.7, 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.3.10. Validation

B.3.10.1. Validation of cost-effectiveness analysis

Base case deterministic cost-effectiveness results, presented in Section B.3.7, suggest mean life expectancy for post-ibrutinib MCL patients is [redacted] following KTE-X19 infusion and [redacted] in absence of KTE-X19. As illustrated in Section B.3.3, median survival has not yet been reached for either PFS or OS in the ZUMA-2 Cohort 1 mITT group; validation of absolute and relative survival estimates associated with KTE-X19 within the anticipated patient group is intrinsically difficult.

In a recent report from the HMRN, survival data was provided on UK patients diagnosed with MCL between September 2004 and August 2017.[21] The report showed that, of those patients who were receiving third-line treatment, median survival was 7.2 months.[21] It should be noted, however, that due to the time horizon over which these data were collected, this likely is an underestimation because of

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the subsequent introduction of novel agents during this time; notably rituximab at first line and ibrutinib at second line. As reported in Section B.1.3.4 and used to inform comparator estimates in the cost-effectiveness analysis, since the introduction of these novel therapies, various observational studies (post BTKi failure) have been conducted, with the reported median survival ranging from 6 to 12.5 months. In our base case economic analysis, based on a meta-analysis of four studies, median survival for in the SoC arm was [redacted].

The structure, inputs and assumptions of the cost-effectiveness analyses were reviewed during a 3 April 2020 meeting with (i) Dr Sunil Iyengar, Consultant Haematologist at The Royal Marsden NHS Foundation Trust and (ii) Dr Jonathan Lambert, Consultant Haematologist at University College London Hospitals NHS Foundation Trust, referenced throughout this document. In the spirit of transparency we hope to embody in this submission, we enclose the meeting report, signed off by all attendees, as a documented reference.[47]

Prior to submission (April 2020), the cost-effectiveness model itself was quality-assured by the internal processes of the external economists who built the economic model. In these processes, an economist not involved in model building reviewed the model for coding errors, inconsistencies and the plausibility of inputs; this was done as a thorough sheet-by-sheet check. The model was also subject to review against a checklist of known modelling errors and questioning of assumptions; the checklist followed was based on publicly available and peer-reviewed checklists.[114-116] Examples of some basic validity checks include the following:

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

B.3.11. Interpretation and conclusions of economic evidence

There can be little doubt that the clinical evidence for KTE-X19 in r/r MCL is both highly impressive and vitally important for the NHS patient group it represents. The lack of control arm in ZUMA-2 is explained by the absence of a standard of care in the post-BTKi setting; a placebo control arm would be deemed unethical. A systematic review identified no prospective PFS or OS Kaplan-Meier data for potential comparator treatments, further highlighting the absence of a standard of care and evidence for effective treatments in post-BTKi patients. Similarly, the small sample sizes observed in the ZUMA-2 and observational comparator studies identified reflect the rare nature of this disease.

Each element that underlines the value of KTE-X19 in r/r MCL, from the step-change clinical effectiveness results to the paucity of existing evidenced options and poor outlook for patients in its absence, is also a challenge for accurate estimation of cost-effectiveness. Mindful of this, and as described throughout Section B.3, the methods and data used to analyse the cost effectiveness of KTE-X19 for r/r post-ibrutinib MCL patients have been carefully considered and justified, and are believed to be the most appropriate available for decision-making.

The key strength of the economic evaluation is the transparent and flexible framework within which it harnesses the latest available pivotal ZUMA-2 data and best available comparative data from published sources, benefitting from relevant NICE DSU Technical Support Documentation recommendations and consistent with the NICE reference case and the decision problem at hand.

The generalisability of the evidence underpinning the economic evaluation to the contemporary NHS England treatment setting is strong. At NHS Consultant review, the ZUMA-2 mITT cohort baseline characteristics were considered comparable to the published retrospective studies in the post-ibrutinib setting.[47] All these patients are slightly younger and fitter than the typical UK 3rd line patient, but the ZUMA-2 mITT group are notable for the high proportion (62%) who were BTKi-refractory at baseline.[47] Less than a fifth of patients are ibrutinib-refractory in current practice, and ibrutinib-refractory outcomes are notably poor.[47] As such, the naïve comparative

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effectiveness analysis underpinning the economic results may bias against KTE-X19.

While validation of the estimated and expected long-term benefit of KTE-X19 based on ZUMA-2 evidence with external data currently impossible, the analysis highlights both the plausible cost-effectiveness of KTE-X19 as an end-of-life therapy and that key uncertainties are those that can be attenuated through further, planned ZUMA-2 data collection.

Overall, the cost-effectiveness analysis presents a compelling case for KTE-X19 as a clear candidate for CDF approval; this would both allow access to this transformative therapy to the patient community that so need it, and allow time and further evidence before a final decision.

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B.5. Appendices

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

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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

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

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Supplementary ZUMA-2 data

Appendix M: Summary of base-case analysis inputs

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

KTE-X19 for treating relapsed or refractory mantle cell lymphoma

[ID1313]

Clarification questions

May 2020

File name	Version	Contains confidential information	Date
ID1313 KTE-X19 company response to ERG clarification letter v1.0_AICCIC	1.0	Yes	02/06/2020

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

ZUMA-2

A1. PRIORITY QUESTION: Patient flow in ZUMA-2

a) **Please outline how patients were identified for screening and enrolment in ZUMA-2 and in which setting screening took place.**

The number of patients screened for eligibility are detailed below. The screening period started when patients signed the informed consent form, and at that point, patients received a unique subject identification number. Prior to consent, no data were collected. We understand screening took place at the investigative sites: as per protocol “all investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation”.

b) Please provide the following information for ZUMA-2: numbers of patients screened for eligibility, number ineligible/excluded with reasons and who declined prior to enrolment phase for cohorts 1 & 2.

A total of 135 patients were screened for eligibility; 30 of whom were not subsequently enrolled to any cohort of ZUMA-2. Of these 30 patients, 17 patients met one of the exclusion criteria, 11 patients did not meet one of the inclusion

criteria, and 2 patients both met one of the exclusion criteria and did not meet one of the inclusion criteria. No patient declined enrolment.

A2. PRIORITY QUESTION: Assessment of minimal residual disease in ZUMA-2

a) Please outline the method used to measure minimal residual disease (MRD).

Minimal residual disease (MRD) (1 in 100,000 cells) was assessed as an exploratory analysis. MRD was assessed in cryopreserved peripheral-blood mononuclear cells obtained at baseline and at months 1, 3, and 6 and was analysed by means of next-generation sequencing with the use of the clonoSEQ assay (Adaptive Biotechnologies).

b) Please provide results of the MRD analysis, specifically MRD in the modified intent to treat (mITT) population at a sensitivity of 10^{-6} (or 10^{-5} if 10^{-6} is not available) at timepoints 3-months, 6-months and 12-months.

c) Of the patients with MRD at 4 weeks, how many sustained this at 6 months and beyond?

MRD analysis is provided at a sensitivity of 10^{-4} to 10^{-6} at timepoints 4-weeks, 3-months and 6-months in Table 1 to Table 3. Data are not available for 12-months. Of the patients with no detectable residual disease at 4 weeks (n=24 at a sensitivity of 10^{-5}), [redacted] ([redacted]%) also had no detectable residual disease at 3 and 6 months.

The potential use of MRD data to inform a relationship between depth of response and longer-term outcomes for the economic modelling was considered during its design. However, the number of patients on whom this data is available was considered too small to make any meaningful conclusions (along with its exploratory nature), as confirmed by clinical experts consulted during development of the evidence submission.

Table 1: Minimal residual disease at a sensitivity of 10^{-4} (Cohort 1; mITT)

[redacted]

Key: mITT, modified intent-to-treat.

Table 2: Minimal residual disease at a sensitivity of 10^{-5} (Cohort 1; mITT)

[redacted]

Key: mITT, modified intent-to-treat.

Table 3: Minimal residual disease at a sensitivity of 10^{-6} (Cohort 1; mITT)

[redacted]

Key: mITT, modified intent-to-treat.

d) The company submission (CS) states MRD was measured in 29 patients. Please explain why this was measured in only 29 patients and why these specific 29 were selected.

As noted in the response to A2a, MRD was not a pre-specified efficacy endpoint of ZUMA-2, but rather assessed as an exploratory analysis. MRD was assessed in cryopreserved peripheral-blood mononuclear cells obtained at baseline and at months 1, 3 and 6.

MRD was unable to be assessed in all patients due to the lack of availability of a formalin-fixed paraffin-embedded tumour biopsy sample for calibration, which was required by the methodology and used to establish dominant rearranged IgH (VDJ or DJ), IgK, or IgL receptor gene sequences tracked over time in blood.

e) Please provide any evidence that depth of response is associated with improved survival outcomes.

The strongest evidence that depth of response is associated with improved survival outcomes is the overall survival (OS) stratified by response analyses. The Kaplan-Meier plot in Figure 1 shows a substantial extension to life for patients experiencing a complete response (CR), compared to those experiencing a partial response (PR) or no response (NR) (modified intent-to-treat [mITT] analysis set).

Figure 1: Overall survival by best objective response using central assessment (IRRC) per Lugano classification (Cohort 1; mITT)

Key: CI, confidence interval; CR, complete response; NE, not estimable; NR, no response; PR, partial response; mITT, modified intent-to-treat.

As summarised on Page 46 of the company submission (CS), of patients who achieved a CR, only %% had died at data cut-off (); the estimated 12-month OS rate was % and the estimated 24-month OS rate was %. Of patients alive at data cut-off, % () had an ongoing response (an additional had been censored for duration of response due to allogenic stem cell transplant consolidation of their KTE-X19-induced remission). In comparison, of patients who achieved a partial response (PR), % had died at data cut-off (). Of patients alive at data cut-off, 46% () had an ongoing response.

We have also looked at the 12-month survival rate stratified by MRD status (10^{-5} senstivity) at Week 4, Month 3 and Month 6, as depicted in Figure 2. A general trend towards improved survival in patients with no detectable residual disease detected is observed, however, as noted above, the number of patients on whom this data is available is considered too small to make any meaningful conclusions (along with its exploratory nature).

Figure 2: Survival rate at Month 12 by MRD status (Cohort 1; mITT)

[redacted]

Key: LCI, lower confidence interval; MRD, minimal residual disease; NE, not estimable; OS, overall survival; UCI, upper confidence interval.

A3. PRIORITY QUESTION: Please provide the number and proportion of patients with pancytopenia (including grading) at 3-months, 6-months and 12-months from ZUMA-2 in the modified intent-to-treat (mITT) and full analysis set (FAS).

Pancytopenia is not a Common Terminology Criteria for Adverse Events (CTCAE) term and was not a Medical Dictionary for Regulatory Activities (MedDRA) preferred term used for adverse events (AE) collected during the investigational product treatment period.

It was a MedDRA preferred term used for AEs collected during the conditioning chemotherapy period, where [redacted] in Cohort 1 had Grade 3 pancytopenia.

The number of patients with thrombocytopenia, neutropenia or anaemia during the investigational product treatment period are provided for the safety analysis set in Table 23 of the CS. Safety data for the investigational product treatment period could not collected for the full analysis set (FAS), that is, additional patients to those included in the safety analysis set did not enter this study period.

The number of patients with thrombocytopenia, neutropenia or anaemia at 6-months and 12-months in the safety analysis set are provided in Table 4 and Table 5.

Table 4: Patients with thrombocytopenia, neutropenia or anaemia at 6-months

[redacted]

Table 5: Patients with thrombocytopenia, neutropenia or anaemia at 12-months

[redacted]

A4. Subsequent therapy in ZUMA-2

a) Please provide the number and proportion of patients enrolled in ZUMA-2 who received [redacted] as a subsequent therapy and responded to [redacted] following KTE-X19.

b) Please provide the number and proportion of patients enrolled in ZUMA-2 who received [redacted] as a subsequent therapy and responded to [redacted] following KTE-X19.

The number and proportion of patients who received [redacted] as a subsequent therapy are provided in Table 12 of the CS, but re-presented below in Table 6 for ease of reference.

Table 6: ZUMA-2 mITT subsequent anti-cancer therapy summary

	KTE-X19 (n = 68)
Subsequent anti-cancer therapy, n (%)	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Response data to subsequent therapy were not captured, as this was not part of the statistical analysis plan for ZUMA-2. Considering the ZUMA-2 trial enrolled patients whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi), and the high proportion of patients with disease refractory to BTKi (62%), expectation of a response to subsequent targeted therapy, particularly repeat BTKi, is likely to be low.

A5. On page 29 of the company submission, it states the mITT is used as it 'best represents the decision problem population and was used in subsequent economic analysis'. Please expand on the justification for using the mITT population to represent the decision problem rather than the FAS.

The mITT analyses provide a more accurate estimate of efficacy and safety that could be expected with KTE-X19 treatment in clinical practice, compared to the FAS analyses that includes data for patients not treated with KTE-X19. The mITT analysis set also aligns to the costing framework proposed for KTE-X19 where the NHS cover costs only when KTE-X19 is administered to the patient.

A scenario analysis is incorporated into the updated model to consider using the FAS population to represent the decision problem. This is further detailed in the response to question B1.

A6. The ERGs examination of the PFS, DOR and OS KM survival curves highlights that the extent of censoring in ZUMA-2 is high at two different timepoints (e.g. between 8 and 12 months and 25 and 30 months for the OS data, (Figure 13, page 46)):

a) Please identify the reasons for the censoring of patients in the PFS, DOR and OS analyses and their frequency (number of patients), by time point: up to

6 months, between 7-12 months, between 13-24 months, and 25 or more months.

Reasons for the censoring of patients in the progression-free survival (PFS), duration of response (DOR) and OS analyses by timepoint are summarised in Table 7 to Table 9. At all timepoints, the majority of censoring was due to ongoing response in the case of PFS and DOR analyses and for OS analysis, all censoring was due to patients being alive.

Table 7: Censoring reasons for progression-free survival (Cohort 1; mITT)

[redacted]

Key: mITT, modified intent-to-treat; PFS, progression-free survival; SCT, stem cell transplant.

Table 8: Censoring reasons for duration of response (Cohort 1; mITT)

[redacted]

Key: DOR, duration of response; mITT, modified intent-to-treat; SCT, stem cell transplant.

Table 9: Censoring reasons for overall survival (Cohort 1; mITT)

[redacted]

Key: mITT, modified intent-to-treat; OS, overall survival.

b) The high extent of censoring at different timepoints, if due to administrative censoring (end of follow-up), suggests different waves of recruitment into the study. Could the company justify this and detail recruitment for ZUMA-2? Could the company comment on any potential differences between patients recruited earlier and later in ZUMA-2 by reporting the baseline characteristics of the patients by time of entry into ZUMA-2: up to 6 months, 7-12 months, 13-24 months, 25+ months from the start of recruitment.

Baseline characteristics of patients by potential follow-up time since enrolment are provided in Table 10. Although some differences are observed across groups, there are no clear trends and the low patient numbers prevent any meaningful comments to be made. However, there are no clinical rationale as to why patients baseline characteristics would differ due to date of recruitment.

Table 10: Baseline characteristics of patients by potential follow-up time since enrolment (Cohort 1; mITT)

	≤6 months (n=4)	>6 to ≤12 months (n=25)	>12 to ≤24 months (n=11)	>24 months (n=28)
Median age, years	[redacted]	[redacted]	[redacted]	[redacted]
(range)	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥ 65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage, n (%)				
II	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]
ECOG, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
s-MIPI risk, n (%)				
Low	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Ki-67 proliferation index at diagnosis, n/N (%)				
≥ 30%	[redacted]	[redacted]	[redacted]	[redacted]
≥ 50%	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow involvement, n (%)				
Extranodal disease[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
MCL morphology, n (%)				
Classical	[redacted]	[redacted]	[redacted]	[redacted]
Blastoid	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Median no. of prior therapies (range)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior therapies, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
Prior anthracycline or bendamustine, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-CD20 mAb, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

	≤6 months (n=4)	>6 to ≤12 months (n=25)	>12 to ≤24 months (n=11)	>24 months (n=28)
Prior auto-SCT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior BTKi, n (%)				
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Both	[redacted]	[redacted]	[redacted]	[redacted]
Relapsed or refractory disease, n (%)				
Relapse after auto-SCT	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to most recent prior therapy	[redacted]	[redacted]	[redacted]	[redacted]
Relapse after most recent prior therapy	[redacted]	[redacted]	[redacted]	[redacted]
Received bridging therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: auto-SCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IAS, inferential analysis set; 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], induction plus consolidation/maintenance and/or all treatments occurring between sequential complete responses were counted as 1 regimen.

A7. Appendix E subgroup analyses – please present these results for the mITT dataset. Please also present ECOG status subgroup results for the 'Ongoing response' and 6-month PFS outcomes.

Subgroup analyses requested are provided across Figure 3 to Figure 5. However, as acknowledged in the CS, it should be noted that patient numbers in several subgroups are small, and interpretation should therefore be limited to trend analyses and considered only for exploratory purposes.

Figure 3: Forest plot of response in pre-planned subgroups using central assessment (IRRC) per IWG Lugano classification (Cohort 1; mITT)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Key: auto-SCT, autologous stem-cell transplant; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; LCI, lower confidence interval; MCL, mantle cell lymphoma; mITT, modified intent-to-treat; ORR, objective response rate; s-MIPI, simplified Mantle cell lymphoma International Prognostic Index; SPD, sum of product diameter; UCI, upper confidence interval.

Figure 4: Forest plot of ongoing response in key subgroups using central assessment (IRRC) per IWG Lugano classification (Cohort 1; mITT)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Key: auto-SCT, autologous stem-cell transplant; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; LCI, lower confidence interval; MCL, mantle cell lymphoma; mITT, modified intent-to-treat; ORR, objective response rate; s-MIPI, simplified Mantle cell lymphoma International Prognostic Index; SPD, sum of product diameter; UCI, upper confidence interval.

Figure 5: Forest plot of 6-month PFS rate in key subgroups using central assessment (IRRC) per IWG Lugano classification (Cohort 1; mITT)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Key: auto-SCT, autologous stem-cell transplant; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; LCI, lower confidence interval; MCL, mantle cell lymphoma; mITT, modified intent-to-treat; ORR, objective response rate; PFS, progression-free survival; s-MIPI, simplified Mantle cell lymphoma International Prognostic Index; SPD, sum of product diameter; UCI, upper confidence interval.

A8. Baseline subgroup data for bridging status: please provide a comparison of the baseline data (similar to Table 7, page 29-30 of the CS) for the mITT dataset with the columns comparing bridging patients and no-bridging patients. Please provide detail not given in Table 7, giving separate rows for ECOG 0 and ECOG 1, number of prior regimens (a row for each), s-MIPI risk category (a row for each of the 3 categories) and disease stage (a row for each).

A comparison of the baseline data for patients by bridging therapy status is provided in **Table 11**. The small patient numbers and exploratory nature of these analyses warrant caution to be applied when interpreting these data. However, general trends of patients who received bridging therapy being of higher s-MIPI risk, higher performance status, higher Ki-67 proliferation index and more likely to have been refractory to their most recent prior therapy holds face validity.

Table 11: Baseline characteristics of patients by bridging therapy status (Cohort 1; mITT)

	Had bridging therapy (n=25)	**No bridging therapy (n=43)**
Median age, years (range)	[redacted]	[redacted]
Age ≥ 65 years, n (%)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Disease stage, n (%)		
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
ECOG, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
s-MIPI risk, n (%)		
Low	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]
High	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Ki-67 proliferation index at diagnosis, n/N (%)		
≥ 30%	[redacted]	[redacted]
≥ 50%	[redacted]	[redacted]
Bone marrow involvement, n (%)	[redacted]	[redacted]

Extranodal disease[a], n (%)	[redacted]	[redacted]
MCL morphology, n (%)		
Classical	[redacted]	[redacted]
Blastoid	[redacted]	[redacted]
Other	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Median no. of prior therapies (range)[b]	[redacted]	[redacted]
Number of prior therapies, n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
Prior anthracycline or bendamustine, n (%)	[redacted]	[redacted]
Prior anti-CD20 mAb, n (%)	[redacted]	[redacted]
Prior auto-SCT, n (%)	[redacted]	[redacted]
Prior BTKi, n (%)		
Ibrutinib	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]
Both	[redacted]	[redacted]
Relapsed or refractory disease, n (%)		
Relapse after auto-SCT	[redacted]	[redacted]
Refractory to most recent prior therapy	[redacted]	[redacted]
Relapse after most recent prior therapy	[redacted]	[redacted]

Key: auto-SCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IAS, inferential analysis set; 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], induction plus consolidation/maintenance and/or all treatments occurring between sequential complete responses were counted as 1 regimen.

Meta-analysis

A9. Please provide full details of all steps undertaken in the meta-analysis (MA) and all the files required to reproduce the MAs performed, including details of:

a) data sources used including raw data extraction tables;

b) R script used to run the MA (and any functions required), the R data and results files – so the ERG can replicate the analyses.

Steps undertaken in the meta-analysis (MA) are described in Appendix D of the CS.

The requested files to allow reproduction of the MA are delivered alongside this response document:

- ‘A9-a - SOC data extraction’ contains data extraction for patient characteristics, response outcome, and pseudo individual patient level data generated from digitized Kaplan-Meier curves for all trials.
- ‘A9-a - SOC trial survival’ contains parametric survival for OS and PFS for each trial.
- ‘A9-b – JAGScode’ contains JAGS code for survival parameter pooling.

Indirect treatment comparison

A10. PRIORITY QUESTION: The company synthesised data from two cohorts to obtain PFS for standard of care and from four cohorts to obtain OS data. Following examination of the studies and feedback from our clinical advisors, McCulloch et al. appears to be the study which better reflects the patients and care in the NHS at present. However, we have concerns that there may be important differences in prognostic factors between the patients in ZUMA-2 and the patients in McCulloch. For this reason, we would like the company to conduct a matching adjusted indirect comparison of ZUMA-2 with McCulloch et al.

a) Please conduct a MAIC of ZUMA-2 mITT with McCulloch et al. Please use McCulloch et al (2020) given that it includes more patients and a longer follow-up.

McCulloch, R., Visco, C., Eyre, T.A., Frewin, R., Phillips, N., Tucker, D.L., Quaglia, F.M., McMillan, A., Lambert, J., Crosbie, N. and Rule, S. (2020), Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. Br J Haematol. doi:10.1111/bjh.16416

A matching-adjusted indirect comparison (MAIC) has been performed to compare ZUMA-2 to McCulloch et al., 2020. This MAIC was matched based on five out of the

six baseline characteristics of highest relevance: number of prior treatments, prior autologous stem cell transplant (ASCT), response (i.e. objective response rate) to prior BTKi, mantle cell lymphoma international prognostic index (MIPI), and blastoid morphology; duration on prior BTKi therapy was not reported in McCulloch et al., 2020 and therefore could not be adjusted for. Prior ibrutinib use and proportion of males were the only two other covariates reported in McCulloch et al., 2020; these were not included in the matching analysis but the reported baseline values were well-balanced between both studies.

Patient characteristics for McCulloch et al., 2020 were not always reported at the start of rituximab, bendamustine and cytarabine (R-BAC) treatment. Where reported, measurements at start of R-BAC was used for the MAIC; otherwise, those taken at other time-points (e.g. at diagnosis) were used. Out of the five matched characteristics, blastoid morphology was the only characteristic that was reported at diagnosis only. Instances of transformations from classical MCL to the Blastoid variant are rare[1], therefore, we assumed this proportion would stay stable over time and could be included in the MAIC.

Study design differences between McCulloch et al., 2020 and ZUMA-2 are important to consider. McCulloch et al is retrospective in design; patient data were retrospectively retrieved from hospital and lymphoma network records, rather than prospectively collected.

After matching, the effective sample size (ESS) was reduced to [redacted]. Figure 6 presents McCulloch et al (2020)-MAIC-adjusted ZUMA-2 mITT OS and PFS data alongside equivalent unadjusted data. The relatively dramatic event-driven drops in the MAIC-adjusted data indicate the high weight given to some patients in the MAIC analysis, reflected in the low ESS. Figure 7 shows the data in Figure 6 alongside digitised OS and PFS KM data from McCulloch et al., 2020.

It should be acknowledged that 12/36 patients (33%) treated with R-BAC were consolidated with allogenic stem cell transplant (alloSCT) or donor lymphocyte infusion (DLI) in the McCulloch study.[2] This is the at the higher end of clinical expert estimates for how many patients treated at third-line receive alloSCT consolidation which were <15% and <30% on consultation.[3] Despite this, the median PFS and OS

times reported were markedly lower in the McCulloch study than those observed with KTE-X19 in ZUMA-2. Although patients appear to respond well to R-BAC treatment, these data suggest responses are short-lived in the majority, reflecting the current limitations of most treatments available as discussed in Section B.1.3.4 of the CS.

[redacted]

Figure 7: Figure 6 data alongside digitised OS and PFS KM data from McCulloch 2020

[redacted]

b) Please comment on the plausibility of the assumptions imposed by the MAIC analysis, given the recommendations in the NICE DSU TSD18.

Based on the number of patients in ZUMA-2 (n=68), a limited number of characteristics were included in the MAIC weighting; however, based on expert input the six most relevant characteristics were accounted for (except for duration on prior BTKi therapy as this was not reported in McCulloch et al., 2020). We note that as with any analysis of single-arm or non-comparative studies, there will always be uncertainty regarding any unknown or unmeasured prognostic factors and effect-modifiers that are not captured in the chosen model which may influence the outcome of interest. Important factors highlighted here include study design (prospective versus retrospective) as well as unobservable treatment-effect modifying patient characteristics.

The reduced list of variables did not include two other patient characteristics (i.e. prior ibrutinib use and proportion of males) that were reported in McCulloch et al., 2020 or Stage III+ disease stage; these characteristics appear well-balanced across both studies, but McCulloch et al Staging data are only reported at initial diagnosis. Other potential variables, for example, duration on prior BTKi therapy, Ki67, extranodal disease, and bone marrow involvement were not reported in McCulloch et al. 2020; therefore, we are unable to assess their comparability to those reported in ZUMA-2. As discussed earlier, patient characteristics for McCulloch et al. 2020 were not always reported at the start of standard of care (i.e. start of R-BAC). Blastoid morphology, which was used in the matching, was measured only at diagnosis, but this characteristic was assumed to be relatively stable over time.

All indirect comparisons were carried out on linear predictor scales used for evidence synthesis of each outcome in accordance with NICE DSU TSD18.[4] Despite our efforts to ensure the most appropriate models were used, we acknowledge that the models still rely on the assumptions, and as such cannot be considered as robust as having randomised controlled trial (RCT) data. Moreover, the MAIC analysis results in such a low ESS for the adjusted comparisons, naïve (unadjusted) comparisons that preserve the original sample size will arguably have less uncertainty, if on balance the difference in prognostic factors, are not all falling in favour of one treatment or the other (discussed further below).

c) Provide a table similar to Table 18, page 66 in the CS with the characteristics of the patients in ZUMA-2 pre- and post-MAIC (mean, median, or number of patients per discrete categories, as relevant). Please include both the characteristics included in the MAIC and those which were excluded but had been selected as potentially relevant (as per B.2.9.1.1. page 64, also including age). Include a comparison with the McCulloch et al. 2020 patient characteristics for comparison purposes.

Table 12 shows the data requested. After matching, the ESS was [redacted]. Although this could be seen as supportive of the ERG concerns that there may be important differences in prognostic factors between the patients in ZUMA-2 and the patients in McCulloch, it also leaves a substantially low sample size on which comparisons are being made.

Qualitative assessment of the key differences observed in patient characteristics across trials suggest the ZUMA-2 population had better prognosis than the McCulloch population when considering s-MIPI risk, but worse prognosis when considering treatment history (number of prior therapies and prior response to BTKi). Note, although the split between Stage III and IV disease was not reported in McCulloch et al., all patients had Stage III/IV disease at diagnosis.

Table 12: Baseline characteristics of patients in ZUMA-2 (Cohort 1; mITT) before and after matching to McCulloch 2020

	Observed ZUMA-2	Weighted ZUMA-2	McCulloch 2020
N / ESS	68	[redacted]	36
No. of prior therapies	3.3	[redacted]	2
Prior ASCT, %	42.6	[redacted]	41.7
Prior BTKi ORR, %	38.2	[redacted]	58.3
MIPI low, %	42.4	[redacted]	19.2
MIPI intermediate, %	43.9	[redacted]	23.1
Blastoid variant, %	25	[redacted]	19.4
Prior BTKi duration[a]	11.4	[redacted]	Not reported
Ki67 ≥30, %	58.8	[redacted]	Not reported
Ki67 ≥50, %	50	[redacted]	Not reported
Disease Stage III, %	11.8	[redacted]	Not reported
Disease Stage IV, %	85.3	[redacted]	Not reported
Prior ibrutinib, %	85.3	[redacted]	86.1
Male, %	83.8	[redacted]	80.6
Extranodal disease, %	55.9	[redacted]	Not reported
Bone marrow involvement, %	54.4	[redacted]	Not reported

Key: ASCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; ESS, effective sample size; MIPI, Mantle Cell Lymphoma International Prognostic Index; mITT, modified intent-to-treat; ORR, overall response rate.
Notes: Grey cells present characteristics included in the matching; a, matched on median of each scenario.

d) Please provide all relevant code so the ERG can replicate the analysis.

Files to allow replication of the analysis are delivered alongside this response document as follow:

- ‘A10-d - SOC data extraction A10’ contains data extraction for patient characteristics, response outcome, and individual patient level data generated from digitized Kaplan-Meier curves for McCulloch et al. 2020.
- ‘A10-d - SOC trial survival’ contains parametric survival for OS and PFS for McCulloch et al. 2020.
- ‘A10-d - ZUMA-2 survival’ contains parametric survival for OS and PFS for MAIC weighted ZUMA-2.
    - Comparison of OS and PFS between ZUMA-2 and McCulloch et al., 2020 used the best fitting model (log normal) parameters from ‘SOC trial survival A10’ and the best fitting model (Gompetz) parameters from ‘ZUMA-2 survival A10’.
- Rproject ‘Files for A10.Rproj’ and code ‘survival comparison.R’ provide code used to derive the survival and hazard over time from these best fitting models and average HR and mean survival up to 33 months.

Please note the vendor approach contains parametric survival analysis as standard for the MAIC, however we don’t feel the adjusted data are sufficient for informative parametric modelling.

A11. Baseline characteristics for MAIC Section B.2.9.1.1 CS (page 64)

a) How was the order of relevance of the initial list of baseline characteristics decided?

A targeted search of the existing literature was performed to help identify important characteristics with prognostic value in the relapse/refractory MCL population. In addition, given the limited number of included studies evaluating ‘standard of care’ (SOC), we also considered all other common baseline patient characteristics reported in ZUMA-2 and in the comparator studies as potential covariates.

Clinical experts were then sought to provide input and suggestions on the list of baseline characteristics and their order of relevance. This list was initially reviewed and confirmed by Kite medical team (Kite: Enrique Granados; Zahid Bashir (MB BS; MSc Clinical Oncology); Damla Kilic (MD; Internal medicine specialist)). Based on

consolidated feedback, the first six patient characteristics listed in Section B.2.9.1.1 of the CS (that is, number of prior therapies, prior ASCT, duration on prior BTKi therapy, response to prior BTKi therapy, MIPI, and blastoid morphology) were rated as most relevant whereas the last six variables were deprioritised. After multiple rounds of discussions with Kite, the full list of baseline characteristics, ranked by relevancy in terms of prognostic value for OS was finalised. Note that this full list was subsequently validated by several clinicians from the UK and Canada through expert interviews (John Kuruvilla, MD (Canada); Graham Collins, MD (UK); Keith Wilson, MD (UK)). In summary, no further revision to the initial list and ranking was deemed necessary, and this full list was considered for the MAIC. However, after reviewing the results using the full list of covariates, it was decided to include only the six most relevant characteristics as this led to more conservative and clinically plausible results while also giving a higher ESS (see further details below).

b) Regarding the sentence at the bottom of page 64, "The list of baseline characteristics considered within the MAIC were therefore reduced (through internal expert consultation)." Please provide any explanatory documentation relating to this expert consultation and its findings.

Initially, for the MAIC, the weights were generated to match the full list of patient characteristics of ZUMA-2 trial. Given the low ESS (n=[redacted]), we explored reducing the list of patient characteristics for the MAIC by removing those of lesser relevance from the model. Based on earlier discussion around prioritization (see response above), six of the 12 patient characteristics were removed from the model (Ki67, disease staging, prior BTKi therapy type, sex, extranodal disease, and bone marrow involvement). Weights generated based on this reduced list led to larger, more practical ESSs in all analysis scenarios. There were fewer patients with extreme weights, and the weighted Kaplan-Meier curves for OS and PFS shifted downwards which gave a more conservative estimate of the prognostic factor direction of effect.

c) Please outline why Ki67 was not included as a baseline characteristic of interest in the final MAIC. Please replicate the results of the MAIC and include the baseline characteristic Ki67.

Given the low ESS when matching using the full list of baseline characteristics, the weights were generated to match a reduced list of characteristics of higher relevance. This reduced list did not include Ki67.

We explored the impact of Ki67 inclusion in the model on the ESS and the ZUMA-2 OS Kaplan-Meier curve. The ESS after matching to the pooled characteristics from all four SOC studies was [redacted] using the initial priority list, and was [redacted] using the priority list plus Ki67.

As shown in Figure 8 and Figure 9, the adjusted OS Kaplan-Meier curves for KTE-X19 using the initial priority list that did not include Ki67 (Figure 8) and that including Ki67 (Figure 9) were comparable in terms of the magnitude and direction of the shift. Given this, we have not proceeded with replicating the results of the MAIC to include Ki67 as we do not anticipate the results of the MAIC estimates to be significantly different with or without adjusting for Ki67. In addition, excluding Ki67 is the more conservative approach because adding Ki67 to the reduced list shifted the weighted ZUMA-2 OS KM curve slightly upwards (Figure 9 vs Figure 8).

Figure 8: Unadjusted and matching-adjusted Kaplan–Meier plots for overall survival – matched to all included studies (Cohort 1; mITT) using the initial priority list of baseline characteristics

Key: MAIC, matching-adjusted indirect comparison.

Figure 9: Unadjusted and matching-adjusted Kaplan–Meier plots for overall survival – matched to all included studies (Cohort 1; mITT) using the initial priority list of baseline characteristics plus Ki67

Key: MAIC, matching-adjusted indirect comparison.

Systematic literature review

A12. In Appendix D, Updated SLR literature flow (page 36) and the PRISMA flow diagram (Figure 2) state that there are 12 included studies that were taken through to data extraction. Table 11 and Table 12 only include 10 studies (16 publications), from which 5 studies (and ZUMA-2) are included in the main submission in the meta-analysis. Please clarify the numbers, giving reasons for any subsequent exclusions.

Apologies for the confusion. There were 12 studies conducted in patients who had previously received a BTK inhibitor and were therefore taken through to data extraction. However, only 10 of these studies provided data exclusively in the post-BTKi setting and were thus taken through to initial feasibility assessment for subsequent meta-analysis and indirect treatment comparison (ITC).

Details of the two studies from which data were extracted but not considered for meta-analysis and ITC are provided below.

	Jain et al. 2019[5]	Hughes et al. 2019[6]
Study design	Retrospective observational	Retrospective observational
Study population (n)	Adults who had received venetoclax for r/r MCL as a salvage measure (n=24)	Adults who had received venetoclax for r/r NHL (n=34), including patients with r/r MCL (n=10)
Prior BTK inhibitor	92% had previously been exposed to ibrutinib or other BTK inhibitor (22/24) 71% had progressed on ibrutinib or other BTK inhibitor (17/24)	Of patients with r/r MCL, 90% had previously been exposed to ibrutinib (9/10)
Study treatment	Venetoclax ± obinutuzumab ± BTK inhibitor	Venetoclax
Study location	USA	USA
Timescale	Not reported	April 2016 – January 2019
Key: BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma; r/r, relapsed or refractory.		

A13. The descriptions of the search in Appendix H, page 143 refers to "the same literature search strategy, in terms of the data sources investigated was performed as was done for the SLR of the published cost-effectiveness studies in Appendix G". The searches reported in Appendix G cover the following databases - MEDLINE, Embase, MEDLINE In-Process, The Cochrane Library, HTA database, NHS EED, DARE, EconLIT, EconPapers and the CEA Registry and EBM Reviews HTA database were searched. The only database search strategies reported in Appendix H are for MEDLINE(PubMED), Embase, Cochrane Library, EconLIT. Please confirm whether the additional databases were searched. If they were searched, please provide the search strategies used and the number of records identified.

All the data sources mentioned in Appendix G were also searched for Appendix H. The search tables were not included in the original submission as all the databases requested had no hits for the time frame 2019 to 2020. The databases that were searched and had no hits included the ones below. The search terms and the tables for recording search hits across all these databases are included below.

- CRD York registry which was used to search NHS EED, Health Technology Assessment Database (HTAD) and DARE

- EconPapers
- CEA registry

University of York Centre for Reviews and Dissemination search terms

#	Search terms	No. of hits
	Disease	
1	MeSH DESCRIPTOR Lymphoma, Mantle-Cell EXPLODE ALL TREES	8
2	"Mantle cell lymphoma" OR "Mantle-cell lymphoma"	14
3	MCL	5
4	mantle AND cell AND lymphoma	17
5	mantle-cell AND lymphoma	17
6	#1 OR #2 OR #3 OR #4 OR #5	18
7	#6 (restricted to 2019 to 2020)	0

EconPapers search terms

#	Search terms	No. of hits
	Disease	
1	Mantle cell lymphoma	0

CEA Registry search terms

#	Search terms	No. of hits
	Disease	
1	Mantle cell lymphoma	0

In addition, EBM HTA reviews consist of seven databases, which can be searched by Ovid. Out of these, the Cochrane database of systematic reviews (CDSR), Cochrane clinical answers (CCA), Cochrane Central Register of Controlled Trials (CCTR) were searched using the Cochrane.com interface. In addition, Health technology assessment database (HTAD), Economic evaluation database (NHS EED) and The Database of Abstracts of Reviews of Effectiveness (DARE) were searched using CRD York interface. Further, ACP Journal Club and Cochrane Methodology Register (CMR) were not searched. The searches for these databases are provided in appropriate sections. The databases that have been searched across

the project are comprehensive and cover almost all biomedical journals and hence chances of missing a relevant study are negligible.

A14. a) The description of the search on Appendix I, page 169 refers to "An SLR was performed to identify published studies on quality of life/utilities in adult patients with r/r/ MCL". Please confirm if this is correct? If so, please clarify if this is different to the search described in Appendix H i.e. "An SLR was performed to identify published studies on health-related quality of life (HRQoL)/utility data in adult patients with r/r MCL.

b) Please repeat steps outlined in question A13 for Appendix I, page 169.

Apologies for the confusion: quality of life/utilities in Appendix I, page 169 is a typographical error. The wording should have been "An SLR was performed to identify published studies on cost and resource use in adult patients with r/r/ MCL". This section includes data for cost and resource use and is different from the quality of life/utilities section.

All the data sources mentioned in Appendix G were also searched for Appendix I. The search tables were not included in the original submission as all the databases requested had no hits for the time frame 2019 to 2020. The databases that were searched and had no hits included the ones below. The search terms and the tables for recording search hits across all these databases are included below.

- CRD York registry which was used to search NHS EED, Health Technology Assessment Database (HTAD) and DARE
- EconPapers
- CEA registry

University of York Centre for Reviews and Dissemination search terms

#	Search terms	No. of hits
	Disease	
1	MeSH DESCRIPTOR Lymphoma, Mantle-Cell EXPLODE ALL TREES	8
2	"Mantle cell lymphoma" OR "Mantle-cell lymphoma"	14
3	MCL	5
4	mantle AND cell AND lymphoma	17
5	mantle-cell AND lymphoma	17
6	#1 OR #2 OR #3 OR #4 OR #5	18
7	#6 (restricted to 2019 to 2020)	0

EconPapers search terms

#	Search terms	No. of hits
	Disease	
1	Mantle cell lymphoma	0

CEA Registry search terms

#	Search terms	No. of hits
	Disease	
1	Mantle cell lymphoma	0

As per our response to A.13, we believe that the databases that have been searched across the project are comprehensive and cover almost all biomedical journals and hence the chances of missing a relevant study are negligible.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY QUESTION: Health outcomes and costs of the patients who did not receive KTE-X19

The costs of leukapheresis and of conditioning therapy are included for those who did not undergo KTE-X19 infusion using cost multipliers. This approach

does not capture the long-term life expectancy and QALYs, and long-term costs of those patients, in contrast to the approach in TA554 and TA567.

Please update the model so that the health outcomes and costs of the patients who did not receive KTE-X19 are fully considered in the model. One approach is to use a simple decision tree, as per the approach taken in TA554 and TA567. Please revise the economic model so that this approach can be used in combination with other scenarios.

The mITT sample comprises the 68 patients in Cohort 1 who received KTE-X19 at a dose of 2 x 106 anti-CD19 CAR T-cells/kg body weight. As detailed in the response to question A5, we reasoned that this analysis set reflects the decision problem population, and therefore based the CS economic analysis on this group.

In response to this question, we have specified a scenario analysis in an updated version of the submitted cost-effectiveness model submitted alongside this response, that considers the decision problem from the perspective of the FAS for ZUMA-2. In this scenario, the health outcomes and costs of the ZUMA-2 patients who were intended to but did not receive KTE-X19 are accounted for, similar to the approach used in TA554 and TA567. The model structures used in these appraisals included an initial decision tree element to capture the outcomes of patients who did and did not continue to infusion; this was done by first splitting the population into three categories (branches in the decision tree):

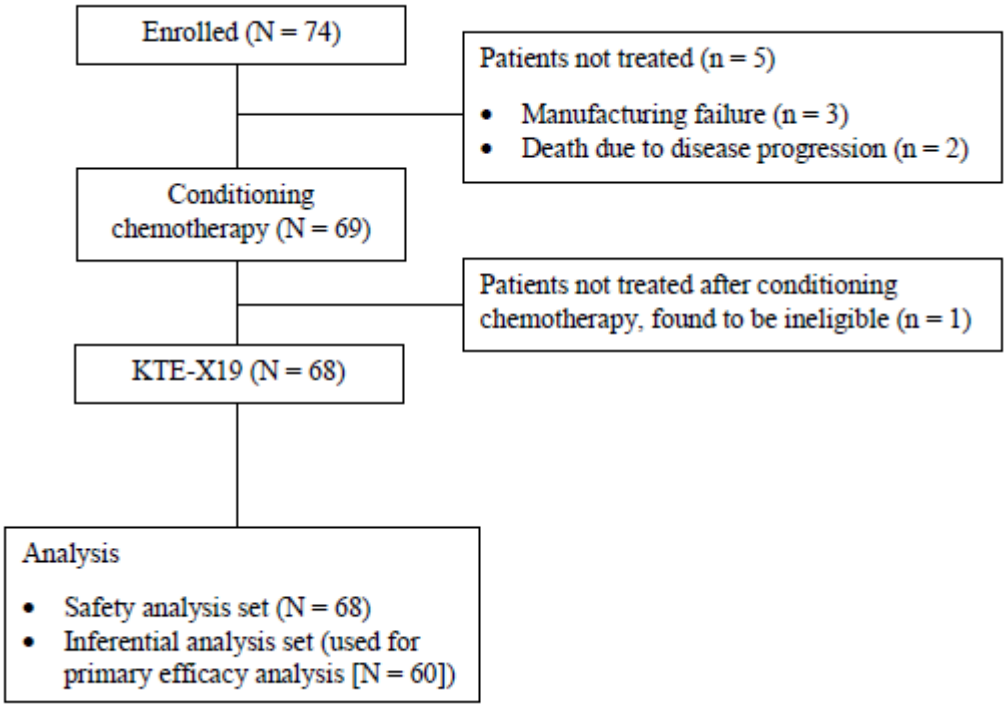
- Continue to infusion
- Discontinue due to manufacture failure or adverse events prior to infusion
- Death event prior to infusion

Different assumptions were used to assign different health outcomes and costs to each of these groups.

In ZUMA-2, the patient disposition data for Cohort 1 is presented below in Figure 10. Of the 74 patients enrolled, KTE-X19 was successfully manufactured for 71 patients (96%) and administered to 68 patients (92%). Of the three patients for whom KTE-X19 manufacturing failed, none proceeded to additional leukapheresis. Two patients who had successful manufacturing of KTE-X19 died from progressive disease before

receipt of conditioning chemotherapy and, after the receipt of conditioning chemotherapy, one patient with ongoing atrial fibrillation was deemed to be ineligible for KTE-X19 infusion.

Figure 10: Patient disposition data for Cohort 1 of ZUMA-2 (KTE-X19)



To capture the information in Figure 10 in the cost-effectiveness analysis, the FAS population was split up into three patient categories, shown in Table 13.

Table 13: FAS population in ZUMA-2: proportions in each patient group

Patient categories	N	%
A: mITT	68	91.9%
B: do not receive KTE-X19 due to manufacturing failure or ineligibility	4	5.4%
C: do not receive KTE-X19 due to death following disease progression	2	2.7%
Total FAS population	74	100.0%
Key: FAS, full analysis set; mITT, modified intent to treat		

Consistent with TA554 and TA567, and of relevance to all three patient categories, QALYs were not applied during the decision tree period of the model. This is a simplifying assumption that omits a small number of QALYs for the KTE-X19 arm. Other assumptions used to apply health outcomes and costs to each of the patient

categories are also consistent with those used in TA554 and TA567; these are as follows:

- Table 13 Patient Category A: these are the proportion of patients who successfully proceed to infusion of KTE-X19 (mITT population). Discounted costs and QALYs are as per the company submission (CS) base case deterministic analysis.

- Table 13 Patient Category B: these are the patients who do not receive KTE-X19 due to manufacturing failure or ineligibility. The discounted costs and QALYs from the standard of care (SoC) arm are used (directly linked to SoC results in the model). It is assumed that these patients would revert to treatment with the relevant comparator therapy.

- Table 13 Patient Category C: these are the patients who do not receive KTE-X19 due to death following disease progression. These patients are associated with no further accrual of costs or QALYs.

The overall costs and QALYs for the FAS are then calculated as the weighted average of the three patient categories. Of importance, the base case model already captures the costs of leukapheresis and conditioning chemotherapy for patients who do not proceed to KTE-X19 infusion (as well as the mITT population). Therefore, these pre-treatment costs are included in this scenario but were not separately built into the approach described above.

A separate sheet, “FAS scenario”, is created in the updated cost-effectiveness model to present the key inputs and calculations for the analysis. The key calculations are also presented in Table 14 below.

Table 14: FAS scenario analysis results

Patient categories	N	%	One-off costs	One-off QALYs	One-off LYs
A: mITT	68	91.9%	[redacted]	[redacted]	[redacted]
B: do not receive KTE-X19 due to manufacturing failure or ineligibility	4	5.4%	[redacted]	[redacted]	[redacted]
C: do not receive KTE-X19 due to death following disease progression	2	2.7%	[redacted]	[redacted]	[redacted]
Total FAS population	74	100.0%	[redacted]	[redacted]	[redacted]

Key: FAS, full analysis set; LYs, life years; mITT, modified intent to treat; QALYs, quality adjusted life years

Using the updated cost-effectiveness model, a comparison of the top-line model results between the mITT (base case) and FAS is presented below. As expected, the mean expected total cost per patient for KTE-X19 decreases in the FAS scenario as the 8.1% (6 out of 74) of FAS patients do not incur the drug cost for KTE-X19; while the mean expected per-patient total QALYs also decrease because patients who did not receive KTE-X19 have worse survival and quality of life. Overall, there is a small increase in ICER for the FAS scenario (£64 per QALY) compared to the mITT base case.

Table 15: Base-case deterministic cost-effectiveness results (ZUMA-2 mITT)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 16: Deterministic cost-effectiveness results, ZUMA-2 FAS scenario

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B2. PRIORITY QUESTION: Plausibility of a long-term survivor fraction

a) Recent evidence from other treatments for MCL first-line patients suggests that despite prolonged remissions, a continuous pattern of relapses was observed (Eskelund et al, 2016). Therefore, the long-term survival fraction suggested by the mixture cure model and the plateau in the survival curves may not mean that patients are no longer at risk of relapse. Please justify the use of this assumption given the evidence in patients with MCL in previous lines of therapy.

Eskelund, CW et al. (2016), 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. Br J Haematol, 175: 410-418. doi:10.1111/bjh.14241

Data on the long-term survival prospects for post-ibrutinib MCL patients who benefit from KTE-X19 infusion are absent and will only accrue with the passage of time. Currently available evidence is intrinsically limited, both in the scarcity of post-ibrutinib MCL outcomes data generally and in the radically different nature of CAR T-cell therapy and its ability to induce high rates of deep response where conventional therapies fail.

The data on survival prospects for post-ibrutinib MCL patients are those identified by the systematic review of clinical evidence and informing comparator arm estimates in the economic analysis underpinning the CS. The evidence base for relapsed / refractory MCL patients reflects both the small number of patients with this condition and the lack of medical innovation to date, particularly in the post-ibrutinib setting.

The Eskelund et al study the ERG highlight presents valuable evidence on long-term prospects for newly diagnosed MCL patients who are treated with intensified first-line regimens containing cytarabine, rituximab and consolidation with high-dose-therapy, followed by autologous stem cell transplantation (SCT). The authors present 15-year follow-up data (median follow-up 11.4 years, range 4.9 years - 14.7 years) from a sample of 159 patients treated within a Phase II study, that demonstrate long response and survivorship for many, with half of the patients remaining alive at the time of analysis. The analyses conducted included comparisons versus general population survival data, for (i) all 159 patients from baseline, (ii) the 139 patients

with complete response (CR) after 1 year, (ii) the 96 patients with CR after 5 years and (iv) the 59 patients after 10 years. These analyses indicate survival prospects to improve with depth of CR. The survival prospects for those with CR at 5 and 10 years [Figures 3(C) and (D) in Eskelund et al] appear to be very good, closely following the age- and gender-matched general population trends overlain, with some separation after several years. However, numbers remaining at-risk over time are not reported, limiting the ability of the reader to interpret the tails of these curves. Eskelund et al conclude with a call for prospective studies to investigate novel agents in the frontline setting, perhaps wary of complacency given the success of contemporary frontline treatment for autologous SCT-eligible MCL patients. The unmet need in the small post-ibrutinib MCL population that KTE-X19 can address is part of the same story.

Perhaps the most pertinent observation by Eskelund et al is that, unsurprisingly, CR matters - the more durable the CR, the closer OS is to that of the age-equivalent general population. In inducing unprecedented rates of CR (65%, mITT group) of great depth (83% of the 29 patients tested showed no evidence of Minimal Residual Disease on molecular investigation, as reported in Section B.2.6.5 of the CS), the evidence from ZUMA-2 makes long-term disease-free survival a plausible treatment goal for KTE-X19.

b) Please justify the use of a standardised mortality ratio of diffuse large B cell lymphoma to this patient population.

The standardised mortality ratio (SMR) of 1.09 applied to general population survival data for long-term survivors in the cost-effectiveness analysis was first reported by Maurer et al,[7] as reported in page 117 of the CS. As the ERG highlight, this was based on data from diffuse large B-cell lymphoma (DLBCL) patients. Specifically, those in a sample of 820 newly diagnosed DLBCL patients treated with rituximab and anthracycline-based chemotherapy who remained event-free at 24-months. Findings from these patients confirmed findings from another 767 newly diagnosed DLBCL patients given similar treatment in different centres, reported in the same study.

The Maurer et al study has provided convincing evidence that patients with newly diagnosed, previously treated DLBCL who achieve event-free status at 24 months have a subsequent overall survival similar to that of the age- and sex-matched general population. The SMR of 1.09 from Maurer et al informed the TA559 committee's recommendation for Cancer Drugs Fund (CDF) use of axicabtagene ciloleucel CAR T-cell therapy in DLBCL or large B-cell lymphoma after two or more systemic therapies, based on its plausible cost-effectiveness. In TA559, it was unclear how evidence from patients with event-free survival 24 months after frontline rituximab-chemotherapy translated to prospects for refractory patients with good initial outcomes after CAR T-cell infusion, shown in limited follow-up from the Phase I/II ZUMA-1 study for axicabtagene ciloleucel. As for this appraisal, there were no long-term data for the step-change CAR T-cell therapy.

It can, of course be argued that DLBCL is a different disease to MCL. In DLBCL, cure is considered the treatment goal. When patients are first diagnosed in newly diagnosed MCL this is not, generally, considered a likely outcome. It could be that one type of B-cell lymphoma is, inherently, incurable and the other is not. However, this seems less plausible than the argument that the existing treatments for DLBCL are better than those for relapsed MCL, where different and better therapies are needed. Indeed, for those patients with relapsed or refractory DLBCL where CDF access to axicabtagene ciloleucel is now permitted, cure was not in most cases a realistic expectation prior to the introduction of CAR T-cell therapy.

The TA559 interim recommendation for use through the CDF with further data collection from ZUMA-1 protects NHS England against uncertainty in long-term prospects for axicabtagene ciloleucel patients, while allowing interim access to a small group of refractory lymphoma patients with high unmet need. Since the recommendation was made, a further analysis of ZUMA-1, after a minimum three-year follow-up, has shown that the early plateau in the OS curve is maintained.[8]

Of course, plausibility does not equate to certainty and a CDF recommendation with further data collection from ZUMA-2, similar to that followed in TA559, can serve a similar purpose here.

c) Please discuss whether there is evidence from patients with MCL that could be used to inform the standardised mortality ratio. For example, we are aware of one potentially relevant study – Eskelund et al (full reference above). Please discuss the implications of this study and investigate whether it could be used to inform the standardised mortality ratio of long-term survivors.

Following the account of Eskelund et al, Maurer et al and the absence of other potentially relevant studies we provide in response to parts a) and b), it may remain to directly address whether Eskelund et al offer better data than Maurer et al to inform long-term survival prospects for those ibrutinib-refractory MCL patients anticipated to have long-term survivorship following KTE-X19.

First, the applicability of the respective patient groups and treatment regimens to this appraisal. The Eskelund et al data are from MCL patients, while the Maurer et al data are from DLBCL patients. However, both are in newly diagnosed, previously untreated lymphoma patients, in comparison to the relapsed and refractory lymphoma patient group directly affected by this appraisal (and those directly affected by TA559). Further, neither Eskelund et al nor Maurer et al report evidence in patients treated with CAR T-cell therapy.

Second, the relative sample sizes informing the two studies. The samples informing the Maurer et al analyses (baseline samples of n=767 and n=820 in the primary and validation datasets, respectively) are far larger than the sample of patients informing the Eskelund et al analysis (baseline n=159), allowing far greater confidence in the findings of the former. Of course, as the findings of interest for this appraisal (and TA559) are survival prospects of the subgroups of patients who demonstrate durable response or event-free survival, these estimates are based on smaller samples still, with the Eskelund et al findings for those with CR after 1 year, 5 years and 10 years based on samples of n=139, n=96 and n=59, respectively.

Thirdly, reporting differences across the two studies. Maurer et al report SMR parameter estimates and confidence intervals directly, whereas Eskelund et al do not. Further, though Eskelund et al report the findings of primary relevance here as survival curves (Fig 3), censoring points are not shown, nor are changes in the number remaining at risk over time. While the data reported in Eskelund et al could

be used to estimate a SMR, this would require substantial analyst inference and guesswork.

In short, while long-term survivorship for post-ibrutinib MCL patients following successful CAR T-cell therapy is unevidenced, in line with the mechanism of action of KTE-X19 we share the hope and anticipation of the clinical and patient community of very good long-term prospects. This reflects the high rate of deep, durable CRs achievable with KTE-X19, the importance of CR to long-term outcome highlighted by Eskelund et al and the approach taken in TA559 to predict long-term survival after CAR T-cell therapy for lymphoma. There is reason to hope for plausible outcomes that are similar to age- gender-matched general population outcomes in those ZUMA-2 patients with good outcomes to date, yet we recognise that down-weighting of survival outcomes may be more appropriate for interim decision-making. On reflection of the evidence from Maurer et al and Eskelund et al, the data from Maurer et al and used in TA559 stand up as the more robust and appropriate, in absence of more relevant data.

B3. PRIORITY QUESTION: Mixture cure modelling

a) Please explain how background mortality was incorporated in the estimation of the mixture cure models. Was the standardised mortality ratio of 1.09 used in the estimation?

Within the mixture cure models there are two groups of patients. One group is specified as functionally ‘cured’ and the other is defined as ‘non-cured. The `cured’ patients are assumed to follow age- and sex matched general population mortality. The `non-cured’ patients are subject to cancer-specific hazards which are modelled and estimated using one of the standard parametric functions.

The background hazard adjustment of 1.09 applied to the background mortality was not used in the estimation of the mixture cure models. This was to ensure that this adjustment could be applied post-hoc and changed.

b) Please provide the required code, with comments explaining each line, along with the data required so that the ERG can replicate and validate the company’s analyses.

We are not able to share patient-level data; however, our vendors are happy to share their code as commercial-in-confidence material. We submit these alongside this response, within the .R files 'MasterFile_forNICE' and 'NICE_Functions'.

c) Please list the diagnostic tests that were conducted to validate the estimated mixture cure models and their results, along with their interpretation.

Only AIC and BIC were calculated to validate the estimated mixture cure models, as presented in the CS. The values for all mixture-cure models (apart from generalised gamma which was excluded due to non-convergence) were similar. This similarity suggests that there is little difference between the goodness of fit of the models.

d) Please provide the 95% confidence intervals around the estimated long-term survivor fraction for all the mixture cure models that were estimated for both PFS and OS.

Table 17 and Table 18 provide the requested long-term survivor fraction and the associated 95% confidence interval for both OS and PFS.

Table 17: KTE-X19 implied long-term survivor fractions for Overall Survival and 95% confidence intervals

Model	Implied long-term survivor fraction Mean (95% CI) (%)
Exponential	[redacted]
Generalised gamma*	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Weibull	[redacted]
Key: NA, not applicable **Notes:** * The generalised gamma model did not converge and was therefore omitted from the model base case selection.	

Table 18: KTE-X19 implied long-term survivor fractions for Progression Free Survival and 95% confidence intervals

Model	Implied long-term survivor fraction Mean (95% CI) (%)
Exponential	[redacted]
Generalised gamma*	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Weibull	[redacted]
Key: NA, not applicable **Notes:** * The generalised gamma model did not converge and was therefore omitted from the model base case selection.	

e) Please comment on how the long-term survivor fraction compares with (i) the proportion of patients who had a complete response over time and (ii) with the proportion of patients who had no detectable disease over time.

Table 10 in the CS reported the proportion of mITT KTE-X19 patients who achieved CR; 65% (95% CI (52.2%, 75.9%)). The long-term cure fractions estimated by mixture-cure models, reproduced above, are slightly lower than this CR rate, with overlap across the respective CIs.

As described in our response to Question A2 and summarised on Page 46 of the CS, of the 44 patients who achieved a CR, only [redacted]% had died at data cut-off ([redacted]); the estimated 12-month OS rate was [redacted]% and the estimated 24-month OS rate was [redacted]%. Of patients achieving CR and alive at data cut-off, [redacted]% ([redacted]) had an ongoing response (an additional [redacted] had been censored for duration of response due to allogenic stem cell transplant consolidation of their KTE-X19-induced remission).

In comparison, of patients who achieved a partial response (PR), [redacted]% had died at data cut-off ([redacted]). Of patients alive at data cut-off, 46% ([redacted]) had an ongoing response.

Section B.2.6.5 in the company submission presents the results of the proportion of patients with no detectable disease. Twenty-four of the 29 patients (83%) who were

analysed for minimal residual disease were found to have no detected residual disease at four weeks. Similarly, 79% of those analysed at six months (19 patients) were found to have no detected residual disease.

f) Please comment on the biological plausibility that the long-term survivor fraction for PFS(that is, pre-relapse) estimated by the mixture cure models is smaller than the long-term survivor fraction for OS, as this would imply that some of the long-term survivors have relapsed and became long-term survivors following a subsequent treatment.

The biological plausibility of long-term survivorship for post-progression patients is inherently less certain than that for those without a progression event following CAR T-cell therapy. As presented in Section B.2.6.7 of the CS, 17 of the 20 patients who progressed had a subsequent anti-cancer therapy post-progression. It is plausible that this may lead to long-term survivorship for some.

g) Please provide the data and report the Kaplan-Meier curve of post-progression survival of the patients in ZUMA-2. The objective of this analysis is to understand if ZUMA-2 provides evidence that patients who relapse could be long-term survivors as suggested by the differences in the long-term survivor fractions.

Figure 11 presents the Kaplan-Meier (KM) curve of post-progression survival of the ZUMA-2 mITT patients, as requested.

We attach the data in a separate file submitted alongside this response document, within the .R files ‘MasterFile_forNICE’ and ‘NICE_Functions’.

Figure 11: Post Progression survival for patients in the ZUMA-2 modified intention to treat dataset

[redacted]

B4. PRIORITY QUESTION: Alternative approaches to survival extrapolation

a) Please justify why only mixture cure models were considered as an alternative to the standard parametric models and why other methods such as flexible parametric modelling using splines, landmark models, or mixture modelling methods other than cure, as explained in Ouwens et al, were not explored.

Ouwens, M.J.N.M., Mukhopadhyay, P., Zhang, Y. et al. Estimating Lifetime Benefits Associated with Immuno-Oncology Therapies: Challenges and

Approaches for Overall Survival Extrapolations. PharmacoEconomics 37, 1129–1138 (2019). https://doi.org/10.1007/s40273-019-00806-4

Splines were considered in our initial analyses, and we report on them in response to B4b) below. Between the simplicity of the standard parametric models and the flexibility of the mixture cure models, we did not consider the spline models to add considerable marginal value to the analysis. Particularly given the lack of a clear clinical interpretation of their functional form. An additional concern was dependency on knot placement.

General mixture models were also considered (using same distribution for both groups). However, these models did not pass initial face validity tests and had numerous issues; either:

- The models failed to converge
- They predicted just one group (90%+), essentially collapsing to a standard parametric model
- They generated implausible results such as PFS being greater than OS
- Some combination of the above

Our suspicion is that this is mostly driven by data limitations (the general mixture models typically require more parameters to be estimated compared to the standard distributions and mixture cure models).

Figure 12 presents the general mixture models for PFS and OS, over a 35-year time horizon. Figure 13 illustrates the often heavily skewed group membership, and Figure 14 illustrates some of the inconsistencies between OS and PFS. In addition, the extrapolations in Figure 12 do not indicate a survival profile that is considerably different in shape from those illustrated by our mixture cure models (which are used in the base case analysis).

[redacted]

[redacted]

[redacted]

Landmark models were not explored in initial analyses, due partly to data constraints. Landmark models are considerably more data hungry that the other models considered in our analyses. Both in terms of parameters requiring estimation (in that sense, they are similar to mixture cure models) and in terms of how the data must be partitioned to estimate the individual components of the model. First, a post-

baseline landmark time must be chosen, after which any patients who have already left the risk set can no longer contribute information to the extrapolations. Second, at the landmark point, patients are split into 2 or more groups based on observed characteristics. Extrapolations are then drawn from these eroded subgroups of patients.

As reported in Section 9.1.1.1 of the CSR, of the 60 patients in the IAS sample, [redacted] patients initially had a PR or SD, and [redacted] ([redacted]%) of these patients went on to achieve a CR after a median of [redacted] months (range: [redacted] to [redacted] months). Initial response assessment was scheduled at 4 weeks; from this, 12 months could be a reasonable timepoint at which further response maturity could be considered highly unlikely.

To consider the plausibility of a landmark approach, partitioning by CR status at 12 months, post-hoc analysis of the mITT group (n=68) has been undertaken. Of those with a last reading other than CR, only 4 patients remain at-risk for a progression event; we feel extrapolations based on such data would be a poor basis for decision-making.

b) Please fit flexible parametric models using restricted cubic splines.

These models have been fitted. Figure 15 presents the results of these models graphically over the observed data period for both OS and PFS. Similarly, Figure 16 presents the results of these same models for OS and PFS but presented over the lifetime extrapolation. The results in terms of AIC, BIC, median survival and the proportion of patients alive at several timepoints are reported in the response to Question B5 part c.

Like the “standard” parametric models presented in the CS, Figure 16 illustrates how each of these spline models provides a poor fit to the long-term survival expectations for those continuing to benefit from KTE-X19 infusion. Clinical advice received and documented in CS alongside developing understanding of the likely benefit of CAR T-cell therapy in those with ongoing response leads us to believe that these restricted cubic spline fits to OS and PFS data from the latest ZUMA-2 database lock are no more useful than the standard parametric model fits, for decision-making.

Figure 15: Results of the spline models fitted over the observed data period for both OS and PFS

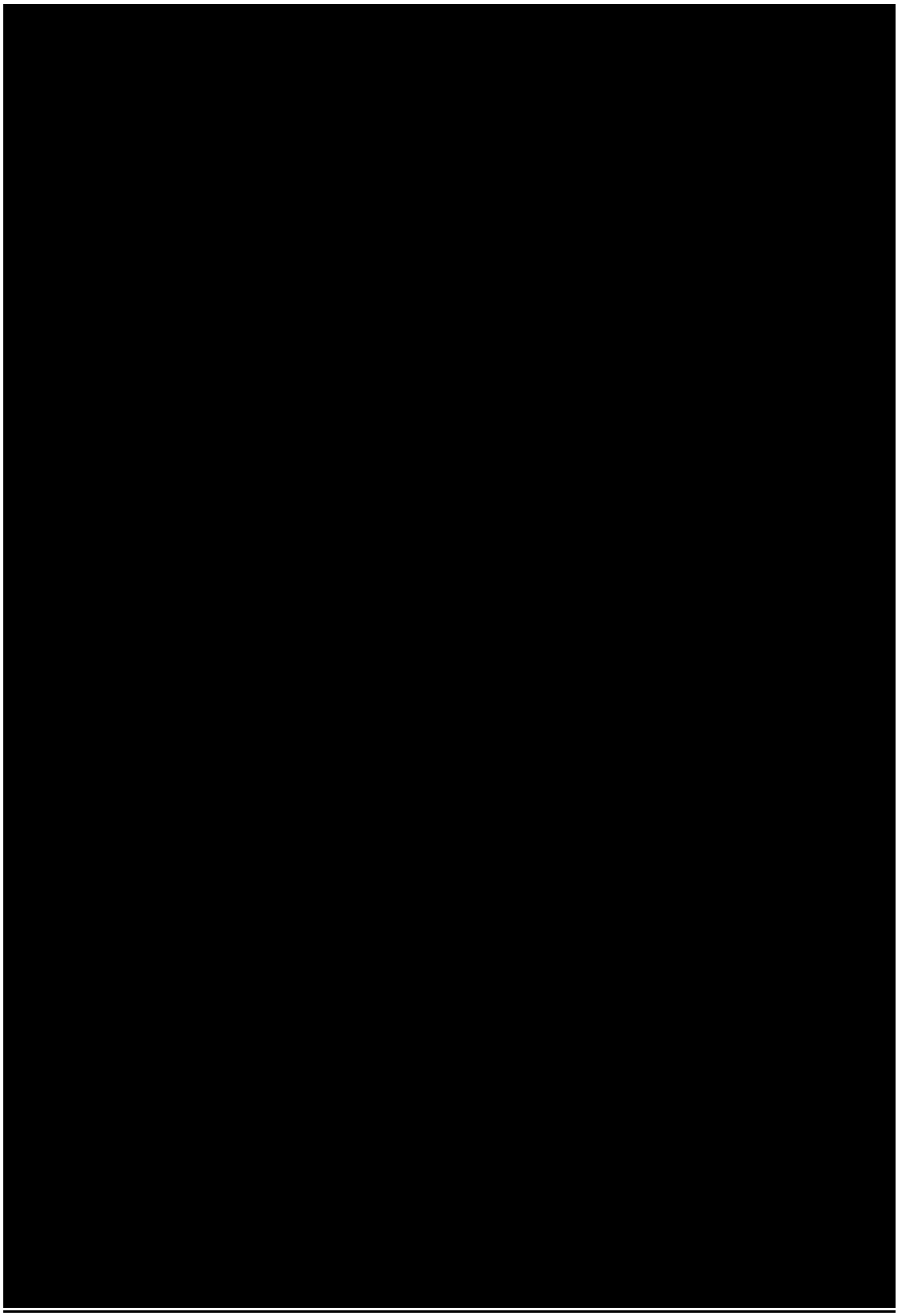
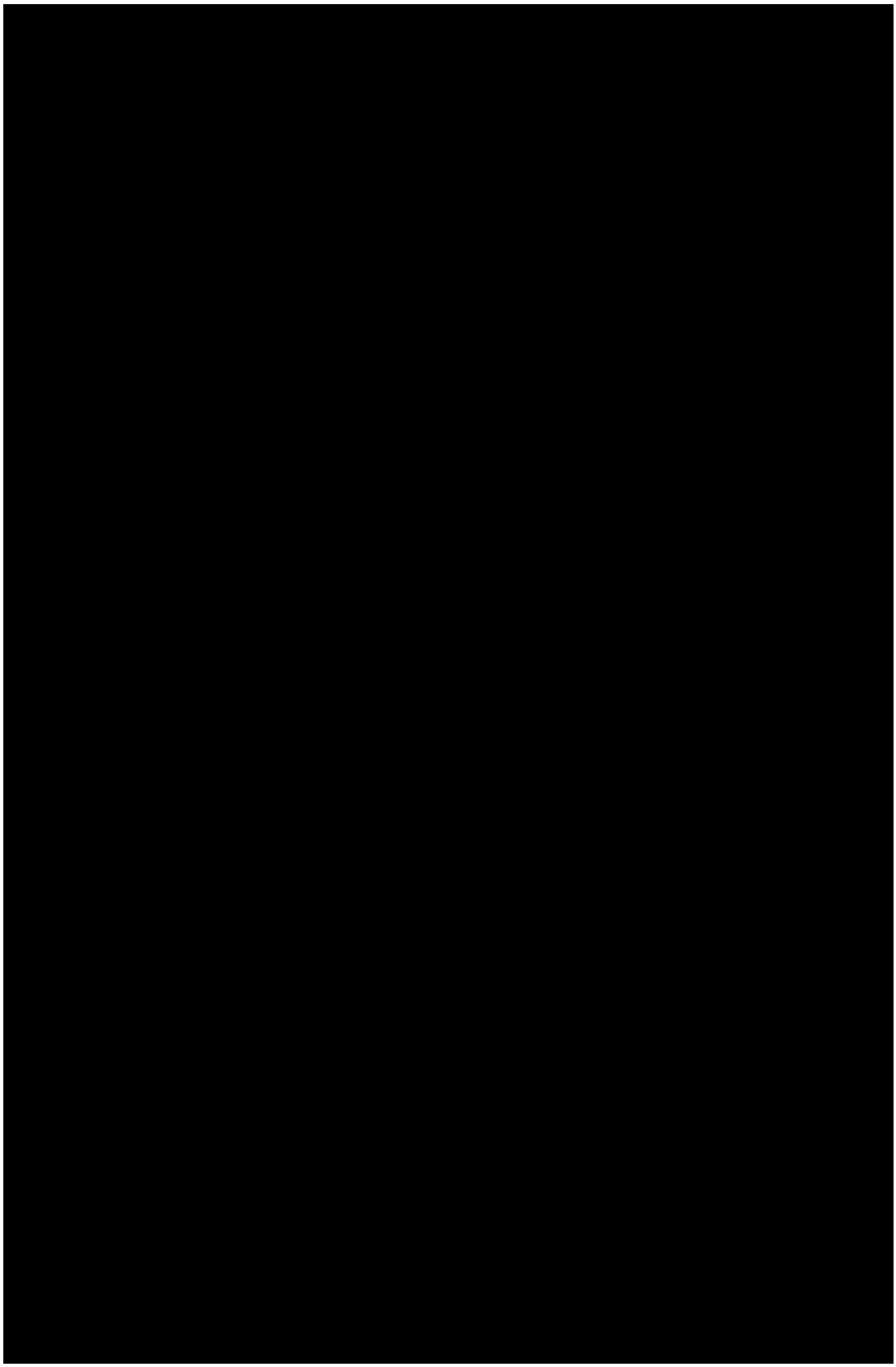


Figure 16: Results of the spline models fitted to the mITT ZUMA-2 data over the extrapolation period for both OS and PFS



c) Please provide all necessary details and code used to estimate these new survival curves so that the ERG can replicate analyses.

We are not able to share patient-level data; however, our vendors are happy to share their code as commercial-in-confidence material. We submit these alongside this response, within the .R files 'MasterFile_forNICE' and 'NICE_Functions'.

d) Please provide a revised economic model which includes functionality to select the alternative survival curves listed above.

The revised cost-effectiveness model we include alongside this response document contains the functionality for the user to select the parametric models illustrated in our response to part b). As stated in our response to part b), we consider each of these spline models provides a poor fit to the long-term survival expectations for those continuing to benefit from KTE-X19 infusion.

B5. PRIORITY QUESTION: Alternative structural approaches to survival extrapolation

a) Figure 7 (Document B page 40) and Figure 12 (Document B page 45) suggest that patients who attained complete response have longer response and longer survival. Therefore, a landmark model may be appropriate to represent this heterogeneity. Please fit landmark models to the PFS and OScurves, using a clinically appropriate landmark (e.g. complete response at a specific time point, none or minimally detectable disease at a specific time point). Please justify the choice of landmark.

As reasoned in our response to B4.a), with consideration of an appropriate landmark, we do not consider the ZUMA-2 data sufficient to support a landmark analysis.

b) Please provide an alternative model, where the OS and PFS distributions can be informed by standard parametric extrapolation models until a specific time point, and after that time point, the mortality is informed by general population mortality adjusted with a standardised mortality ratio (that specific time point has to be justified by the clinical literature, and different options can be explored, such as 1 years, 5 years and 10 years).

As per the ERG's request, the revised cost-effectiveness model submitted alongside this response has been updated to include the functionality to explore these assumptions.

This functionality allows the user to select (i) the initial parametric model structure, (ii) the timepoint at which mortality switches to age-and gender-adjusted general population equivalent, and (iii) an SMR to apply to general population mortality data, as requested. For choices regarding each of these elements, we refer the user to our CS and responses to questions A2, B2, B3 and B4 in this document.

Each of these choices is important and should be carefully justified, including the selection of an appropriate timepoint at which to apply SMR-adjusted general population mortality, if using this approach. As reported in the CS and earlier in this response document, in ZUMA-2, KTE-X19 was shown to induce CR rates of [redacted]% (for the mITT group) of great depth (83% of the 29 patients tested showed no evidence of Minimal Residual Disease on molecular investigation). For the ZUMA-2 mITT group (N=68), [redacted] patients ([redacted]%) were CR at last reading and censored or at-risk. The depth of response in ZUMA-2 supports an expectation of long-term disease-free survival KTE-X19. Among patients who achieved a CR (N=[redacted]), only [redacted] patients ([redacted]%) had died at data cut-off; the estimated 12-month OS rate was [redacted]%, and the estimated 24-month OS rate was [redacted]%. The high level of MRD observed in patients treated with KTE-X19 is also considered a further positive sign of the potential for long-term survivorship with KTE-X19 treatment, as MRD-negative status has previously been shown to correlate to longer PFS and OS in the MCL setting.

The response data observed in ZUMA-2 can be used to evidence the theory that there are two groups of KTE-X19-treated patients: those who respond to therapy and are able to maintain this response and achieve long-term survivorship, and those who do not respond and continue to progress. This explains the flattening of the KM curves (in both OS and PFS), as those patients who are not able to achieve CR drop out, while those who are able to achieve CR maintain their response and have survival similar to that of the age- and gender-matched general population. While long-term data from ZUMA-2 does not exist to show that patients who achieve CR continue to survive after the data cut-off (median follow-up in mITT group = [redacted]

months), in the broader NHL setting, CAR T-cell therapy survival curves are starting to show an observed plateau with no downward tail, representing long-term survivorship. As discussed in the CS, in recently reported 3-year survival data from ZUMA-1, only four deaths were observed since the 2-year follow-up (patients at risk, n=51).[8]

c) Please report a table that lists the different models (each standard parametric model, each mixture cure model, and the models fitted in points 1-2 of this question), similar to Table 1 of Ouwens et al, including AIC, BIC, average OS at different time points, and proportion of patients alive at different time points.

Table 19 presents AIC, BIC, median survival and the proportion of patients alive at a series of time points for the data fitted to the ZUMA-2 mITT dataset, for standard parametric, mixture cure and spline models, for both OS and PFS. No further models were fitted in response to part a). Summarising results for this way for the range of scenarios allowed by the functionality incorporated in response to part b), given the multifactorial user decision-making required, is less straightforward.

Table 19: AIC, BIC median survival and proportion of patients alive at key time points for parametric models, mixture cure models and spline models for the overall survival and progression free survival models fitted to the ZUMA-2 mITT dataset

Model	AIC	BIC	Survival in years									
			Median	1	2	5	10	15	20	25	30	40
Overall Survival												
Parametric												
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixture Cure												
MCM Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCM Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCM Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCM Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCM Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCM Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Model	AIC	BIC	Survival in years									
			Median	1	2	5	10	15	20	25	30	40
MCM Generalized gamma												
Splines												
1 knot spline hazard												
1 knot spline normal												
1 knot spline odds												
2 knot spline hazard												
2 knot spline normal												
2 knot spline odds												
Progression Free Survival												
Parametric												
Weibull												
Exponential												
Gompertz												
Log-normal												
Log-logistic												
Gamma												
Generalized Gamma												
Mixture Cure												
MCM Weibull												
MCM Exponential												
MCM Gompertz												

Model	AIC	BIC	Survival in years									
			Median	1	2	5	10	15	20	25	30	40
MCM Log-normal												
MCM Log-logistic												
MCM Gamma												
MCM Generalized gamma												
Splines												
1 knot spline hazard												
1 knot spline normal												
1 knot spline odds												
2 knot spline hazard												
2 knot spline normal												
2 knot spline odds												

d) Please provide all necessary details and code used to estimate these new survival curves so that the ERG can replicate analyses.

No additional survival curves have been estimated in response to B5 a) to c).

e) Please provide a revised economic model which includes functionality to select the alternative survival curves listed above. Additionally, the revised economic model should include the option to switch the extrapolation from a parametric model to the general population mortality adjusted with a user-specified standardised mortality ratio at a user-specified time point as per point 4.

We provide alongside this response a revised cost-effectiveness model with additional user functionality to select additional survival assumptions, as per our responses to parts a) and b) of this question, and our response to question B4.

B6. PRIORITY QUESTION: MAIC using McCulloch et al.

a) Please fit the survival models listed above (standard parametric models, mixture cure models, flexible parametric models and landmark models) to the matched ZUMA-2 population of question A10 and provide the full results including confidence intervals, AIC and BIC statistics, and graphical comparison of the extrapolation versus Kaplan-Meier curves.

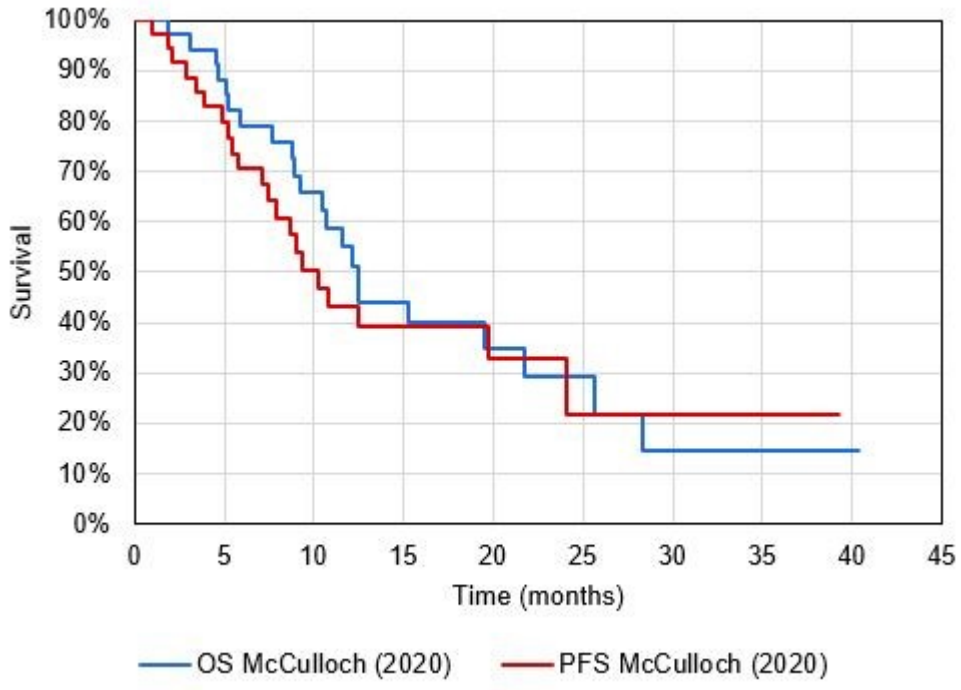
Continuing the thread of our response to A10, we are concerned that the MAIC-adjusted results are not sufficiently reliable for meaningful survival modelling, based on the small effective sample size.

b) Please provide a revised economic model which includes these scenarios, with the functionality that these scenarios can be run probabilistically.

In lieu of a robust MAIC-adjusted cost-effectiveness comparison to McCulloch et al (2020) data, the model has been updated to include a naïve comparison to these data. This comparison can be selected using the 'Literature-based meta-analysis' options on the 'Main board' sheet of the model.

Figure 17 presents digitised OS and PFS KM data for McCulloch et al. (2020).

Figure 17: McCulloch et al. (2020) KM data



McCulloch et al. (2020) has been included in the model in line with the other comparator options. Standard parametric survival models were used to extrapolate KM data over the model time horizon; and smoothed hazard plots and goodness-of-fit (AIC) statistics were used to determine the most appropriate parametric model for OS and PFS, whilst also remaining aware of clinical expert opinion.

Parametric survival models fitted to McCulloch et al. (2020) OS KM data are presented in Figure 18 with corresponding AIC statistics, summary statistics and landmark survival estimates presented in Table 20. Smoothed hazard plots for the OS KM data compared to each parametric survival model are presented in Figure 19.

[redacted]

Table 20: OS survival standard parametric curve AIC statistics and landmark survival estimates, McCulloch (2020)

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion surviving at each landmark value			
					6 months	1 year	2 years	5 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.
Notes: Mean and median values are provided in units of months. Projected OS values here are not accounting for background mortality correction.

[redacted]

In line with our approach for the submitted base-case, the lognormal model was selected as the most appropriate model for OS. The lognormal model provides a mid-range estimate in the context of all the parametric survival models fitted and has the best statistical fit according to the AIC. In addition, the smoothed hazard plots show that the lognormal model provides a good reflection of the hazard over time when compared with the OS KM data.

PFS

Parametric survival models fitted to McCulloch et al. (2020) PFS KM data are presented in Figure 20 with corresponding AIC statistics, summary statistics and landmark survival estimates presented in Table 21. Smoothed hazard plots for the PFS KM data compared to each parametric survival model are presented in Figure 21.

[redacted]

Table 21: PFS survival standard parametric curve AIC statistics and landmark survival estimates, McCulloch (2020)

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion surviving at each landmark value			
					6 months	1 year	2 years	5 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

[redacted]

Initially, the lognormal model was considered the preferred approach for modelling PFS data in line with CS base-case structural assumptions. However, when the lognormal model for PFS was tested alongside the lognormal model for OS, the PFS curve was above the OS curve demonstrating a lack of face validity. Therefore, the Weibull model was selected as this falls below the lognormal OS curve and is aligned with clinical expectation of 2-3% PFS at 5 years.[3]

Results of the naïve comparison of KTE-X19 and SoC, based on the unadjusted ZUMA-2 mITT data and McCulloch et al. [2020] data, are presented in Table 22. Base-case submitted results are presented in Table 23 for comparison.

Table 22: Deterministic cost-effectiveness results based on McCulloch (2020) and unadjusted ZUMA-2 mITT data

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 23: Base-case deterministic cost-effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

c) Please provide full details of all steps undertaken in the indirect treatment comparison (ITC). This includes all of the files required to reproduce the MAIC including details of data source used and R script used to run the ITC.

Please see the response to A10.

B7. Patients in ZUMA-2 who were retreated

The cost-effectiveness model uses data from the mITT Cohort 1, which includes patients who were retreated, although re-treatment is not expected to be included in the anticipated marketing authorisation.

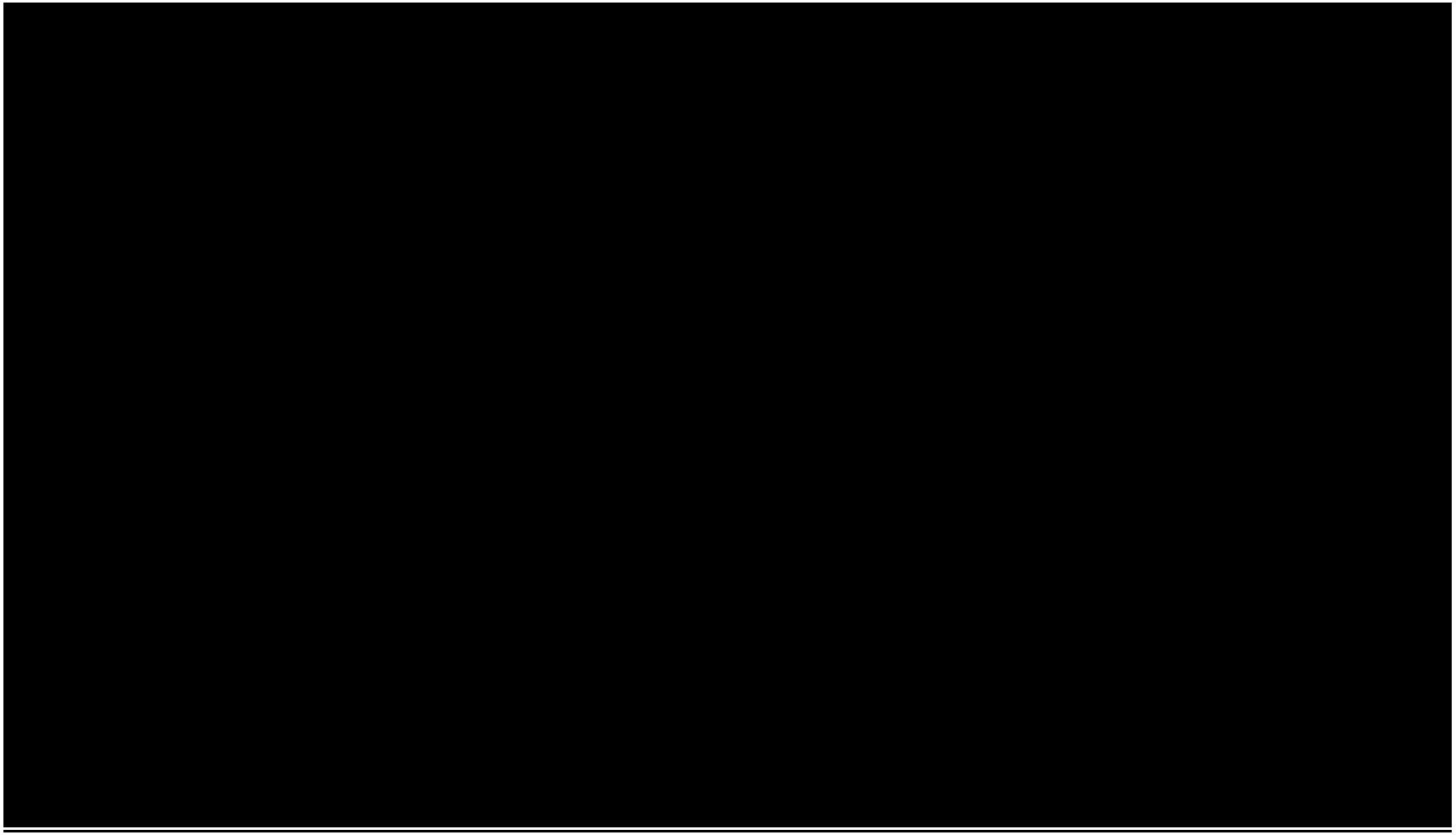
Please report the Kaplan-Meier curves for OS where patients who were retreated are censored at the last available disease assessment date prior to retreatment. Please provide the ERG with the data so that it can replicate the curves.

As reported in Section B.2.6.6 of the CS, 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.[9] 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].

As requested, Figure 22 shows the OS KM curve, re-censored to include censoring at the last available disease assessment point prior to retreatment.

As requested, these data are provided alongside this response, in the .xlsx file "F_14_2_12_4a_erg_b7_os_cen_mitt_c1"

Figure 22: Kaplan-Meier Plot of Overall Survival (Cohort 1: KTE-X19) (mITT Analysis Set, N = 68), retreated patients re-censored



B8. Uncertainty in Kaplan-Meier curves

Please provide Kaplan-Meier curves for PFS and OS for the mITT cohort of ZUMA-2 and for the McCulloch et al (2020) cohort with 95% confidence intervals as recommended by Morris et al.

Morris TP, Jarvis CI, Cragg W, et al. Proposals on Kaplan–Meier plots in medical research and a survey of stakeholder views: KMunicate. BMJ Open 2019;9:e030215. doi: 10.1136/bmjopen-2019-030215

The Kaplan-Meier curves for PFS and OS for ZUMA-2 and McCulloch et al., 2020, with 95% confidence intervals as requested, are presented in **Figure 23** to **Figure 26**.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

B9. Adverse events associated with KTE-X19

a) The cost-effectiveness model assumes that patients who have cytokine release syndrome (CRS) have a hospital stay of 4 days in the intensive care unit, as per previous TA. What was the average length of stay in ICU for patients who experienced CRS in ZUMA-2? Please update the model to reflect the length of stay in ICU observed in ZUMA-2.

The average length of stay in an intensive care unit (ICU) was derived from the ZUMA-2 Cohort 1 safety analysis set (mITT group; N=68). This was derived from a listing of ICU admission and discharge dates by subject ID (note, this listing was not available from the CSR). The mean length of ICU stay for these patients was [redacted]. It should be noted that this listing is not specific to patients requiring ICU stay to manage CRS; it includes all mITT patients that were admitted to the ICU. The total number of patients who visited an ICU was [redacted]. As reasons behind ICU admissions are not reported, it is difficult to determine how well these data reflect expected practice in NHS England.

While the limitations of the data are noted, we have included a scenario to test the impact of alternative ICU length of stay assumptions. Specifically, the cost-effectiveness model scenario assumes [redacted] of patients require an ICU stay for a duration of [redacted]. The impact of this scenario on base case deterministic cost-effectiveness results is shown below, across Table 24 and Table 25. The increased ICU stay costs attributed to the KTE-X19 arm resulted in an increase of £742 to the base case ICER.

Table 24: Base-case deterministic cost-effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 25: Deterministic cost-effectiveness results, alternative assumptions used to model ICU costs

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

b) The cost-effectiveness model assumes that patients use 1 cycle of tocilizumab. To explore this assumption, please report the mean and standard error for the number of doses of tocilizumab received by patients in ZUMA-2 who received the treatment for adverse events of any grade.

The number of patients requiring treatment with tocilizumab, used in the company submitted cost-effectiveness model was derived from ZUMA-2 mITT group (N=68). Of these patients, [redacted] received tocilizumab ([redacted]). These patients include those who are given tocilizumab for the treatment of AEs and those who are not; for example, some patients were given tocilizumab prophylactically.

In response to this question, we have derived the number of tocilizumab doses received for each of these [redacted] patients. From this, the mean number of tocilizumab doses received is [redacted], and the standard error is [redacted].

c) Following on from Question A3, please include pancytopenia over the first year after KTE-X19 infusion in the adverse events considered in the revised economic model, both in terms of its disutility and in terms of the heath care cost of managing it.

As detailed in the response to question A3, pancytopenia was not a MedDRA preferred term used for AEs collected during the investigational product treatment

period, although it was for AEs collected during the conditioning chemotherapy period, where [redacted] in Cohort 1 had Grade 3 pancytopenia. The cost-effectiveness model includes all Grade 3 and 4 AEs occurring in ≥ 10% of the ZUMA-2 cohort, consistent with the limits of CSR reporting; therefore, the costs and utility decrement associated with pancytopenia were not modelled because the incidence was less than the cut-off of 10%.

In the cost-effectiveness model, AEs are reported separately for those that are KTE-X19-related and those that are conditioning-chemotherapy-related. For both, the number of patients with neutropenia, thrombocytopenia or anaemia were reported. Where these met the cut-off applied (Grade 3 and 4 AEs occurring in ≥ 10% of the ZUMA-2 cohort), the associated costs and utility decrements were modelled. Including pancytopenia as an independent AE in addition to neutropenia, thrombocytopenia and anaemia would likely result in double-counting. However, we acknowledge that if a patient suffers from deficiencies of all three types of blood cells (i.e. red blood cells, white blood cells and platelets), the costs required to manage this and the impact on patient health-related quality of life are likely to be heightened. Therefore, a scenario has been tested whereby a greater cost and utility impact has been attributed to Grade 3/4 thrombocytopenia. To do this, the following assumptions were applied:

- The incidence of patients who had Grade 3/4 thrombocytopenia in ZUMA-2 is equal to the incidence of patients with pancytopenia (i.e. all patients experiencing thrombocytopenia are assumed to also have anaemia and neutropenia). Thrombocytopenia was chosen because, out of the three AE terms, this had the lowest incidence.

- The duration of pancytopenia would be double that of thrombocytopenia. Thrombocytopenia was chosen as, out of the three AE terms, this had the longest mean duration.
- The cost of managing pancytopenia would be double that of managing neutropenia, thrombocytopenia and anaemia separately (i.e. the cost of two bed days rather than one).

Applying the above assumptions, this scenario is modelled whereby 5.9% patients experience pancytopenia for a mean duration of 126 days, and the cost of managing

pancytopenia is £921.98. The impact of this scenario on base case deterministic cost-effectiveness results is shown below, across Table 26 and Table 27. This scenario resulted in a slight increase in costs and slight decrease in QALYs for the KTE-X19 arm, resulting in an increase of £202 to the base case ICER.

Table 26: Base-case deterministic cost-effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 27: Deterministic cost-effectiveness results, alternative assumptions used to model the impact of pancytopenia

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B10. Long-term outcomes of long-term survivors

The cost-effectiveness model assumes that long-term survivors have the same health-related quality of life and the additional cost of a GP appointment every 6 months as the age- and sex-matched UK general population.

a) Please could the company justify the assumption that long-term survivors have the same health-related quality of life.

The long-term health-related quality of life of post-ibrutinib MCL patients in long-term remission following KTE-X19 infusion, like the long-term survival prospects for such patients, is unevidenced. The CS base case analysis assumes those who remain disease-progression free for 5 years then have age- and gender-matched general population health related quality of life.

The primary supportive evidence base for this assumption is the ZUMA-2 dataset. The EQ-5D-3L data collected and reported in Section B.3.4.2 of the CS suggest very good health-related quality of life in patients following KTE-X19 infusion; corresponding to a utility level similar, once adjusted for age and gender, to that observed by Ara and Brazier (2010) in general population survey data.[10] The switch to Ara and Brazier utility data at 5 years is effectively a continuation of the trend in utility in the progression-free model health state, from the initial ZUMA-2 patient-derived estimate of [redacted] applied at baseline and adjusting for ageing over model cycles using the trend observed by Ara and Brazier.

It is of course inherently difficult for another to judge how a patient will feel in long remission from post-ibrutinib MCL, following CAR-T cell therapy. How would life be after experiencing the symptoms and knowing the prognosis of MCL after two failed lines of treatment, then experiencing long, asymptomatic survival? How would this compare with the mean, age- and gender- equivalent experience of others in society?

In TA559, the ERG-preferred analysis assumed general population-equivalent utility (and costs) for those in pre-progression from 52 months onwards following CAR T-cell therapy infusion, also in the absence of long-term data.

b) Our clinical advisers commented that patients who receive CAR T-cell therapies are expected to be followed-up in clinic yearly for a number of years. Do you expect this to be the case for KTE-X19? Please discuss the length of follow-up and services involved for KTE-X19 and update the economic model accordingly.

In the CS base case, we assume a Haematologist visit every 2 months for progression-free patients, for the first 5 years following CAR T-cell infusion, based on TA502 assumptions. This may be an over-estimate; visit regularity may be tapered

down gradually within the next 5 years. Once acute toxicity is dealt with; and most likely after the first year of follow-up; visits may simply be quick in-person consultations with no real “services” (scans, biopsies, etc) provided, unless the patient shows signs of disease progression.

We acknowledge uncertainty in follow-up care for patients who remain in remission; from month 60, we assumed a GP visit every six months in the CS. If ERG expert advice suggests a clinic visit every year, we infer this to correspond to a Clinical Haematology outpatient attendance. This is applied as a cost of £173.39, using NHS reference costs 2018-2019 (Total Outpatient Attendance, Service code 303, Clinical Haematology). We maintain the CS base case assumption of the equivalent of a GP visit every 6 months. Table 28 shows results from the CS base case analysis, with this alternative assumption applied for long-term remission management; the base case deterministic ICER increases by £146 to [redacted].

Table 28: CS base case analysis, applying ERG expert advice for long-term (5 years+) remission follow-up after KTE-X19 infusion

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B11. Analysis of health-related quality of life data from ZUMA-2

Please provide the results and goodness of fit of all the regression models that were explored for the analysis of health-related quality of life data from ZUMA-2.

To determine the relevant covariates to be included in the analysis of health-related quality of life data from ZUMA-2, different linear mixed effects regression models for repeated measures were implemented. Each model included an additional independent variable. The potential covariates investigated were age, gender and

assessment point, which was either defined as the number of days since treatment (day, continuous), the number of visits since screening (visit, continuous), or by a visit identifier (visit_1, visit_2, visit_3, visit_4, dummy coding). Table 29 shows the requested results and statistics for each regression model explored.

Table 29: ZUMA-2 quality of life analyses

Model 1					
	Coefficient	**SE**	**Df**	**t statistics**	**p-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]				
BIC	[redacted]				
PFS utility (mean)	[redacted]	[redacted]			
Model 2					
	Coefficient	**SE**	**Df**	**t statistics**	**p-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]				
BIC	[redacted]				
PFS utility (mean)	[redacted]	[redacted]			
Model 3					
	Coefficient	**SE**	**Df**	**t statistics**	**p-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]				
BIC	[redacted]				
PFS utility (mean)	[redacted]	[redacted]			
Model 4					
	Coefficient	**SE**	**Df**	**t statistics**	**p-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit_2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit_3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit_4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]				
BIC	[redacted]				
PFS utility (mean)	[redacted]	[redacted]			
Significance level: * 10%; ** 5%; *** 1%					

B12. Clarification of elements of the Excel model

a) **In the cost-effectiveness model, in the `Base-case results` sheet, why are the total costs subsequent allo-SCT costs excluded in the formulas in cells D18 and D19?**

Thank you for highlighting the issue with the formulae in sheet “Base-case results”, cells D18 and D19. The issue has now been corrected in the updated cost-effectiveness model, with the ability to revert to submitted assumptions available to the user in sheet “Main board”.

To explain fully, total allo-SCT costs should have been excluded from the formulae in sheet “Base-case results”, cells D18 and D19, as allo-SCT costs for pre-progression and post-progression are included separately to facilitate reporting of costs per health state. However, we erroneously included total allo-SCT costs included in the formulae. This only affects the undiscounted results– the formulae in the corresponding cells of the discounted results table are correct, thus base-case discounted cost effectiveness results are not affected. Table 30 outlines the undiscounted base-case results as per the submitted model. Updated undiscounted results are provided in Table 31.

Table 30: Undiscounted base-case deterministic cost-effectiveness results – submitted model

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 31: Undiscounted base-case deterministic cost-effectiveness results – updated model

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

b) For standardised mortality ratio (SMR) values above 2.8, the economic model breaks down because in the `Life Tables' sheet it calculates SMR-adjusted, gender-specific probability of death values above 1. The issue is that the SMR is applied to the annual mortality probability from life tables (life table sheet: columns D, E). This is resulting in probabilities exceeding 1, which then lead to errors in the monthly cycle estimates (column I). Please correct the model by converting the annual probabilities to rates before applying the SMR then estimating monthly probabilities from the adjusted annual rate.

Thank you for highlighting this and reminding us of best practice when applying SMRs. The issue has now been corrected in the updated cost-effectiveness model on the 'Life Tables' sheet with the ability to revert to submitted calculations available to the user in sheet "Main board".

The correction has been applied using the method requested by the ERG. First, annual probabilities of death were converted to annual rates, before applying the SMR and calculating the monthly probability of death from the adjusted yearly death rate. Separate columns have been used for each separate step to facilitate review.

Submitted base-case cost-effectiveness results are presented in Table 32 with updated base-case results presented in Table 33. Updated results show the ICER has decreased by £17.

Table 32: Base-case deterministic cost-effectiveness results – as submitted

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 33: Base-case deterministic cost-effectiveness results – updated

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B13. Costs of treatment with KTE-X19

a) Please justify the current approach to calculating the per diem cost of administration of KTE-X19 and of administration of conditioning therapy.

The following steps were followed to calculate the per diem elective hospitalization cost of KTE-X19 administration and monitoring, and conditioning chemotherapy administration:

- First, the weighted average of elective inpatient healthcare resource groups (HRGs) for malignant lymphoma, including Hodgkin's lymphoma and NHL, from the latest NHS reference costs (2018-2019),[11] was used to determine the *per stay* cost of an elective inpatient. This was £4,333.30.

- Second, the average length of stay of patients informing these NHS reference costs was derived from the Hospital Episode Statistics;[12] this was 9.4 days. We acknowledged that this was less than the mean length of stay observed in the ZUMA-2 trial following KTE-X19 infusion ([redacted]) and greater than the 3 days required for the administration of conditioning chemotherapy.

- To enable the elective inpatient costs to be adjusted to take into account differing length of stays, which were informed by the ZUMA-2 data rather than an assumption, we calculated a per diem elective inpatient cost which could then be scaled up by the required length of stay. This per diem cost was calculated by dividing the average elective inpatient stay cost by the average elective inpatient length of stay (i.e. £4,333.30/9.4 days).

The above approach was similar to the approach used in TA559 to calculate infusion and monitoring costs, though some modifications were made. In TA559, the same NHS reference costs were used (weighted average of elective inpatient HRGs for malignant lymphoma, including Hodgkin's lymphoma and NHL); however, a different approach was used to adjust the costs to cover a longer length of stay. The mean length of stay observed in the ZUMA-1 trial for axicabtagene ciloleucel was 17.6 days, which is 7.2 days longer than that reported for malignant lymphoma in the Hospital Episode Statistics database. Rather than calculating the per diem elective hospitalization cost using the same cost code to cover costs of the full length of stay (17.6 days), the weighted average cost of elective inpatient excess bed day HRGs was used instead. This provided the per diem cost, which was then multiplied by 7.2 and added on to the weighted average of elective inpatient HRGs cost.

In the most recent NHS reference cost database (2018-2019), used to inform our cost-effectiveness analysis for KTE-X19, the costs of elective inpatient excess bed day HRGs are no longer included, hence our use of a different approach to deriving a per diem cost.

In TA559, conditioning chemotherapy administration was captured as a non-elective long-stay hospitalization rather than as an elective inpatient stay. In our cost-effectiveness analysis of KTE-X19, an elective inpatient stay was used based on NHS consultant input; these experts explained that patients receiving conditioning

chemotherapy would likely be required to stay in a hotel close to the hospital site, rather than staying in the hospital as an inpatient.[3] Given the administration costs were likely to be somewhere between that of an outpatient and an inpatient, we assumed the cost of an elective inpatient stay (which are lower than the cost of a non-elective inpatient stay). Again, to more accurately cost for the length of stay required, the per diem elective hospitalization cost was used. It was assumed that patients would be hospitalized for 3 days (the number of days receiving conditioning chemotherapy) and that patients would not need to stay any longer for monitoring, therefore the per diem cost was multiplied by 3.

b) Please use the approach taken in TA559 to calculate the cost of the administration of KTE-X19 and the cost of administration of conditioning therapy. Please include these costs (as per TA559) in the economic model as a scenario.

As noted above in response to part a, in the most recent NHS reference costs (2018-2019), the costs of elective inpatient excess bed day HRGs are no longer included, therefore the exact approach taken in TA559 cannot be used. However, to reiterate, these approaches are very similar and the differences in results that these approaches give is expected to be negligible. To demonstrate, in TA559, the weighted average cost of elective inpatient excess bed day HRGs was calculated to be £422.79; this is compared to the calculated per diem cost of £460.99 used in the economic analysis of KTE-X19.

To acquiesce as best we can to this request, a scenario has been incorporated into the cost-effectiveness analysis whereby the approach used to calculate the cost of administration of conditioning chemotherapy follows that taken in TA559 as closely as possible. In essence, conditioning chemotherapy administration is costed as a non-elective long-stay hospitalization, using the non-elective long-stay HRGs for malignant lymphoma, including Hodgkin's and Non-Hodgkin's, in the NHS reference costs (2018-2019) (Table 34). The mean cost was used, weighted by the number of cases; this was calculated to be £5,679.32.

Table 34: Malignant lymphoma non-elective long-stay healthcare resource groups

Currency code	Currency description	Number of cases	Unit cost
SA31A	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 15+	1,609	£9,418
SA31B	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 10–14	1,923	£6,523
SA31C	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 6–9	2,060	£4,755
SA31D	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 4–5	1,259	£4,216
SA31E	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 2–3	1,078	£3,637
SA31F	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 0–1	742	£3,404
Key: CC, complication and comorbidity.			

A comparison of the top-line model results between our base case approach (conditioning chemotherapy administration is costed as a 3-day elective inpatient stay) and the requested scenario is presented below in Table 35 and Table 36, respectively. Costing conditioning chemotherapy administration as a non-elective long-stay hospitalization results in an increase of £752 to the base case ICER.

Table 35: Base-case deterministic cost-effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; mITT, modified intent to treat; QALYs, quality-adjusted life years; SoC, standard of care.							

Table 36: Deterministic cost-effectiveness results, conditioning chemotherapy administration costed per TA559

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

c) The CS Document B, page 91 states that "Treated patients align to the costing framework proposed for KTE-X19 where only patients treated are paid for by the NHS, and the lack of restriction to follow-up avoids any potential selection bias.". Please provide more details on this "costing framework" and discuss whether there are any resource use or cost implications to the NHS to operate it.

The NHS will not incur in any treatment costs if a patient does not get infused; the cost of a patient that is not infused will be covered by Gilead. The only costs NHS England will incur will be those associated with NHS preparation prior to infusion (e.g. leukapheresis, conditioning chemotherapy); these were accounted for in the CS base case cost-effectiveness analysis.

B14. Training and additional infrastructure requirements

a) Please discuss whether providing treatment with KTE-X19 will require clinicians and nurses to undergo additional training beyond that required to provide other CAR T-cell therapies.

Handling, administration and care of patients receiving KTE-X19 are very similar to the already commercially available product axicabtagene ciloleucel. As we only expect KTE-X19 to be delivered in centres already qualified to administer axicabtagene ciloleucel, the additional training requirement will be minimal and largely restricted to updating key staff to changes in the details of the Risk Management Materials which we expect to be modified slightly to incorporate details

of both axicabtagene ciloleucel and KTE-X19. The training required will, in most cases, be incorporated into the annual refresher training already mandated for axicabtagene ciloleucel and will consist of a brief face-to-face (or possibly online) training session delivered on-site by the Kite medical team.

b) Please discuss whether providing treatment with KTE-X19 requires any additional investment in infrastructure or processes beyond that which is already in place to provide other CAR T-cell therapies.

NHS England have established a framework of delivery centres spread across the UK to provide commercially available CAR-T treatment. Due to the rare nature of MCL, the addition of KTE-X19 is not expected to exceed the capacity of these centres or require any additional infrastructure.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

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

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

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

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	Senior Medical Writer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma.
4b. Has the organisation received any funding from the	Kite, a Gilead company – £53,938: Sponsorship of education and training/survivorship events; publications; core services

manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Roche Products (rituximab) - £12,000: Sponsorship of education and training/survivorship events; publications; core services
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We asked patient contacts who we support to comment. We also had a call-out on our social media channels for patients with a relevant diagnosis to come forward who would like us to consider their views. We sent questionnaires to people who responded, asking about their experience of current treatment and what they think might be the advantages or disadvantages of new treatments, with particular emphasis on quality of life. We have used their responses as the basis of this submission. We have also included information based on our prior experience with patients with this condition, and on patient responses to previous consultations on CAR T-cell therapy for other types of lymphoma.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	People with mantle cell lymphoma typically develop swollen lymph nodes initially. The lymphoma tends to grow quickly and often affects other parts of the body – such as the bone marrow or spleen – by the time it is diagnosed. Symptoms can include low blood counts, infections, abdominal pain and diarrhoea. As well as the symptoms of the lymphoma itself, patients report that the side effects of treatment significantly impact on quality of life. Chemotherapy can be very intensive and, in some cases, prolonged. Side effects are considerable. One patient noted that 'It was more a case of living with the effects of the chemotherapy treatment for nearly 6 months, rather than living with the lymphoma.' For patients who are fit enough, treatment can involve a stem cell transplant. This can result in an extended inpatient stay, prolonged time off work and serious side effects, all of which can have a massive physical, psychological and financial impact on both patients and carers. After successful treatment, some patients are left with prolonged fatigue, which can affect their ability to return to their usual work, hobbies, social activities or travel. Frequent hospital appointments can also be disruptive for patients and their carers. Recurrent infections – or the fear of recurrent infections – can also be an issue. One patient reported not being able to see his grandchildren often for fear of picking up infections. His wife had also limited her normal activities to reduce the risk of passing infections to him. It is common for mantle cell lymphoma to relapse after treatment. As well as the physical effects of relapse, this has a significant psychological impact on both patients and their carers. Patients and carers report finding it difficult to come to terms with the uncertainty of living with a cancer that is incurable.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Although first-line treatment is usually successful at putting mantle cell lymphoma into remission, it can cause significant side effects, some of which can be life-threatening. One patient told us they had experienced neutropenic sepsis on three separate occasions during a course of cytarabine-based chemotherapy. This resulted in a long hospital admission for supportive care. Although current treatments are often successful, they do not provide long-term remissions. Mantle cell lymphoma almost always relapses and requires more treatment.
8. Is there an unmet need for patients with this condition?	Patients feel there is a clear need for a well tolerated treatment that provides longer-lasting remissions – or, ideally, a cure.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The potential for durable remissions or even 'cure' was seen as a huge benefit, particularly if the side effects can be managed effectively. Patients feel this is a potentially life-saving treatment. Patients felt that this treatment could offer hope for people with relapsed or refractory disease who may have few other options. One commented, 'With this comes hope, which all cancer patients need.' Some patients felt that having a single infusion, rather than the repeated cycles necessary with chemotherapy, is an advantage.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients were concerned that the treatment can have serious and even life-threatening side effects. However, most felt that these would be 'worth the risk' for the potential of a long-term cure. Some people were concerned over the possibility of a prolonged hospital admission. One said, 'A month or more of being very unwell may be difficult, particularly for older people.' There could also be practical issues of transportation or accommodation for people who live some distance from their treatment centre, and difficulties of travelling for their carers. However, it's worth noting that some patients preferred the idea of being treated at a specialist centre to a more local but less specialised hospital.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Some patients felt that, given the risk of serious side effects, the potential long-term benefits of the treatment would be more worthwhile for younger people than older people, who are more likely to have other health issues. However, patients felt that everyone should be able to access the best treatments available, if those treatments are medically appropriate and potentially beneficial for them.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	If patients are required to stay close to the treatment centre for the first month after treatment (as with other CAR T-cell therapies), this could make it difficult for disadvantaged patients, who may not have the financial means to arrange suitable accommodation, to access treatment unless accommodation could be provided free of charge.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to	

be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • Mantle cell lymphoma can have a significant physical, psychological and financial impact on patients and their carers. • Current treatments do not result in durable remissions and most people experience relapse. • KTE-X19 has the potential to significantly improve outcomes in mantle cell lymphoma, potentially providing longer-term remissions than current options. • Potential side effects are serious and would need to be carefully monitored and managed. • Practical issues such as transport and accommodation near treatment centres need to be considered.

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Professional organisation submission

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR

3. Job title or position	RCP registrar
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	KTE-X19 is a chimeric antigen receptor T cell product targeting CD19. A conditioning chemotherapy regimen of fludarabine and cyclophosphamide is administered followed by a single infusion CAR transduced autologous T cells administered intravenously. KTE-X19 uses the XLP™ manufacturing process that includes T-cell selection and lymphocyte enrichment. Lymphocyte enrichment is a necessary additional step in certain B-cell malignancies with evidence of circulating lymphoblasts. ZUMA-2 is a single-arm, multicentre, open-label phase 2 clinical trial involving 74 enrolled/leukapheresed adult patients (≥18 years old) with mantle cell lymphoma (MCL) whose disease is refractory to or has relapsed following up to five prior lines of therapy, including anthracycline or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy and the BTK inhibitors ibrutinib or acalabrutinib. The objectives of the clinical trial were to evaluate the efficacy (60 patients) and safety (68 patients) after a single infusion of KTE-X19 in this patient population. The primary endpoint for the study was objective response rate (ORR). ORR in this trial is defined as the combined rate of complete responses and partial responses as assessed by an Independent Radiology Review Committee.

	The aim therefore is to stop disease progression and induce remission. It is unknown to date whether any patients will be cured from relapsed, refractory mantle cell lymphoma with this approach, primarily because the follow up of the trial is too short to make that conclusion.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Patients who enter a partial response (where the sum of the products of the diameter of up to 6 nodal, measurable masses reduce by 50% or greater) or better (i.e. an overall response by the standard Cheson criteria). Clearly, complete responses (where no residual disease remains on CT imaging or bone marrow evaluation) are more desirable and are known to predict the duration of response in both patients treated with CAR-T therapy, BTK inhibition and immunochemotherapy.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, patients with mantle cell lymphoma whose disease progresses following initial response or is refractory to a Bruton's tyrosine kinase (BTK) inhibitor have a limited survival. This is currently in the region of 6-12 months - depending on number of prior lines of treatment, patient fitness and other clinical and histopathological characteristics.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	At present, there is no gold standard of care available for patients whose MCL progresses following a BTK inhibitor. Options over the recent past have been dependent on patient fitness, medical comorbidity and the availability of clinical trials. Recently, a venetoclax monotherapy within a small UK compassionate use scheme produced an overall response rate of 55% with a median progression free survival of 3.2 months in 20 heavily pre-treated patients (Eyre et al, 2019). This agent is not routinely available in this setting. In early 2020, results of a retrospective analysis of 36 patients treated with rituximab-bendamustine-cytarabine (R-

	BAC) were published (McCulloch et al, 2020), suggesting improved response rates (ORR 83%) and median PFS of 10 months. See answer to question 11 for more details. This option is a standard approach now in the UK, where immunochemotherapy is the main option post BTK inhibitor therapy outside of clinical trials.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. The UK British Society for Haematology (McKay et al, 2018) have published guidelines on the management of patients with mantle cell lymphoma. These are broadly followed,however they also state that there is no clear standard of care post BTK inhibition. Treatment options are as stated above, with R-BAC probably the most popular in generally fit patients.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No, as described there is no clear standard of care following BTK inhibition. Outside of clinical trials, the treatment pathway is well defined for first and second line therapy. Patients who are typically fit under 65 years old will receive a cytarabine (ara-C)-based induction treatment (R-DHAP or R-maxiCHOP/High dose Ara-C) followed by an autologous stem cell transplant and then rituximab maintenance. Patients over 65 years are more typically treated with either R-CHOP followed by rituximab maintenance or Bendamustine plus rituximab. NHS England commissioning for ibrutinib mandates second line use and therefore this remains a clear standard of care for all patients (outside of a clinical trial and without clear contraindication) for patients at first relapse. As stated above, therapy following this is typically immunochemotherapy again and will somewhat depend on what a patient has previously received. It is probably most commonly now R-BAC although systemic, national evaluation of treatment approaches here have not been performed.
• What impact would the technology have on the current pathway of care?	Much in the way the current system for CAR-T cell works in the UK for DLBCL, it would seem likely that patients would be referred to a regional centre and then on for assessment at a designated CAR-T centre. This is clearly subject to change to difficult to comment on in detail. This approach is clearly very different from patients receiving standard immunochemotherapy at the patients local treatment centre.
10. Will the technology be used (or is it already used) in	CAR-T therapy would be used in patients progressing with MCL following ibrutinib based therapy. The elements that will influence whether this is considered an appropriate option will be a) fitness / performance status b) desire for patient to travel to a CAR-T cell centre c) patient age and comorbidities d) available trial options e) social and caregiver support network.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Current care involves the use of outpatient-based immunochemotherapy which is widely applicable across all district general and tertiary referral hospitals across the UK. CAR-T therapy is clearly very different – the adverse event profile is different, as is the patient referral pathway is different. At present based on the UK model this would be available at a limited number of specialist centres across the UK.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Following BTKi failure (refractory disease, progressive disease through ibrutinib or other BTK inhibitor (e.g. acalabrutinib) if received on a clinical trial for relapsed, refractory MCL. This would also include patients stopping a BTK inhibitor due to intolerance who then develop subsequent disease progression.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The infrastructure for the widespread applicability of CAR-T cell therapy has begun development across the UK following the licensing and NHS England commissioning of Yescarta and Kymriah for patients with relapsed, refractory diffuse large B cell lymphoma (DLBCL) and B cell acute lymphoblastic leukaemia (B-ALL). At present, two phases of site opening across the UK has occurred. Sites require JACIE accreditation, intensive care facilities, neurology specialty availability, cellular therapy expertise, a clear MDT network of referral and site expertise, amongst other factors. Clearly any decisions about KTE-X19 will require careful consideration regarding the referral practices, the requirement (or otherwise) of a similar national expert panel for MCL patients, and an understanding that across the population, the R/R MCL patient population is typically older than those with DLBCL or ALL.
11. Do you expect the technology to provide clinically	Yes, potentially. The follow up of the data presented within ZUMA-2 is still fairly short (Wang et al, ASH Abstract 2019; median follow up 12.3 months), however there is clearly a high response rate and early signs of durability of response to KTE-X19. The closest comparison at the moment is R-BAC, which has an overall response rate of 83% (complete response 60%) and 31% were bridged to allogeneic stem cell transplant (alloSCT). The median progression-free survival was 10.1 months (95% confidence interval (CI) 6·9-13·3) and median overall survival was 12·5 months (95% CI 11·0-14·0). It is hard to care across

meaningful benefits compared with current care?	cohorts and this particularly challenging comparing selective trial-fit (ECOG 0-1) patients treated in mainly large US tertiary cancer centres against a retrospective UK/Italian cohort. That said, the ZUMA-2 trial was generally a high risk group of patients who were heavily pre-treated. We know from previous analysis (Martin et al, 2016) that treatment following BTK inhibition in more heavily pre-treated patients results in a median OS of approximately 4-6 months. So this therapy is likely to provide a meaningful benefit to patients.
• Do you expect the technology to increase length of life more than current care?	This is hard to assess although see the comments in point 11. The median PFS was 10.1 months and median OS was 12.5 months in the R-BAC cohort. The median PFS is not reached in ZUMA-2 with a 12 months PFS 61% and 12 month of 83%. Despite the lack of randomised data and the immaturity of follow up of ZUMA-2 it is very possible that KTE-X19 improves length of life versus current care.
• Do you expect the technology to increase health-related quality of life more than current care?	Again, this is assessing across two very different treatment strategies with different toxicities: immunochemotherapy will risk cytopenias, infection and fatigue. However, KTE-X19 results in grade 3 or greater cytokine release syndrome in 15% of patients and grade 3 or greater neurological toxicity in 31% within the selected trial population. These events are relatively short lived but have a major impact on the individual's health-related quality of life during the early phase of the study.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The clinical trial only included patients with an ECOG of 0-1 and by definition these patients were typically fit to travel in the US (predominantly) for a clinical trial. One of my concerns here is that there is the combination of a very fit patient population with very poor disease characteristics – high MIPI, high % refractory to a BTKi, 1/3 of patients with adverse histopathology (pleomorphic or blastoid MCL), high Ki67%, median prior lines 3. These are highly selective patients almost by definition; it is challenging to think of these patients in routine practice as the patients with these characteristics often have an ECOG of 2 or worse and may struggle to travel for a clinical trial.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult to use because of the reasons already stated in previous sections. The practical implications will be similar to those the experience to date from the DLBCL and B-ALL CAR-T cell programmes in the UK. This field as well as both infrastructure and experience of treatment units is quickly evolving.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is not certain at this stage. At present there is a national expert panel that act effectively as gate keepers for CAR-T therapy in DLBCL and ALL, assessing patient eligibility for therapy. The criteria are broadly based on the trial entry criteria for these disorders for the licensing trials, although not exclusively.
15. Do you consider that the use of the technology will result in any substantial health-	Not that I can think of although again it is important to stress that the follow up here with the trial data presented is short and as such the durability of response data is relatively immature.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – this is a very innovative approach in mantle cell lymphoma and represents a clear development from the standard of care therapies that are available now. This therapeutic approach looks to improve on the overall response rates of patients with heavily pre-treated MCL post BTK inhibition for which there is no clear standard of care therapy at present.
• Is the technology a 'step-change' in the management of the condition?	Yes – I think it will be, with the caveats of immaturity of follow up and the patient selection within the clinical trial that I have discussed above.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – as above

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No – CAR-T therapy is not available in the UK for MCL and there have been no recent clinical trials in the UK in the post BTK inhibitor treatment space. Patients do not typically receive treatment with cellular therapy post BTK inhibition unless they go onto receive an allogenic stem cell transplantation, which represents a minority of patients.
• If not, how could the results be extrapolated to the UK setting?	By comparison to patients receiving therapy in the post BTK inhibitor space as discussed above.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate, duration of response, tolerability and overall progression-free survival. Yes these are measured within the phase II ZUMA-2 trial.
• If surrogate outcome measures were used, do they adequately predict	N/A

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Our experts note that it would be interesting to know the number of patients assessed for eligibility who did not ultimately pass this assessment and undergo subsequent leukapheresis. This would provide a more realistic idea of the intention-to-treat population and contextualise the results in a more accurate manner.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	The closest population is the R-BAC patient population, although the challenges of cross comparison have already been discussion (McCulloch et al, 2020 British Journal of Haematology).

21. How do data on real-world experience compare with the trial data?	See 20.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	This potentially has the same issue that are faced with CAR-T therapy from DLBCL and B-ALL in terms of the issues highlighted above; namely the requirement for many patients to travel to a CAR-T cell centre, the need for logistical and social/caregiver support and a level of fitness that will enable safe recovery from cytokine release syndrome and neurotoxicity.
22b. Consider whether these issues are different from issues with current care and why.	This cellular therapy has a very unique site of side effects and will initially only be given at pre-specified, geographically distinct treatment centres across the UK.
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains	

uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your submission. • No clear standard of care exists in R/R MCL patients in who have progressed or relapsed through a BTK inhibitor. • CAR-T therapy in R/R MCL displays high response rates in heavily pre-treated mantle cell lymphoma patients following BTK inhibitor failure • The trial population is hard to replicate in clinical routine practice; patients with such poor risk characteristics are often not 'trial fit' • CAR-T therapy in R/R MCL looks to provide durable responses although the median follow up of ZUMA 2 is short at present. • Patients will need to be physically fit enough to withstand CRS and neurological toxicity and happy to travel to CAR-T treatment sites	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Lymphoma (mantle cell, relapsed, refractory) - KTE-X19 [ID1313]

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

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Andrew DAVIES**
2. Name of organisation	University of Southampton and University Hospitals Southampton

3. Job title or position	**Professor of Haematological Oncology and Consultant Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	KTE-X19 is given to induce remission in patients with relapsed/refractory mantle cell lymphoma (MCL) and to prevent progression. It is too early in the follow-up of patients to know if it will result in any cures of the disease.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant achievement would be to obtain remissions, particularly complete remissions, and to demonstrate significant progression-free survival.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Chemotherapy is not curative, ibrutinib in the second line is not curative. Ultimately all patients will progress; further options are required. Allogeneic transplantation has been used in some patients who achieve a second remission with ibrutinib but the numbers that are performed each year are very small as this is not an appropriate option, due to toxicity, for the majority of patients.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Patients will typically receive first line immunochemotherapy. The regimens typically used are R-CHOP or R-bendamustine. For the younger/fitter patients more intensive induction regimens may be used which include high-dose cytarabine with a first remission consolidated with high-dose chemotherapy and peripheral blood progenitor cell rescue. Maintenance rituximab after achieving a response may be used. At the time of relapse, a BTK inhibitor (*ie* ibrutinib is used).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The British Society of Haematology (BSH) Guidelines give a very clear outline of UK practice. They are fully representative of treatment algorithms employed in the NHS. McKay et al. Guideline for the management of mantle cell lymphoma. First published: 16 May 2018 https://doi.org/10.1111/bjh.15283
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is very clearly defined as outlined in the BSH Guidelines. There may be some subtle differences in the choice of chemotherapy backbones during induction. The sequence of use of ibrutinib as a second line therapy is defined by the NICE guidance [TA 502]. '*Ibrutinib is recommended as an option for treating relapsed or refractory mantle cell lymphoma in adults, only if: they have had only 1 previous line of therapy'.* Clinicians across the NHS are fully in agreement with this approach. This represents international standards. Allogeneic transplantation to consolidate second remission following ibrutinib is infrequently employed due to the significant toxicity. There are no standard third line and beyond therapies; treatment choices are individualised and may include further immunochemotherapy. In a study of R-BAC used post ibrutinib failure in UK and Italian centres (n=36), most patients responded to treatment (83%), but PFS was only 10.1 months (8.6 months with censoring for transplant) and median overall survival (OS) 12.5 months (McCulloch et al. Br J Haematol. 2020 https://doi.org/10.1111/bjh.16416); this is somewhat better than previous reports of therapy after failure of ibrutinib (reviewed by Rule Hematol Oncol. 2019; 37(S1):66-9).

• What impact would the technology have on the current pathway of care?	The availability of KTE-X19 would provide a new third-line option for patients with MCL. For patients with one prior line of therapy, the median progression free survival from ibrutinib is 25.4 months (95%CI: 17.5-57.5) in pooled study data (Rule et al. Haematologica. 2019 May; 104(5): e211–e214). In the UK real-world analysis of 169 patients it was reported as 16.5 months (95% CI :11.5 to 21.5) (McCulloch et al. Blood (2019) 134 (Supplement_1): 3993). In the latter study 40% of patients progressed within 1 year of starting ibrutinib with a median overall survival post ibrutinib of only 3.6 months. Clearly additional therapy for the third-line settling is required.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology will be used in the same way as other CAR-T cell therapies in the NHS. CAR-T cells are already being used in selected centres for diffuse large B-cell lymphoma DLBCL) and other aggressive B-cell lymphomas along and acute lymphoblastic leukaemia. Axicabtagene ciloleucel and Tisagenlecleucel are accessed through the Cancer Drugs Fund.
• How does healthcare resource use differ between the technology and current care?	As a cellular therapy, KTE-X19 provides a distinct therapeutic modality to those currently available for the management of MCL. This is advantageous as will overcome other mechanisms of disease therapeutic resistance.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist CAR-T centres only, currently limited to certain centres by NHS-England provision.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment will be required to deliver KTE-X19 as the technology will already be established in CAR-T centres. It is near the same product as being used for DLBCL. Each site will require local training, but all sites will already be qualified for CAR-T cell delivery.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Long-term follow-up data is limited for KTE-X19 in MCL however there are many durable responses in excess of 24 months. It is anticipated that this will translate in to improved overall survival.
• Do you expect the technology to increase health-related quality of life more than current care?	It is expected that quality of life (QoL) will be increased as patients will have a greater chance of achieving remission and of being disease free compared to current therapy, although there is no direct comparator data. There will be an initial decline in QoL due to immediate hospitalisation and toxicity associated with KTE-X19 delivery.
13. Are there any groups of people for whom the technology would be more or	KTE-X19 would not be suitable to the frail patient population because of toxicities associated with the technology including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and prolonged cytopenias.

less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	KTE-X19 will be more difficult to deliver than immunochemotherapy in the third line setting but is delivered in specialist centres that are used to the assessment of patients and care of short and long-term toxicities associated with CAR-T cell therapy. This will require increased health care utilisation including possibility of intensive care unit stays, speciality services input (eg neurology, radiology, microbiology, immunology etc), infectious complications and need for long-term immunoglobulin replacement Ent. It is however a single epiode of care. For patients it will require travel to specialist centres for assessment and delivery of therapy, along with a need to stay near the centre in the imemedaute 28 days post-delivery.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	There will be no requirement for stopping/starting rules beyond fitness for the technology.

Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	In line with the observed prolonged progression-free survival observed in some patients following KTE-X19 it is hope that the technology will be able to provide a cure for a sub-set of patients. Further follow-up is clearly required but it would be in-line with the observed benefit of CAR-T cell therapy in other B-cell malignancies. Given that this is a single episode therapy, rather than ongoing rounds of immunochemotherapy it is anticipated that this is associated with an improved outcome for patients.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is a highly innovative technology and a major step forward in the care of patients with MCL.
• Is the technology a 'step-change' in the	Yes. It offers a distinct mechanism of action, high chance of response and prolonged progression free survival.

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Third line therapies lack durable efficacy. New therapeutic approaches are clearly required.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Short-term toxicities of CRS, ICANS and infection clearly have an adverse impact upon QoL. Some longer-term toxicities such as hypogammaglobulinemia and cytopenias may have an effect also on QoL, but study data suggests that QoL is better than baseline by six months.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	The study data was collected from participating patients in the United States, France, Germany and The Netherlands. The pathways of care in these countries is identical to the UK and the data fully extrapolatable.

• What, in your view, are the most important outcomes, and were they measured in the trials?	The progression-free survival achieved by these patients post KTE-X19 is the most important and remarkable feature of this data.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The high complete response rates observed are of clear importance and will predict the prolonged PFS.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	No

appraisal guidance [TA502] and [TA207]	
22. How do data on real-world experience compare with the trial data?	There is no real-world data of KTE-X19 in MCL. Real-world data from the use of CAR-T therapy in high-grade B-cell cell lymphomas in the UK demonstrates that results from a population-based setting are similar to those obtained in clinical trials (Kuhnl et al. Blood (2019) 134 (Supplement_1): 767).
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- There is an urgent need for effective therapies in patients with MCL that have progressed after ibrutinib (third line plus).
- KTE-X19 provides a therapeutic with a novel mechanism of action which is independent of chemotherapy.
- KTE-X19 is delivered as a single episode and is associated with high overall and complete response rates.
- Theses responses are durable with many patients alive and free of disease 24 months post therapy.
- Toxicity and resource utilisation following KTE-X19 is in line with other funded CAR-T cell products used for the treatment of patients with relapsed and refractory B-cell malignancies.

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Lymphoma (mantle cell, relapsed, refractory) - KTE-X19 [ID1313]

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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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Toby Eyre**
2. Name of organisation	**Oxford University Hospitals NHS Foundation Trust, on behalf of RC of Pathologists**

3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? **x** 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)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x** yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	KTE-X19 is a chimeric antigen receptor T cell product targeting CD19. A conditioning chemotherapy regimen of fludarabine and cyclophosphamide is administered followed by a single infusion CAR transduced autologous T cells administered intravenously. KTE-X19 uses the XLP™ manufacturing process that includes T-cell selection and lymphocyte enrichment. Lymphocyte enrichment is a necessary additional step in certain B-cell malignancies with evidence of circulating lymphoblasts. ZUMA-2 is a single-arm, multicentre, open-label phase 2 clinical trial involving 74 enrolled/leukapheresed adult patients (≥18 years old) with mantle cell lymphoma (MCL) whose disease is refractory to or has relapsed following up to five prior lines of therapy, including anthracycline or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy and the BTK inhibitors ibrutinib or acalabrutinib. The objectives of the clinical trial were to evaluate the efficacy (60 patients) and safety (68 patients) after a single infusion of KTE-X19 in this patient population. The primary endpoint for the study was objective response rate (ORR). ORR in this trial is defined as the combined rate of complete responses and partial responses as assessed by an Independent Radiology Review Committee. The aim therefore is to stop disease progression and induce remission. It is unknown to date whether any patients will be cured from relapsed, refractory mantle cell lymphoma with this approach, primarily because the follow up of the trial is too short to make that conclusion.

8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Patients who enter a partial response (where the sum of the products of the diameter of up to 6 nodal, measurable masses reduce by 50% or greater) or better (i.e. an overall response by the standard Cheson criteria). Clearly, complete responses (where no residual disease remains on CT imaging or bone marrow evaluation) are more desirable and are known to predict the duration of response in both patients treated with CAR-T therapy, BTK inhibition and immunochemotherapy.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, patients with mantle cell lymphoma whose disease progresses following initial response or is refractory to a Bruton's tyrosine kinase (BTK) inhibitor have a limited survival. This is currently in the region of 6-12 months - depending on number of prior lines of treatment, patient fitness and other clinical and histopathological characteristics.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	At present, there is no gold standard of care available for patients whose MCL progresses following a BTK inhibitor. Options over the recent past have been dependent on patient fitness, medical comorbidity and the availability of clinical trials. Recently, a venetoclax monotherapy within a small UK compassionate use scheme produced an overall response rate of 55% with a median progression free survival of 3.2 months in 20 heavily pre-treated patients (Eyre et al, 2019). This agent is not routinely available in this setting. In early 2020, results of a retrospective analysis of 36 patients treated with rituximab-bendamustine-cytarabine (R-

	BAC) were published (McCulloch et al, 2020), suggesting improved response rates (ORR 83%) and median PFS of 10 months. See answer to question 11 for more details. This option is a standard approach now in the UK, where immunochemotherapy is the main option post BTK inhibitor therapy outside of clinical trials.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. The UK British Society for Haematology (McKay et al, 2018) have published guidelines on the management of patients with mantle cell lymphoma. These are broadly followed, however they also state that there is no clear standard of care post BTK inhibition. Treatment options are as stated above, with R-BAC probably the most popular in generally fit patients.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No, as described there is no clear standard of care following BTK inhibition. Outside of clinical trials, the treatment pathway is well defined for first and second line therapy. Patients who are typically fit under 65 years old will receive a cytarabine (ara-C)-based induction treatment (R-DHAP or R-maxi-CHOP/High dose Ara-C) followed by an autologous stem cell transplant and then rituximab maintenance. Patients over 65 years are more typically treated with either R-CHOP followed by rituximab maintenance or Bendamustine plus rituximab. NHS England commissioning for ibrutinib mandates second line use and therefore this remains a clear standard of care for all patients (outside of a clinical trial and without clear contraindication) for patients at first relapse. As stated above, therapy following this is typically immunochemotherapy again and will somewhat depend on what a patient has previously received. It is probably most commonly now R-BAC although systemic, national evaluation of treatment approaches here have not been performed.

• What impact would the technology have on the current pathway of care?	Much in the way the current system for CAR-T cell works in the UK for DLBCL, it would seem likely that patients would be referred to a regional centre and then on for assessment at a designated CAR-T centre. This is clearly subject to change to difficult to comment on in detail. This approach is clearly very different from patients receiving standard immunochemotherapy at the patients local treatment centre.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	CAR-T therapy would be used in patients progressing with MCL following ibrutinib based therapy. The elements that will influence whether this is considered an appropriate option will be a) fitness / performance status b) desire for patient to travel to a CAR-T cell centre c) patient age and comorbidities d) available trial options e) social and caregiver support network.
• How does healthcare resource use differ between the technology and current care?	Current care involves the use of outpatient-based immunochemotherapy which is widely applicable across all district general and tertiary referral hospitals across the UK. CAR-T therapy is clearly very different – the adverse event profile is different, as is the patient referral pathway is different. At present based on the UK model this would be available at a limited number of specialist centres across the UK.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Following BTKi failure (refractory disease, progressive disease through ibrutinib or other BTK inhibitor (e.g. acalabrutinib) if received on a clinical trial for relapsed, refractory MCL. This would also include patients stopping a BTK inhibitor due to intolerance who then develop subsequent disease progression.
• What investment is needed to introduce the technology? (For	The infrastructure for the widespread applicability of CAR-T cell therapy has begun development across the UK following the licensing and NHS England commissioning of Yescarta and Kymriah for patients with relapsed, refractory diffuse large B cell lymphoma (DLBCL) and B cell acute lymphoblastic leukaemia (B-

example, for facilities, equipment, or training.)	ALL). At present, two phases of site opening across the UK has occurred. Sites require JACIE accreditation, intensive care facilities, neurology specialty availability, cellular therapy expertise, a clear MDT network of referral and site expertise, amongst other factors. Clearly any decisions about KTE-X19 will require careful consideration regarding the referral practices, the requirement (or otherwise) of a similar national expert panel for MCL patients, and an understanding that across the population, the R/R MCL patient population is typically older than those with DLBCL or ALL.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, potentially. The follow up of the data presented within ZUMA-2 is still fairly short (Wang et al, ASH Abstract 2019; median follow up 12.3 months), however there is clearly a high response rate and early signs of durability of response to KTE-X19. The closest comparison at the moment is R-BAC, which has an overall response rate of 83% (complete response 60%) and 31% were bridged to allogeneic stem cell transplant (alloSCT). The median progression-free survival was 10.1 months (95% confidence interval (CI) 6·9-13·3) and median overall survival was 12·5 months (95% CI 11·0-14·0). It is hard to care across cohorts and this particularly challenging comparing selective trial-fit (ECOG 0-1) patients treated in mainly large US tertiary cancer centres against a retrospective UK/Italian cohort. That said, the ZUMA-2 trial was generally a high risk group of patients who were heavily pre-treated. We know from previous analysis (Martin et al, 2016) that treatment following BTK inhibition in more heavily pre-treated patients results in a median OS of approximately 4-6 months. So this therapy is likely to provide a meaningful benefit to patients.

• Do you expect the technology to increase length of life more than current care?	This is hard to assess although see the comments in point 11. The median PFS was 10.1 months and median OS was 12.5 months in the R-BAC cohort. The median PFS is not reached in ZUMA-2 with a 12 months PFS 61% and 12 month of 83%. Despite the lack of randomised data and the immaturity of follow up of ZUMA-2 it is very possible that KTE-X19 improves length of life versus current care.
• Do you expect the technology to increase health-related quality of life more than current care?	Again, this is assessing across two very different treatment strategies with different toxicities: immunochemotherapy will risk cytopenias, infection and fatigue. However, KTE-X19 results in grade 3 or greater cytokine release syndrome in 15% of patients and grade 3 or greater neurological toxicity in 31% within the selected trial population. These events are relatively short lived but have a major impact on the individual's health-related quality of life during the early phase of the study.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The clinical trial only included patients with an ECOG of 0-1 and by definition these patients were typically fit to travel in the US (predominantly) for a clinical trial. One of my concerns here is that there is the combination of a very fit patient population with very poor disease characteristics – high MIPI, high % refractory to a BTKi, 1/3 of patients with adverse histopathology (pleomorphic or blastoid MCL), high Ki67%, median prior lines 3. These are highly selective patients almost by definition; it is challenging to think of these patients in routine practice as the patients with these characteristics often have an ECOG of 2 or worse and may struggle to travel for a clinical trial.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult to use because of the reasons already stated in previous sections. The practical implications will be similar to those the experience to date from the DLBCL and B-ALL CAR-T cell programmes in the UK. This field as well as both infrastructure and experience of treatment units is quickly evolving.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is not certain at this stage. At present there is a national expert panel that act effectively as gate keepers for CAR-T therapy in DLBCL and ALL, assessing patient eligibility for therapy. The criteria are broadly based on the trial entry criteria for these disorders for the licensing trials, although not exclusively.
16. Do you consider that the use of the technology will result in any substantial health-	Not that I can think of although again it is important to stress that the follow up here with the trial data presented is short and as such the durability of response data is relatively immature.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – this is a very innovative approach in mantle cell lymphoma and represents a clear development from the standard of care therapies that are available now. This therapeutic approach looks to improve on the overall response rates of patients with heavily pre-treated MCL post BTK inhibition for which there is no clear standard of care therapy at present.
• Is the technology a 'step-change' in the management of the condition?	Yes – I think it will be, with the caveats of immaturity of follow up and the patient selection within the clinical trial that I have discussed above.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – as above

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	No – CAR-T therapy is not available in the UK for MCL and there have been no recent clinical trials in the UK in the post BTK inhibitor treatment space. Patients do not typically receive treatment with cellular therapy post BTK inhibition unless they go onto receive an allogenic stem cell transplantation, which represents a minority of patients.
• If not, how could the results be extrapolated to the UK setting?	By comparison to patients receiving therapy in the post BTK inhibitor space as discussed above.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate, duration of response, tolerability and overall progression-free survival. Yes these are measured within the phase II ZUMA-2 trial.
• If surrogate outcome measures were used, do they adequately predict	N/A

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Our experts note that it would be interesting to know the number of patients assessed for eligibility who did not ultimately pass this assessment and undergo subsequent leukapheresis. This would provide a more realistic idea of the intention-to-treat population and contextualise the results in a more accurate manner.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA502] and [TA207]	The closest population is the R-BAC patient population, although the challenges of cross comparison have already been discussion (McCulloch et al, 2020 British Journal of Haematology).
22. How do data on real-world experience compare with the trial data?	See 20.

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	This potentially has the same issue that are faced with CAR-T therapy from DLBCL and B-ALL in terms of the issues highlighted above; namely the requirement for many patients to travel to a CAR-T cell centre, the need for logistical and social/caregiver support and a level of fitness that will enable safe recovery from cytokine release syndrome and neurotoxicity.
23b. Consider whether these issues are different from issues with current care and why.	This cellular therapy has a very unique site of side effects and will initially only be given at pre-specified, geographically distinct treatment centres across the UK.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- No clear standard of care exists in R/R MCL patients in who have progressed or relapsed through a BTK inhibitor.
- CAR-T therapy in R/R MCL displays high response rates in heavily pre-treated mantle cell lymphoma patients following BTK inhibitor failure
- The trial population is hard to replicate in clinical routine practice; patients with such poor risk characteristics are often not ‘trial fit’
- CAR-T therapy in R/R MCL looks to provide durable responses although the median follow up of ZUMA 2 is short at present.
- Patients will need to be physically fit enough to withstand CRS and neurological toxicity and happy to travel to CAR-T treatment sites

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NICE National Institute for Health and Care Excellence

Patient expert statement

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

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 conditions and their treatment that is not typically available from other sources.

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Stephen Scowcroft**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

Patient expert statement

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Peter Charles English**
2. Are you (please tick all that	✓ a patient with the condition? ☐ a carer of a patient with the condition?

apply):	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Did your nominating organisation submit a submission?	✓ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	✓ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As Mantle Cell Lymphoma (MCL)is not classed as curable, it is a constant preoccupation. I would be classed as a model patient. I was 65 years-old when diagnosed, but I was extremely fit at the outset of treatment and responded well to it. The visible tumours shrank within days of the first treatment. Although I experienced side-effects such as nausea, fatigue and complete hair-loss, they were not debilitating. My condition was classified as in full remission at the end of chemo/immunotherapy and I was able to withstand an autologous stem cell transplant (ASCT). Therefore I have received what the consultant described as the 'gold standard' of current treatments and hope for a long remission. I am currently well, but am obviously aware of the persistent threat of relapse. I did not require much home care apart from a few weeks after leaving hospital following the ASCT. However, it is impossible to overstate the stress and worry caused to my wife by my life-threatening condition. My father died aged 88. Until I was diagnosed with MCL, I assumed I could expect to live to about 90. Now, anything beyond 75 looks good

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	25 years ago, MCL was a quick death sentence. The treatment regime I underwent is good, but it is only suitable for those who are strong enough at the outset to withstand it. I was at the upper age limit for consideration and it is only due to my lifelong exercise programme that I was able to respond so well to the treatment. Current alternative treatments are basically palliative.
10. Is there an unmet need for patients with this condition?	Yes, many patients are unable to withstand the current optimal treatment as it is too debilitating for them.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	All MCL sufferers live under the threat of relapse. Repeating chemotherapy after relapse is less effective, therefore alternative therapies are still needed.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit more or less from the	

technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: Although not as deadly as it once was, MCL is still a killer. Most sufferers are not fit enough to withstand the current optimum treatment. I've been lucky so far.	

Thank you for your time.

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Evidence Review Group's Report

KTE-X19 for treating relapsed or refractory mantle cell lymphoma

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Declared competing interests of the authors

None

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Rider on responsibility for report

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

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Contributions of authors

Peter Murphy and Alexis Llewellyn wrote the clinical effectiveness sections of the report. Alison Eastwood provided advice, commented on drafts of the report and took overall responsibility for the clinical effectiveness sections. Kath Wright wrote the sections on the search strategies. Georgios Nikolaidis, Dina Jankovic, and Rita Faria critiqued the company's model, wrote the cost effectiveness sections, and conducted the ERG economic analyses. Stephen Palmer provided advice on the cost effectiveness sections and commented on drafts of the report. Rita Faria took overall responsibility for the cost effectiveness sections.

Note on the text

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List of abbreviations

AE	Adverse event
AIC	Akaike information criterion
Allo-SCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
BSH	British Society for Haematology
BIC	Bayesian information criterion
BNF	British National Formulary
BTK	Bruton's tyrosine kinase
CAR	Chimeric antigen receptor
CEA	Cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of response
ECOG	European Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	EuroQol 5-dimension quality of life questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration

HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
IAS	Inferential analysis set
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit
IPD	Individual patient data
IPI	International prognostic index
ITT	Intention-to-treat
ITU	Intensive treatment unit
IV	Intravenous
KM	Kaplan-Meier
MA	Marketing authorisation
MCM	Mixture cure models
mg	milligram
MIMS	Monthly Index of Medical Specialties
MIPI	Mantle Cell Lymphoma International Prognostic Index
mITT	Modified intention-to-treat
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PartSA	Partitioned survival analysis
PfC	Points for clarification
PFS	Progression free survival
PR	Partial response

PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
r/r	Relapse/refractory
R-BAC	Rituximab-Bendamustine Cytarabine
RiBVD	Rituximab-Bendamustine, Velcade, Dexamethasone
RCT	Randomised controlled trial
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology Appraisal
UK	United Kingdom
VBA	Visual Basic for Applications

1 EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

The ERG considers the decision problem in the company's submission to be appropriate and the deviation from the NICE final scope to be justified. The company is positioning KTE-X19 as a 3rd (or later line) therapy for patients with relapsed or refractory Mantle Cell Lymphoma (r/r MCL) who have previously received a Bruton's tyrosine kinase inhibitor (BTKi), in line with the anticipated licensed indication for KTE-X19 (not yet granted by the European Medicines Agency (EMA)). The ERG agrees with the company that allogeneic stem cell transplant (allo-SCT) may be used to consolidate response in a minority of BTKi responders, but should not be considered a comparator to KTE-X19.

1.2 Summary of the key issues in the clinical effectiveness evidence

Clinical evidence of the effectiveness of KTE-X19 is based on the results of a single cohort of 74 patients from an ongoing single-arm, multi-centre, non-randomised trial, ZUMA-2, evaluating the efficacy and safety of KTE-X19 in r/r MCL. The trial recruited adult patients with pathologically confirmed r/r MCL who have previously received BTKi, with an ECOG performance status of 0 or 1. A blended standard of care (SoC) comparator comprising seven retrospective, single-arm trials and one prospective randomized controlled trial (RCT) was synthesised to provide clinical evidence for the SoC. Comparative results of KTE-X19 and SoC were presented as naïve and matching-adjusted indirect comparison (MAIC) results. The ERG believes the response and survival outcomes of ZUMA-2 are promising, given the poor prognosis of 3rd line r/r MCL patients and significant unmet need, although the evidence raises a number of key issues:

1. The precision and magnitude of efficacy and safety estimates from ZUMA-2 are highly uncertain. The limited evidence means survival results may not be robust to small chance variations in prognosis or survival outcomes.
2. ZUMA-2 survival data are immature and survival curves do not provide sufficient evidence of durable long-term survivorship. Median overall survival (OS) and progression-free survival (PFS) were not reached.
3. The generalisability of ZUMA-2 patients is uncertain, and the risk that they may have a more favourable prognosis than patients who would be eligible for KTE-X19 under the anticipated license cannot be excluded.
4. The comparator evidence presented by the company is very limited, and most is not directly relevant to the NHS. The ERG considers the study by McCulloch et al (2020)[1] most relevant to the comparator population, as R-BAC is the most commonly used intervention in the post-BTKi MCL population.

5. Observed baseline imbalances between KTE-X19 and relevant SoC evidence, and results of MAIC analyses suggest unadjusted comparisons supporting the company model are inappropriate.

1.3 Summary of the key issues in the cost effectiveness evidence.

The ERG identified a number of issues with the cost-effectiveness evidence submitted by the company. The ERG highlights the following as key issues, signposts to the relevant section in the report and notes the item number as per Table 19 (pg. 98):

1. Generalisability of the ZUMA-2 population to the UK patient population

In terms of the cost-effectiveness analysis, concerns about the generalisability of the ZUMA-2 population particularly relate to the age at treatment (Section 4.2.3 and item 2), which in turn determines the relevant general population mortality risk and age adjustment to health-related quality of life, and to the generalisability of the health-related quality of life data from ZUMA-2 (Section 4.2.8). The ERG notes that age at treatment has a large impact on the results. Therefore, the ERG explores informing age at treatment from the study informing the long-term outcomes with standard of care (McCulloch et al (2020)[1]) in a scenario (Scenario 5).

2. Long-term PFS and OS of r/r MCL patients after KTE-X19

Given the insufficient evidence to support the assumption of durable long-term survivorship (Section 4.2.6, items 3 and 4), the ERG is concerned that the company's approach, using mixture cure models which rely on the assumption that a proportion of patients are long-term survivors immediately after KTE-X19 treatment and experience an adjusted general population mortality risk, is not sufficiently evidenced (item 5). Furthermore, the ERG considers that alternative extrapolation approaches, such as spline or parametric models with switch points to an adjusted general population mortality risk, are plausible as well as offering more flexibility regarding the timing of the switch point to an adjusted general population mortality risk (item 6). Hence the ERG's base-case employs a spline model for the within-trial period with a switch to an adjusted general population mortality beyond this. Alternative approaches are explored in the ERG's scenario analysis (Scenarios 1-4).

3. Excess mortality risk experienced by long-term survivors

Central to the uncertainty regarding the long-term progression-free and overall survival of r/r MCL patients after KTE-X19 is the excess mortality risk experienced by long-term survivors; that is, the mortality adjustment to the age- and sex-matched general population mortality risk (see Section 4.2.6 and item 7). The ERG notes that the mortality adjustment compared to the general population is uncertain but considers that it is more appropriate to base it on data from MCL patients, as in the ERG

base-case, rather than in data from patients with diffuse large B-cell lymphoma, as preferred by the company. Given the data limitations, the ERG estimated an upper and lower estimate of the mortality adjustment and uses both to inform the ERG base-case results as a range. The ERG highlights that this is a key driver of the cost-effectiveness results.

4. Naïve unadjusted comparison of KTE-X19 *versus* SoC

The ERG notes that the cost-effectiveness results are based on a naïve unadjusted comparison of ZUMA-2 with a meta-analysis of single arm cohort studies (company's base-case) or with a single arm cohort study (McCulloch et al (2020), [1] in the ERG's base-case); hence, the results are affected by unquantifiable bias and are uncertain (see Section 4.2.6 and item 9).

5. The health-related quality of life of durable survivors who have not progressed in the long-term

The ERG considers that the company's assumption that health-related quality of life of patients who have not progressed after 5 years is the same as the age- and sex-matched general population is uncertain and unevidenced (see Section 4.2.8 for details and item 11). In light of the limited evidence, the ERG employs this assumption in its base-case, but explores alternative assumptions in a scenario (Scenario 9).

6. The administration costs of KTE-X19

The ERG notes that there is a [redacted] between the administration costs estimated by the company, which follow a similar approach to previous appraisals of CAR T-cell therapies, and the NHS England tariff, which is based on [redacted] (see Section 4.2.9 and item 12). [redacted] on the NHS England tariff, the ERG was unable to make an assessment regarding which value most accurately reflect the administration costs to the NHS; hence the ERG uses the company's costs in its base-case and the NHS England tariff in scenario 6. The ERG highlights that [redacted].

Other areas of uncertainty and limitations, which have a smaller impact on the results, include the exclusion of the long-term costs and health outcomes of the patients who had leukapheresis but who did not receive KTE-X19 (item 1), the choice of study to inform PFS and OS with standard of care (item 8), the approach to the inclusion of adverse effects due to KTE-X19 (items 10, 17, 18, 19), and some aspects of the approach used to parameterise costs with KTE-X19 and with SoC (items 13, 14, 15, 16).

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions are discussed in Section 6.1 and summarised below:

1. Correcting model errors relating to the calculation of undiscounted costs and the application of the mortality adjustment.
2. Considering the long-term health outcomes and costs of patients who did not receive KTE-X19.
3. Using McCulloch et al[1] to inform PFS and OS of patients receiving standard of care.
4. Excluding the costs of retreatment with KTE-X19.
5. Sourcing the number of doses of tocilizumab from ZUMA-2.
6. Calculating the costs of standard of care based on McCulloch et al (2020).[1]
7. Assuming that long-term survivors have an annual haematology outpatient appointment.
8. Obtaining the number of days in the intensive care unit from ZUMA-2.
9. Including pancytopenia as an adverse event in the model.
10. Predicting PFS and OS of patients after KTE-X19 with spline models during the within-trial period and extrapolating beyond that based on adjusted general population mortality.
11. Adjusting the general population mortality risk with a mortality adjustment estimate based on MCL data from Eskelund et al.[2]

The results of the analyses that led to the ERG's base-case can be found in Table 22. Given the uncertainty in the ZUMA-2 data and the limited evidence on long-term survival in r/r MCL, the ERG considers that it is reasonable to assume that the excess mortality risk experienced by patients who received KTE-X19 and who are alive at the end of the trial follow-up sits between the two values derived from Eskelund et al[2] (estimated as hazard ratios, at 2.36 and 4.37). Table 1 shows the probabilistic results for the ERG's base-case.

Table 1 ICER resulting from ERG's preferred assumptions

Treatment	Total discounted costs	Total discounted QALYs	ICER £/QALY
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook several scenario analyses (see Section 6.1 for methods, Section 6.2.2 and Table 23 for results). Briefly, the ERG's scenarios explore alternative approaches to predict long-term PFS

and OS (Scenarios 1-4), alternative age at KTE-X19 treatment (Scenario 5), and costing (Scenarios 6-8) and HRQoL assumptions (Scenario 9). The scenarios about PFS and OS tested alternative switch points to the adjusted general population mortality risk (Scenario 1), alternative approaches to estimate the proportion of long-term survivors (Scenario 2 and 3) and to long-term extrapolation (Scenario 4). Furthermore, the ERG conducted a univariate sensitivity analysis to the excess mortality risk of long-term survivors using both the ERG base-case and the company's base-case, and to the switch point from the spline models predictions to the adjusted general population mortality risk with the ERG base-case (Section 6.2.3).

In general, most scenario analyses resulted in similar ICER estimates to the ERG's base-case. [redacted]. The lowest ICER range was estimated in analysis 15, which used the company's preferred extrapolation approach (i.e. based on the lognormal mixture cure model), with the ERG's preferred mortality-adjustment for long-term survivors [redacted]. The highest ICER range was estimated in analysis 16, where a single parametric lognormal model is used for extrapolation in conjunction with the ERG's preferred mortality-adjustment (ICER=[redacted]). The univariate sensitivity analysis shows that the ICER increases with greater values of the mortality-adjustment assumed for long-term survivors and is the key cost-effectiveness driver.

Alternative costing assumptions with regards to the duration of IVIG treatment or the composition of SoC did not materially impact the ICER. However, increasing the average age by 2 years from 63.2 years as per ZUMA-2 to 65.2 years as per McCulloch et al[1] increases the ICER to [redacted](Scenario 5). Using the NHS England tariff of [redacted] as an estimate for the administration costs of KTE-X19 (Scenario 6) resulted in an ICER range of [redacted]. Finally, assuming that patients who remain progression-free for more than five years have the health-related quality of life of the age- and sex-matched general population but reduced by a factor of 20%, increases the ICER by around [redacted]/QALY.

The ERG highlights that substantial uncertainty remains, primarily due to the uncertainty associated with the long-term progression-free and overall survival of patients after KTE-X19, the proportion of patients who may be long-term survivors, and lack of evidence to enable the estimation of the excess mortality risk that long-term r/r MCL survivors are subject to compared with the general population.

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Background

This section provides a descriptive summary and critique of the disease, the technology and the positioning of KTE-X19 in the treatment pathway presented in the CS.

- Mantle cell lymphoma (MCL) is a rare and aggressive disease with a poor prognosis with some variation depending on important prognostic factors, including line of therapy, Mantle Cell Lymphoma International Prognostic Index (MIPI), Ki-67, response to previous line of therapy
- Evidence from other treatments in relapsed or refractory (r/r) MCL suggest that long-term survivorship is not yet an established concept in MCL. In the r/r post-BTKi setting, there are limited therapeutic options and as such there is significant unmet need.
- The CS states that treatment options at higher relapse (third and later lines) are not well established. The ERG's clinical advisors believed that Rituximab-Bendamustine Cytarabine (R-BAC) is the most frequently used standard of care treatment in the post-BTKi setting.

2.1.1 Previous NICE appraisals on CAR T-cell therapies or MCL

NICE has previously appraised CAR T-cell therapies in TA554, TA567 and TA559, none of which are in r/r MCL. All were recommended for use within the Cancer Drugs Fund and within a managed access agreement:

- TA554 recommends tisagenlecleucel for relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years.
- TA567 recommends tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after 2 or more systemic therapies.
- TA559 recommends axicabtagene ciloleucel for treating relapsed or refractory DLBCL or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies.

Specifically, for r/r MCL, TA502 recommends ibrutinib as an option for r/r MCL in adults after one previous line of therapy and under a commercial access agreement.

2.1.2 Disease Background

The description of the underlying health problem in the CS was appropriate and relevant to the decision problem. The company focussed the disease overview appropriately on the poor prognosis of MCL with some variation depending on prognostic factors, including line of therapy, MIPI and Ki-67.

As outlined in the CS (B.1.3.1), disease staging is conducted as per the Lugano classification with more advanced staging being associated with worse prognosis.[3] The MIPI, a more specific prognostic tool for MCL, is also discussed in the CS.[4] Clinical advice to the ERG on MIPI suggests it is the best tool for assessing prognosis, however it is rarely used in clinical practice. Furthermore, guidelines from the British Society for Haematology suggests MIPI score does not usually influence treatment decision.[5]

Clinical advisors to the ERG suggested that the length of remission with the previous line of therapy is an important prognostic factor when assessing r/r MCL patients; this is not captured by MIPI. If patients have a poor response to prior therapy, they are more likely to fare poorly with KTE-X19. Poor prognosis and the trend of decreasing survival with each subsequent therapy are correctly outlined in the CS. Although, as stated in the CS, recent use of rituximab (1st line) and ibrutinib (2nd line) has improved survival outcomes.

Of particular importance to this appraisal is the prognosis of patients with r/r MCL in the post BTKi setting, given this is the anticipated position of KTE-X19. Despite a paucity of evidence, as stated in the CS, a recent observational study of 36 patients conducted in the UK and relevant to current practice in the NHS observed a median overall survival (OS) in the post-BTK inhibitor population to be 12.5 months (95% CI 11.0-14.0).[1]

The CS appropriately states that MCL is generally incurable with current treatment and as such there is significant unmet need. Treatments such as immunochemotherapy and autologous stem cell transplant (ASCT) have been shown to allow patients to remain in remission and treatment free for years, but a convincing plateau in survival curves has not been observed.[2] The CS states that KTE-X19 provides the potential for "long term survivorship" to patients with r/r MCL (Section B.1.3.5, CS, pg 19).

The ERG agrees with the company's description of a reduction in the quality of life (QoL) of patients with MCL compared to the general population based on available literature.[6-8] Long-term evidence of the magnitude of the decrement in QoL relevant to the post-ibrutinib population is, however, scarce. The CS also appropriately outlines the unmet need for effective treatments for patients with r/r MCL, and in particular in the post-BTKi population. Clinical advisors to the ERG reiterated the considerable unmet need for this patient population.

The company's description of the incidence of MCL in the UK is appropriate. However, it is not clear how many of these patients would be eligible for KTE-X19 based on the anticipated license. Despite the aggressive nature of MCL and the average age at diagnosis of 73 years old,[9] the ERG's clinical advisors considered approximately 60% of patients with r/r MCL would be fit enough to undergo conditioning and transplantation of KTE-X19 in the post-ibrutinib setting.

The CS correctly states that NICE guidance recommends chemotherapy in combination with rituximab as first-line treatment. Autologous stem cell transplantation is to be considered for those with chemosensitive MCL.[10] NICE guidance recommends the BTKi, Ibrutinib, for treating r/r MCL if patients have only had one previous line of therapy.[10]

The CS does not adequately describe the current standard of care treatment for r/r MCL patients following BTKi failure. The CS states that as no therapies have been prospectively assessed in the post-ibrutinib setting there is no single intervention with proven clinical effectiveness. Clinical advice to the ERG suggests that R-BAC (Rituximab-Bendamustine Cytarabine) is now preferred as the standard of care in this patient population following the results of the retrospective cohort study presented by McCulloch et al.[1]

2.1.3 The technology and the company's anticipated positioning of KTE-X19

KTE-X19 is a chimeric antigen receptor (CAR)-T cell therapy anticipated to be marketed in the UK for the treatment of MCL. The ERG considers the company's description of the technology and the steps involved in the treatment with KTE-X19 to be appropriate. A full description of KTE-X19 is provided in Section 1.2 of the CS. The company summarizes the clinical care pathway for patients with advanced MCL and the proposed position of KTE-X19 in Figure 2 in the CS.

The company proposed KTE-X19 as a higher-relapse treatment option (third- or later-line setting) for patients who have previously received a BTKi. The ERG considers this to be appropriate and in line with the ERG's clinical advice.

2.1.3.1 Comparator

The NICE scope listed established clinical management including but not limited to chemotherapy with or without rituximab and allogeneic haemopoietic stem cell transplant (allo-SCT). The company considered the comparator to be standard of care (SoC) in the absence of KTE-X19, which consists of chemotherapy but not allo-SCT. The ERG agrees with the company's statement that allo-SCT may be used to consolidate response in a minority of BTKi responders, but it should not be considered a comparator to KTE-X19.

The CS states that the treatment options at the later-line setting are not well established. The ERG notes that there is uncertainty regarding the chemotherapy regimens in practice but considers

Rituximab-Bendamustine Cytarabine (R-BAC) to represent the treatment the majority of patients in the post-BTKi setting would receive. One clinical advisor to the company stated that 60-70% in his centre would receive R-BAC in this setting. One clinical advisor to the ERG believed that most centres will use R-BAC predominantly (75-85%) but some patients might receive R-Bendamustine or R-CHOP depending on their fitness and initial therapy. Due to limited data on standard of care, the ERG found that the McCulloch 2020 study of R-BAC[1] provided the best available comparator evidence for the CS. McCulloch was one of only two studies providing both progression-free survival (PFS) and overall survival (OS) data (see Section 3.3), the other being Eyre 2019[11] which assessed Venetoclax, an intervention not licensed for MCL in the NHS (see Section 3.3). The ERG's alternative view on the SOC in the post-BTKi MCL population has implications for the approach to generating a SOC comparator (see Section 3.3 and 3.4).

The company's presented treatment pathway does not provide adequate detail on the use of allogeneic stem cell transplant (allo-SCT) in the higher relapse patient group.

2.2 Critique of company's definition of decision problem

The CS defines the population in accordance with the anticipated licensed indication for KTE-X19 (not yet granted by the European Medicines Agency (EMA)). The anticipated license for KTE-X19 is for the treatment of adults with r/r MCL who have previously received a BTKi.

The CS acknowledges that the wording issued in the final NICE scope differs in that it does not specify that patients will have previously received a BTKi; rather, it states that patients must have received at least two previous lines of therapy. The ERG considers the company's wording change in the scope to align with the anticipated licence for KTE-X19 to be reasonable. The CS considers this population to correspond to the patient population evaluated in the KTE-X19 clinical trials in MCL (i.e. ZUMA-2), albeit the BTKi, ibrutinib, is currently positioned as a 2nd line therapy and is the only BTKi recommended for use in r/r MCL patients in the NHS.

The ERG considers that the company's approach with respect to both the intervention and the SoC is consistent with the decision problem. However, the ERG's view on the most appropriate approach to generating the comparator differs from the company (see Section 3.1.4 and 3.4). Since SoC treatments are relatively similar in terms of costs and benefits, they are not expected to materially impact the cost-effectiveness of KTE-X19. The ERG's comments on the company's decision problem can be seen in Table 2.

Table 2 Summary of decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with r/r MCL who have received at least two previous lines of therapy	Adults with r/r MCL who have previously received a BTK inhibitor	Population description aligned with the anticipated marketing authorisation	The ERG understands the rationale for the amended population addressed in the CS given that ibrutinib is the only BTKi recommended for 2nd line use in r/r MCL.
Intervention	KTE-X19	KTE-X19	N/A	N/A
Comparator(s)	Established clinical management including but not limited to: • Chemotherapy with or without rituximab • Allogeneic HSCT	Established clinical management including but not limited to: • Chemotherapy with or without rituximab	Allogeneic stem cell transplant is not a relevant comparator. It would not be used as an alternative treatment to KTE-X19 for patients who have r/r MCL post-BTKi. Rather, it may be used to consolidate a response to BTKi treatment in a minority of responding patients at second-line. In contrast, KTE-X19 is positioned as a third-line treatment after BTKi failure.	The ERG considers that the company's approach with respect to both the intervention and the SoC is appropriate and consistent with the decision problem. In contrast to the company's clinical advisors, who advised that a blended R-chemotherapy SoC comparator is representative of the UK practice, the ERG's clinical advisors considered that the current standard of care is R-BAC although it may not be used in all patients. The ERG agrees that allo-SCT is not a comparator given it is used as consolidation therapy in

				minority of post-BTKI patients.
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	N/A	The ERG agrees with the outcomes presented in the decision problem. An additional important outcome not listed in the decision problem and included in the CS is minimal residual disease. This was conducted as a post-hoc analysis.
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 patient access schemes for the intervention or comparator technologies will be taken into account.	As per scope.	N/A	N/A
Subgroups	None	None	N/A	N/A

Special considerations including issues related to equity or equality	None	None	N/A	N/A

Abbreviations: allo-SCT, allogenic stem cell transplantation; BTK, bruton tyrosine kinase; CS, company submission; ERG, evidence review group; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; MCL, mantle cell lymphoma; R-BAC, Rituximab, bendamustine and cytarabine.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic review to identify the available clinical evidence for the current treatment options for adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL), including for KTE-X19 and comparator treatments.

Overall, the ERG believe the review methods for searching, selecting, extracting and quality assessing studies were broadly appropriate and the risk that studies relevant to the decision problem may have been missed is very low.

3.1.1 Literature searches

The CS conducted a systematic review (SR) to identify the available clinical evidence for the current treatment options for adult patients with r/r MCL who have received at least one previous line of therapy. The review aimed to identify both evidence for KTE-X19 and potential 'standard of care' comparator studies. Literature searches were broad and included main databases (MEDLINE, EMBASE and the Cochrane library) and key conference proceedings, and were updated up to January 2020. Further details on the searches and study selection are reported in Document B Appendices, section D.1. of the CS.

Points for critique

Overall, the ERG believe the review methods for searching were broadly appropriate and the risk that relevant studies may have been missed by the searches is very low.

Table 3 summarises the ERG's comments on the company's search strategy for clinical effectiveness.

Table 3 ERG appraisal of evidence identification for the effectiveness review

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	Yes	
Were appropriate sources searched?	Yes	The search used: 1. bibliographic databases (PubMED, Embase, Cochrane CDSR, Cochrane CENTRAL) 2. Trial Registers (e.g. ClinicalTrials.gov) 3. Conference Proceedings (as listed) 4. Reference lists from systematic reviews and relevant studies
Was the timespan of the searches appropriate?	Yes	1. The original search was conducted in 2019 and covered from database inception to February 2019.

		2. The update covered January 2019 to January 2020
Were appropriate parts of the PICOS included in the search strategies?	Partly	The search strategies combine terms for mantle cell lymphoma with study type terms for RCTs and/or observational studies. No terms for the I of the PICOS are included e.g. ibrutinib, imbruvica, KTE-X19. No terms are included to focus the search results on the specific population of interest i.e. adult patients with mantle cell lymphoma who have previously received a Bruton tyrosine kinase inhibitor (BTKi)
Were appropriate search terms used?	Partly	1. The full search strategies are provided for each of the databases. 2. In line with best practice, these combine thesaurus terms with free text terms 3. The search of PubMED was intended to identify records from the InProcess section of MEDLINE i.e. those records with no MeSH terms or publication types assigned. The strategy does. however, include both MeSH terms and publication types. Consequently, 28 of the 52 search lines are redundant. A short 5 line search would have been adequate to identify the potential records of interest
Were any search restrictions applied appropriate?	NA	
Were any search filters used validated and referenced?	Yes	1. RCT search filters are applied in both the MEDLINE and Embase searches 2. The filters are not attributed

3.1.2 Study Selection and Data Extraction

Controlled prospective clinical trials, long-term follow-up studies and prospective or retrospective observational cohort studies were eligible for inclusion. Initial eligibility criteria (reported in Document B Appendices, table 9) included all treatment of r/r MCL, irrespective of treatment history, hence a broader population than in the decision problem. However, the final selection criteria did reflect the decision problem, as only studies including adult patients with r/r MCL who have previously received a BTK inhibitor were final includes in the SR. Any comparators for the treatment of r/r MCL including best supportive care were eligible. This approach was taken by the company on the recommendation of their clinical advisors in that treatment options at the higher relapse are not well established.

The company describe that study selection was performed by two independent reviewers with disagreements resolved via a third reviewer. A total of 3,285 potentially relevant titles or abstracts were identified for the review. After primary and secondary screening, 306 unique studies were

identified. The update searches identified 351 potentially relevant titles or abstracts. After primary and secondary screening, 51 additional unique studies were identified. Given the broad eligibility criteria around prior line of therapy, nine studies met the final population eligibility criteria, i.e. patients who have previously received a BTKi. One study was the ZUMA-2 study assessing KTE-X19, and the other eight were of comparator treatments.

Data were extracted from those studies that reported Kaplan–Meier curves for OS or PFS for patients with r/r MCL post-BTKi therapy. Objective response rate (ORR) was also extracted where available. Table 4 outlines the 9 identified studies.

Table 4 Included Studies (adapted from Table 14, pg. 52, Appendix D)

Study	Study design	Population	Number of participants	Location	Treatment
Dreyling 2016[12]	Prospective RCT follow-up	Adults with r/r MCL whose disease had progressed on ≥ 1 rituximab-based regimens and ibrutinib	40	21 countries	Mixed
Epperla 2017[13]	Retrospective RW follow-up	Adults with MCL whose disease had progressed on ibrutinib	29	US	Mixed
Eyre 2019[11]	Retrospective CUP	Adults with r/r MCL whose disease had progressed on ≥ 2 regimens including BTKi	20	UK	Venetoclax
Jain 2018[14]	Retrospective RW follow-up	Adults with MCL whose disease had progressed on ibrutinib	36	US	Mixed
Martin 2016[15]	Retrospective Trial / RW follow-up	Adults with MCL whose disease had progressed on ibrutinib	73	US, UK, Germany & Poland	Mixed
McCulloch 2019[16]	Retrospective RW follow-up	Adults with r/r MCL whose disease had progressed on BTKi	29	UK & Italy	R-BAC
Regny 2019[17]	Retrospective RW follow-up	Adults with r/r MCL whose disease had progressed on ibrutinib	12	France	RiBVD
Wang 2017[18]	Retrospective RW follow-up	Adults with MCL whose disease had progressed on ibrutinib	58	US & UK	Lenalidomide-based
ZUMA-2	Prospective, single arm	Adults with r/r MCL whose disease had progressed on BTKi	74	US, Germany, France & Netherlands	KTE-X19

Note, the company identified McCulloch 2019[16] in their literature search but noted in the CS that since the company analyses was conducted, the data was subsequently published in full with additional data. The ERG report will refer to the updated McCulloch 2020 data[1] in any subsequent critique and analysis.

Points for critique

Methods for selecting and extracting studies were broadly appropriate and attempts were made to minimise the risk of reviewer errors and bias. However, the ERG is concerned that most comparators included in the SR are not directly relevant to the decision problem and may not be reflective of NHS practice (see Section 3.1.4).

3.1.3 Quality assessment

The CS presented separate quality assessments (QA) of ZUMA-2 and the eight comparator studies identified in the SR (see Table 4 for studies). The only study included in the review of KTE-X19 was a single arm, non-randomised trial. The review of comparator studies included one RCT, and seven non-randomised studies.

The Downs and Black checklist[19] was used for quality assessment of the non-randomised studies. The Downs and Black checklist includes items for internal and external validity, as well as quality of reporting. In these studies, 27 questions were answered Yes, No or Unable to determine. The results show all studies broadly scored well on reporting but there were areas of concern regarding the assessment of external validity. For example, the company were unable to determine for both ZUMA-2 and McCulloch if subjects asked to participate and those that went on to participate were representative of the NHS population. The company did, however concluded the staff, places, and facilities were representative of the NHS. The quality assessment revealed issues regarding the internal validity (both bias and confounding) of all studies included in the CS. Unsurprisingly, all studies scored poorly on blinding of participants and investigators, randomisation and whether there was adequate adjusting for confounding. Full results of the company's Down's and Black quality assessment can be seen in Table 23, Appendix D, CS.

The Cochrane Risk of Bias Tool was used for the quality assessment of the RCT. The judgements from this assessment were summarised in Appendix D of the CS, Table 23.

The company concluded the overall risk of bias in ZUMA-2 is thought to be low. No conclusion on the quality of the identified comparator studies was provided.

Points for critique

The choice of QA tools was appropriate given the study designs included. However, the ERG notes that no information was provided to support or justify the decisions that were made and no insight or interpretation was provided in the CS regarding how to arrive at an overall judgement on quality/bias. Of note, the ERG is concerned by the lack of discussion in the CS regarding the company being unable to determine if patients that were asked to participate and those that went on to participate were representative of the NHS population.

Attempts were made to reduce the risk of error and bias in the conduct of the quality assessment as assessment was conducted by two reviewers with a third reviewer consulted for any disagreements.

The approach to quality assessment is broadly appropriate. However, the ERG have significant concerns about the quality of ZUMA-2 and McCulloch 2020 (further details in Section 3.2 and 3.3).

In addition to the company's quality assessment, the ERG conducted a Downs and Black assessment for ZUMA-2 and McCulloch 2020[1] independently (see Appendix A). McCulloch was the only comparator study selected for quality assessment due to the ERG's preference for it to be used to inform the comparator (see Section 3.3, 3.4 and 4.2.6 for further detail). The relevant discrepancies between the company's assessment and the ERG are:

- The company considered the main outcomes in McCulloch to be clearly described. The ERG disagrees as it is unclear from the manuscript if response and progression-free survival (PFS) were measured by an independent panel. In addition, McCulloch states "End of treatment bone marrow assessment was not routinely performed meaning complete response is denoted by CR/CRu (CR unconfirmed)". It is unclear to the ERG how many had CR unconfirmed.
- The company state probability values were not reported in McCulloch. The ERG disagrees given the 95% confidence intervals are reported.
- The company concludes the staff, places and facilities in ZUMA-2 are representative of the NHS. The ERG is unable to determine this.
- The company state the main outcome measures were used accurately in McCulloch. The ERG is able to determine that the overall survival (OS) measures were accurate but is unable to determine this for PFS and CR because the study does not state that independent panel reviewed outcomes or the amount of CR unconfirmed.
- Finally, the CS did not answer the Downs and Black question on whether the study has sufficient power to detect a clinically important effect. The ERG concluded ZUMA-2 does have the power to detect a clinically important effect although due to its limited sample size and immaturity, have remaining concerns about the precision and magnitude of its effect on survival (see section 3.2). The ERG was unable to determine if McCulloch satisfies this criterion.

3.1.4 Evidence synthesis

No meta-analysis was performed for KTE-X19 as only one study (ZUMA-2) was included in the review; the ZUMA-2 trial data are summarised in Section 3.2. The company did, however, conduct a meta-analysis of the pooled/blended 'standard of care' comparator for the post-BTKi r/r MCL population. This is based on the company's assessment that there is no true standard of care in this

population (see Section 2.1.2). OS data could only be pooled from four of the eight included studies and PFS from two (see Table 4). Extracted OS and PFS Kaplan-Meier data were pooled for a fixed-effects model using a two-step approach and used to inform the economic model (see Section 4.2.6).

The company pooled response rates in the form of overall response rate (ORR), complete response (CR) and partial response (PR) from all eight of the included comparator studies. Results were pooled using a fixed-effects model.

Indirect treatment comparison analyses were also conducted comparing the effectiveness of KTE-X19 with a pooled 'standard of care' comparator. These analyses are discussed in more detail in Section 3.4.

Points for critique

The ERG has a number of concerns with the company's approach to the evidence synthesis of a blended comparator. First, the approach generates OS and PFS from pools of studies, some reporting only OS. The ERG considers it inappropriate to base the economic model on PFS and OS taken from separate studies as the correlation between PFS and OS should be preserved (see Section 3.3.1 and 4.2.4).

Second, the company's approach to combining survival data from a number of studies imposes the necessity to fit the same parametric model to all of the SOC studies in order to meta-analyse the model parameters. The ERG is concerned with the use of a global model fit based on the sum of the AICs across a number of survival models. The ERG also notes the study characteristics and baseline characteristics of the combined study populations are heterogeneous, limiting the validity of the synthesised SoC using the fixed-effects meta-analysis (Section 3.3 and 3.4 for further discussion). The composition of the SoC is, however, not expected to materially impact the cost-effectiveness of KTE-X19 (see Section 4.2.4).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1 Relevant trial – ZUMA-2

The company SR of the safety and efficacy of KTE-X19 included a single trial, ZUMA-2. This section provides a summary of key issues regarding the validity of ZUMA-2, followed by a descriptive summary and more detailed critique of the trial design and results presented in the CS.

The ERG's main concerns about the validity of ZUMA-2 are as follows:

- The evidence for KTE-X19 is based on an ongoing single-arm, multi-centre, non-randomised trial using a cohort of 74 patients from this trial. Although the results of the ZUMA-2 trial look promising in a population with poor prognosis and significant unmet need, the ERG believes the CS is supported by very limited evidence of safety and efficacy of KTE-X19. Notably, the precision and true magnitude of survival estimates are highly uncertain.
- Evidence from ZUMA-2, the only trial supporting the CS, is very immature: median PFS and OS were not reached and median follow-up was [redacted] months. Due to the limited evidence, the long-term efficacy of KTE-X19 is highly uncertain and there is currently insufficient evidence to show a curative effect in a subset of patients.
- The lack of randomised comparison means that the relative efficacy and safety of KTE-X19 compared with standard of care is highly uncertain and results are at high risk of bias.
- The population included in ZUMA-2 is likely to be younger and fitter than the general population of r/r MCL patients with prior BTKI therapy, although they are likely to have undergone more prior therapies. Due to concerns about patient selection and patient characteristics, the ERG have some concerns regarding the generalisability of the trial population to patients who would be eligible to KTE-X19 under the anticipated marketing authorisation. Despite these limitations, the clinical advisors to the ERG consider the ZUMA-2 population to be broadly representative of the population informing the company's decision problem.
- Overall, although the effectiveness results of the company trial look promising, the evidence provided by the company for the efficacy and safety of KTE-X19 is highly uncertain. There is currently insufficient evidence to support the assumption that KTE-X19 may lead to lifetime remission in a subset of patients.

3.2.1.1 Study Cohorts

The ZUMA-2 study is an ongoing single-arm, multi-centre, non-randomised trial for adult patients with r/r MCL who have previously received BTKi. ZUMA-2 enrolled patients across four countries: USA, France, Germany and the Netherlands. Following request for clarification, the company reported that 135 patients were initially screened for eligibility. Of those, 30 were ineligible; 17 met one of the exclusion criteria, 11 patients did not meet one of the inclusion criteria, and 2 patients both met one of the exclusion criteria and did not meet one of the inclusion criteria. The company did not provide further details on which criteria these patients did not meet.

Of the 105 enrolled patients, 14 received KTE-C19, and 17 received KTE-X19 at a reduced dose of 0.5×10^6 anti-CD19 CAR T-cells/kg rather than the licensed applied dose of 2×10^6 anti-CD19 CAR T-cells/kg body weight. The first 14 patients initially enrolled to ZUMA-2 were scheduled to receive KTE-C19, manufactured using the company's previous manufacturing process. All subsequently

enrolled patients received CAR T-cell therapy using the updated manufacturing process, KTE-X19. Following early observation of patients treated with KTE-X19 at the licensed dose, a second cohort of ZUMA-2 was opened and enrolled 17 patients to receive a reduced dose of KTE-X19 (Cohort 2). These 17 patients are not included in any subsequent analyses.

The clinical evidence in the CS is based on one cohort of 74 patients from ZUMA-2, known as the full analysis set (FAS). These patients were recruited to ZUMA-2 and received KTE-X19 at the license applied dose, and are referred to as Cohort 1 in the CS.

Of the 74 patients included in the FAS, 68 received KTE-X19 at the licensed dose; this group of patients is referred to as the modified intent-to-treat (mITT) group in the CS. Of the six who did not receive KTE-X19, three had a manufacturing failure, two died due to disease progression and one patient was found to be ineligible following conditioning chemotherapy. The company use the mITT group in subsequent economic analyses (see Section 4.2.3 for further discussion). The CS includes an additional subgroup known as the inferential analysis set (IAS), made up of the first 60 patients treated with KTE-X19 at the licensed dose. An adapted CONSORT flow diagram can be seen in Figure 1.

Points for critique

Patient selection

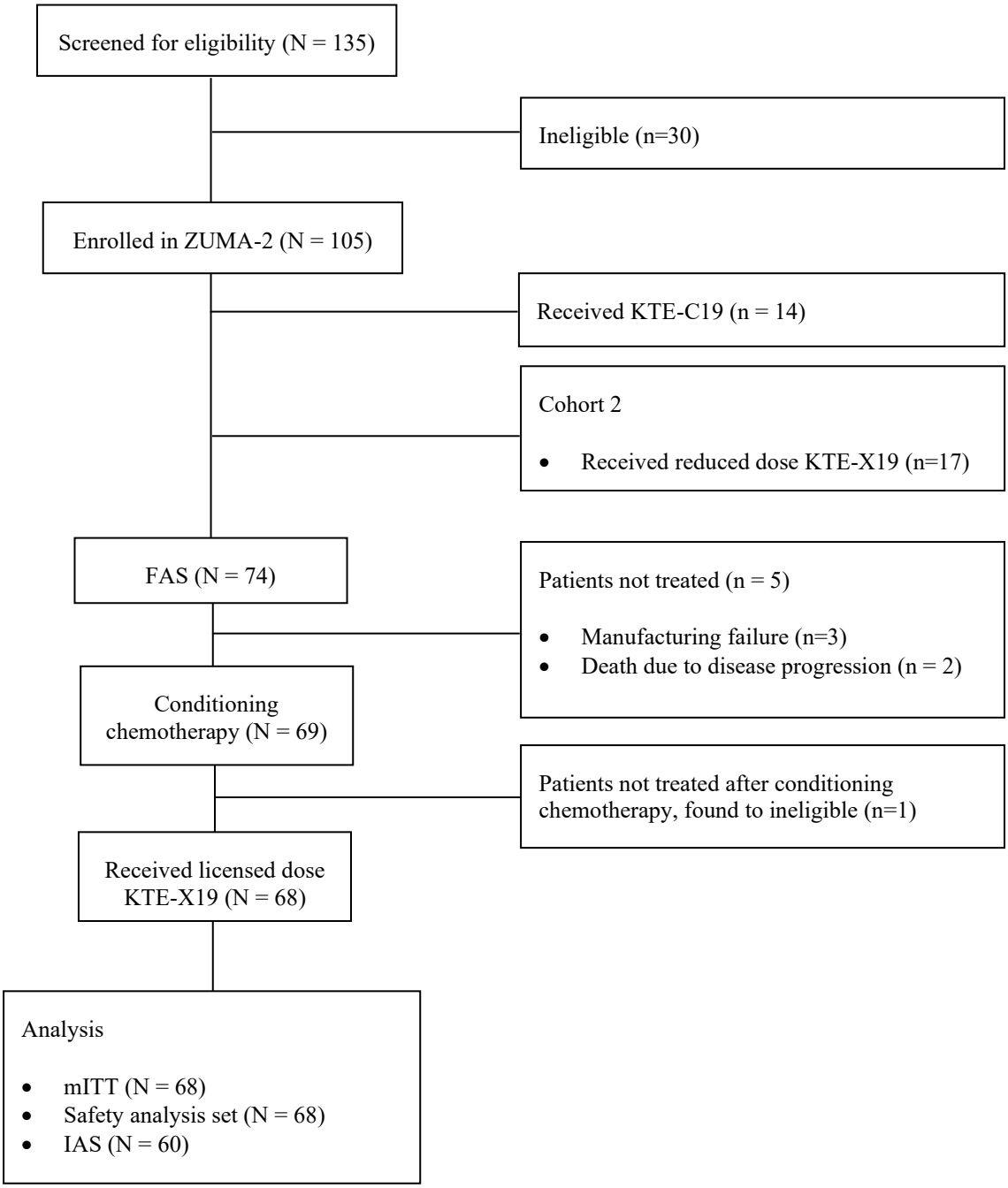
The ERG notes a number of concerns regarding the selection of patients used to inform the effectiveness of KTE-X19.

Both the ERG and the company were unable to determine whether the subjects asked to participate in ZUMA-2 and those that agreed to participate were representative of the entire population from which they were recruited (see Table 23, Appendix D, CS). Despite a requested point for clarification (PfC) to the company, they did not clearly state how patients were identified and in which setting screening took place.

Secondly, the ERG is concerned with the lack of clarity around the inclusion and exclusion from ZUMA-2. The ERG requested details on reasons for exclusions during clarification questions, however the company did not provide adequate detail. Finally, the addition of a separate reduced dose cohort after trial initiation led to the exclusion of a further 17 patients from the expected licenced dose cohort. The ERG found that the decision to exclude these patients from the CS evidence because they did not receive the anticipated licence indication is reasonable. However, it is unclear whether these patients had a better or worse prognosis than the population that received KTE-X19 at the anticipated licence dose based on the reported baseline characteristics (see Table 10 and Table 11, pg. 61-63,

CSR). This uncertainty means that the risk of bias in the selection of the population supporting the CS evidence cannot be excluded.

Figure 1 CONSORT flow diagram of patients included in CS (adapted from Figure 3, pg. 22, CS; Figure 4, pg. 34 CS and PfCs)



Abbreviations: FAS, full analysis set; IAS, inferential analysis set; mITT, modified intent-to-treat.

3.2.1.2 ZUMA-2 Methodology

Patients enrolled in ZUMA-2 and included in the FAS were treated across a number of treatment centres in the USA, France, Germany and the Netherlands. Patients underwent screening, leukapheresis, bridging therapy and infusion of KTE-X19 as described in Section 2.1.3. For a full description of the methodology, see Section 2.3, CS. Retreatment with a second course of KTE-X19 was permitted for those achieving at least a partial response with the first course.

Points for critique

Limited evidence base

The CS efficacy and safety analyses of KTE-X19 are based on a subgroup of 74 patients from a single-arm, open-label, non-randomised trial. Comparative effectiveness results which are derived from single-arm studies are inherently more prone to bias when compared with results from head-to-head and randomised comparisons. The limited number of patients is likely to affect the precision of efficacy and safety estimates. This uncertainty has implications for the robustness of the economic evidence provided in the CS (see Section 4.2.6 for further details). The ERG also have concerns about the potential fragility of results derived from such limited numbers of patients. For instance, small chance variations in survival outcomes may significantly affect the reliability of aggregate estimates. This issue is further explored in Section 6.1.2.1.

Treatment setting

The ERG believe that the company's interpretation that ZUMA-2 represents the staff, places and facilities where patients are to be treated should be interpreted with caution (Table 23, Appendix D, CS). ZUMA-2 was conducted in 33 centres in the US, France, Germany and the Netherlands, with 92% of the full analysis (FAS) set being recruited in the US (Table 14.1.1.3a., ZUMA-2 CSR). The fact that KTE-X19 has not been tested in the UK means that the applicability of the CS evidence to the NHS context is uncertain.

Manufacturing and administration timing

Prior to infusion of KTE-X19, patients undergo conditioning with a non-myeloablative regimen. The CS state that median time from leukapheresis to infusion of KTE-X19 is [redacted] days (range [redacted]). Clinical advice to the ERG outlined the time from approval by the CAR-T panel to leukapheresis is 14 days. The time from leukapheresis to infusion is approximately 30-40 days (28 days for the company to make it and 5-6 days for the conditioning therapy). The company is developing new facilities in Amsterdam, which are not expected to go live until Q2 2022. From then on, the manufacturing time will be 21 days; it will then be comparable to the US data. The ERG considers the current broad range

of time from enrolment to infusion to have implications for eligible patients due to the pace of disease progression and estimated life expectancy; potentially reduced survival and the possibility that patients who have had leukapheresis may no longer be eligible or alive at the time of treatment initiation. An example of this can be seen in ZUMA-2 in which two patients who had successful manufacturing of KTE-X19 but died from progressive disease before receipt of conditioning chemotherapy.

Retreatment

Two patients in the mITT who had disease progression after having an objective response to KTE-X19 were retreated, receiving a second infusion of KTE-X19. The ERG understand that re-treatment is not expected in the NHS. In response to the ERG's PfCs, the company provided the KM curves for OS where re-treated patients were censored at the last available disease assessment data prior to re-treatment. Although the inclusion of these patients may result in an overestimation of the treatment effect of KTE-X19 when compared to the effect expected in the NHS due to potential additional benefit conferred by retreatment, the ERG believe that any increase in survival benefits is minimal. The inclusion of these patients has implications for the economic analyses (see Section 4.2.3).

Subsequent therapies

The second most commonly used subsequent anti-cancer therapy in ZUMA-2 was Venetoclax: [redacted] of patients in the mITT population received it post-progression. Venetoclax is not licensed for treating MCL in the NHS. Ibrutinib was also used as a subsequent anti-cancer therapy: [redacted] of the mITT population received it. As KTE-X19 is only available in the post-BTKi setting, ibrutinib would not be given following KTE-X19. The company states that the likely impact of these salvage therapies on OS will be limited given the line of therapy and the lack of a durable response observed for Venetoclax. The ERG considers this an additional area of uncertainty, but broadly agrees with the company that the impact is likely to be limited.

An additional two patients in ZUMA-2 received allogeneic stem cell transplant (allo-SCT) consolidation subsequent to KTE-X19. Clinical advice to the ERG suggests KTE-X19 should not be used as a bridge to allo-SCT and in reality, this is likely to be very rare. The company asserts that the impact of these patients is likely to be negligible, of which the ERG agrees, but it raises uncertainty in the generalisability of the results and uncertainty in why allo-SCT would be required for a treatment offering the potential of long-term survival.

3.2.1.3 Patient characteristics

The ZUMA-2 population are patients with r/r MCL. Key ZUMA-2 inclusion and exclusion criteria can be seen in Table 5. For a full list of the ZUMA-2 inclusion and exclusion criteria, see Table 6, pg. 23, CS.

Table 5 Key ZUMA-2 inclusion and exclusion criteria (adapted from Table 6, pg. 23, CS)

Inclusion criteria	Exclusion criteria
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.	History of allo-SCT
ECOG performance status of 0 or 1	History or presence of fluid malignant cells or brain metastases; history of CNS lymphoma

Abbreviations: allo-SCT, allogeneic stem cell transplant; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma;

A summary of the key mITT baseline characteristics can be seen in Table 7. For a full list of the FAS, mITT and IAS baseline criteria, see Table 7, pg. 29-30, CS.

Table 6 Key baseline characteristics of patients in mITT (adapted from Table 7, pg. 29-30, CS)

	mITT
Median age, years (range) Mean age, years	65 (38-79) 63
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
Intermediate/high-risk s-MIPI, n (%)	38 (56)
Median no. of prior therapies (range)	3 (1-5)F
Prior auto-SCT, n (%)	29 (43)
Prior BTKi, n (%) Ibrutinib Acalabrutinib Both	68 (100) 58 (85) 16 (24) 6 (9)
Received bridging therapy, n (%) Ibrutinib Acalabrutinib Dexamethasone Methylprednisolone Ibrutinib plus steroid Acalabrutinib plus steroid	25 (37) 14 (21) 5 (7) 12 (18) 2 (3) 4 (6) 2 (3)

Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; MIPI, Mantle Cell Lymphoma International Prognostic Index; mITT, modified intent-to-treat; SCT, stem cell transplant.

Points for critique

The clinical advisors consulted by the Company considered the ZUMA-2 patients broadly representative of UK patients expected to receive KTE-X19. The ERG considers the population included in the company trial is likely to be younger and fitter than the general population of r/r MCL patients, although they are likely to have undergone more prior therapies. Due to concerns about patient selection, representativeness of patient characteristics and limited evidence, the ERG have concerns regarding the generalisability of the trial population to the population who would be eligible to KTE-X19 in the NHS under the anticipated licence.

Age

Clinical advisors to the ERG suggested that ZUMA-2 patients may be younger and fitter than what would be expected in practice. The ERG notes there is a considerable difference in age between those in ZUMA-2 (median age 65 years) and the age of MCL patients at diagnosis in the UK (median age 72.9 years). Mean age from a cohort of mostly UK based post-BTKI patients[1] was 65.2 years at start of R-BAC therapy (personal communication). The mean age of patients in ZUMA-2, as used in the economic analysis, is even lower at 63.2. This may have an impact on the generalisability of the ZUMA-2 results, as older patients and less fit r/r MCL patients are known to have poorer prognosis. The impact of small increases in the ZUMA-2 age on the ICER is considerable and is discussed in Section 4.2.3.

Prior number of therapies

A potential source of bias that could result in ZUMA-2 underestimating the effect of KTE-X19 is due to the prior number of therapies. Clinical advice to the ERG suggests that if KTE-X19 were available in the post-BTKi setting, clinicians would opt to use it as the next therapy following BTKi progression. As a result, NHS patients would likely have had two prior lines of therapy before treatment with KTE-X19. The median number of prior therapies for patients in the FAS was three (Table 6). As with each subsequent treatment line there is worsening prognosis, the ERG considers this baseline characteristic may have introduced negative bias in survival estimates.

Bridging therapies

The baseline characteristics show 37% of patients enrolled in ZUMA-2 had bridging therapy. Of these, the majority (28%) received a BTKi therapy: Ibrutinib (21%) and Acalabrutinib (7%). Clinical advice to the ERG suggested this would not be the treatment given in the NHS. As patients have stopped responding to BTKi in order to be treated with KTE-X19 (according to the anticipated license), it is unlikely patients would be offered a BTKi as a bridging therapy. In addition, 7% of

patients received acalabrutinib, which is not currently available for the treatment of MCL in the NHS. The inclusion of these patients increases the uncertainty in the generalisability of the results. The direction and magnitude of the resulting uncertainty due to the inclusion of these patients is, however, unknown. This uncertainty adds to the caution required when interpreting the results of ZUMA-2.

3.2.1.4 ZUMA-2 Results

The primary outcome measure of ZUMA-2 was ORR, assessed using Independent Radiology Review Committee (IRRC) per the Internal Working Group (IWG) Lugano Classification. Key secondary outcome efficacy measures included duration of response (DOR), PFS and OS. Table 7 summarises the clinical effectiveness of the mITT population from the ZUMA-2 trial. The company felt the mITT population was the best source of evidence to inform the clinical and cost-effectiveness of KTE-X19.

Table 7 Clinical effectiveness of KTE-X19 for key outcomes in ZUMA-2 (mITT population, n=68) (adapted from CS section B.2.6)

	KTE-X19
Response	
Objective response rate (CR + PR), n (%) [95% CI]	[redacted]
Complete response (CR) rate, n (%) [95% CI]	[redacted]
Partial response (PR) rate, n (%) [95% CI]	[redacted]
Stable disease, n (%) [95% CI]	[redacted]
Progressive disease, n (%) [95% CI]	[redacted]
Duration of response, median [95% CI]	[redacted]
Survival	
Progression-free survival, median [95% CI]	[redacted]
Overall survival, median [95% CI]	[redacted]

The 12-month PFS rate is [redacted]% and the 12-month OS rate was [redacted]%.

The CS reported Kaplan-Meier (KM) curves for PFS and OS for the mITT population and the IAS population (see **Figure 2** and **Figure 3**). The CS reported neither median PFS nor OS were reached after median follow-up of [redacted] months. The estimated 12 and 24-month PFS rates were [redacted] and [redacted], respectively. The estimated 12 and 24-month OS rates were [redacted] and [redacted], respectively.

Figure 2 Progression-free survival using central assessment (IRRC) per IWG Lugano classification (Cohort 1; modified intent-to-treat group, from CS Section B Figure 10)

[redacted]

Key: CI, confidence interval; CSR, Clinical Study Report; IRRC, Independent Radiology Review Committee; NE, not estimable.

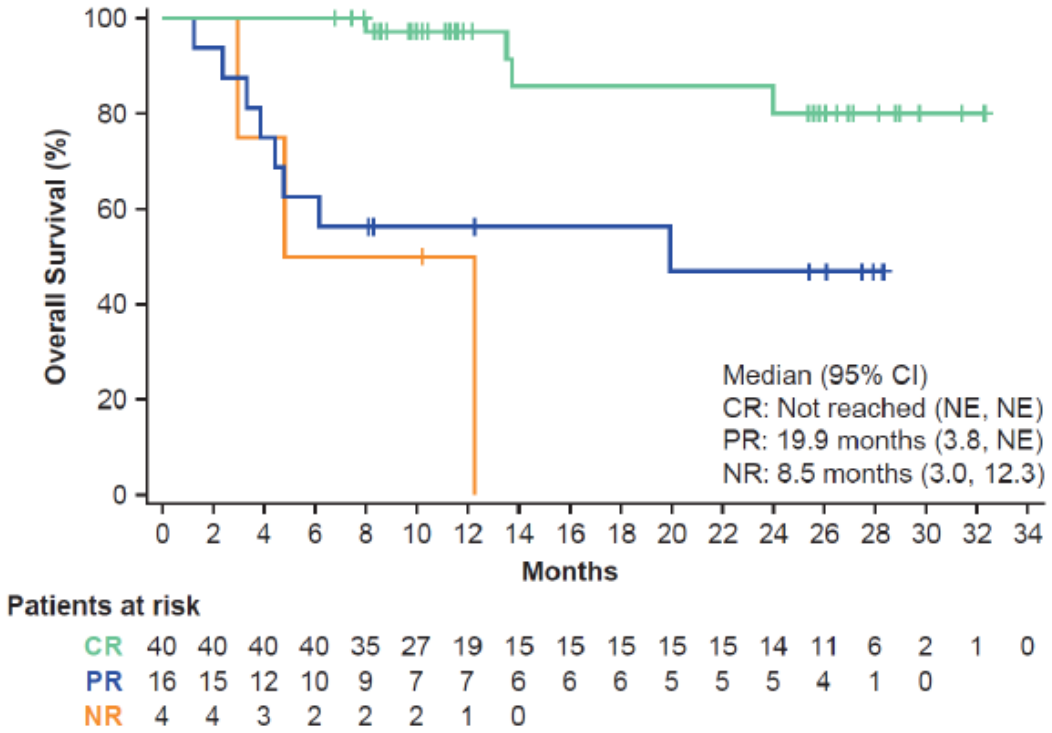
Figure 3: Overall survival (Cohort 1; modified intent-to-treat group, from CS Section B, Figure 13)

[redacted]

Key: CI, confidence interval; CSR, Clinical Study Report; NE, not estimable.

Figure 4 presents OS by best objective response. The ERG agree with the company that the figure shows an extension to life for patients experiencing a complete response (CR) to KTE-X19 treatment compared to patients with partial response (PR). However, given the extent of censoring and immaturity of the data, the ERG considers that the plateaus in the Kaplan-Meier curves cannot be interpreted as providing robust evidence of the extent of long-term survivorship following KTE-X19.

Figure 4: Overall survival by best objective response using central assessment (IRRC) per Lugano classification (inferential analysis set, from CS Section B, Figure 12)



Key: CI, confidence interval; CR, complete response; IRRC, Independent Radiology Review Committee; NE, not estimable; NR, no response; PR, partial response.

The CS presented results of a post-hoc analysis of the assessment of minimal residual disease (MRD) in 29 patients from ZUMA-2. The results showed 24 (83%) had no detectable disease (measured as $<10^{-5}$) at week 4. Following response to clarification questions, MRD analysis was provided with sensitivity at 10-6 and 10-4 at 4 weeks, 3 months and 6 months. The results can be seen in Table 8. In addition, the company provided data that suggests a general trend towards improved survival in patients with MRD (see Question A2, PFCs).

Table 8 Minimal residual disease of the mITT population (adapted from Table 1, 2 and 3, pg. 4-6, PFCs)

	Sensitivity		
	10^{-4}	10^{-5}	10^{-6}
Week 4, n	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted]	[redacted]	[redacted]
Negative, n (%)	[redacted]	[redacted]	[redacted]
Indeterminate, n (%)	[redacted]	[redacted]	[redacted]

Missing, n (%)	[redacted]	[redacted]	[redacted]
Month 3, n	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted]	[redacted]	[redacted]
Negative, n (%)	[redacted]	[redacted]	[redacted]
Indeterminate, n (%)	[redacted]	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]	[redacted]
Month 6, n	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted]	[redacted]	[redacted]
Negative, n (%)	[redacted]	[redacted]	[redacted]
Indeterminate, n (%)	[redacted]	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]	[redacted]
Negative at month 1, 3 and 6, n (%)	[redacted]	[redacted]	[redacted]

Points for critique

The ERG considers the ZUMA-2 response rates and survival results to be promising in a population with significant unmet need and poor prognosis. However, due to limited data the ERG has a number of concerns regarding the magnitude, precision and fragility of the results.

Long-term survival

The ERG considers that the CS evidence is not sufficiently mature to demonstrate that KTE-X19 has the potential to lead to long-term survivorship, and there is considerable uncertainty regarding the long-term effects of KTE-X19 on OS and PFS. Data are insufficiently mature to show a clear plateau suggesting long-term survivorship in responders. The small sample size also means that the results may not be sufficiently robust to small variations in survival outcomes. The impact of this fragility on the ICER is explored in Section 4.2.6.

The ERG notes that from month 24 onwards the KM plots become heavily influenced by censoring of data. In light of this censoring, it is clear that there is considerable uncertainty as to how the slope of the lines will develop beyond 24 months. This uncertainty will only be resolved when data from longer follow up periods become available for many patients. The limited follow-up (median [redacted] months) has implications for the long-term survivorship assumption in the economic model and the proportion assumed to be long-term survivors (see Section 4.2.6). This is particularly concerning as the company assumes the benefits for some patients will still be accrued beyond 30 years.

Similar uncertainties in long-term effectiveness were raised in the NICE appraisal of the CAR T-cell therapy, axicabtagene ciloleucel, for the treatment of diffuse large b-cell lymphoma (DLBCL).[20] Clinical advice to the ERG issued caution regarding the short follow-up and the long-term survival assumptions for KTE-X19. Although for other lymphomas (e.g. DLBCL), there is evidence of long-term remission/cure with non-CAR T-cell treatments,[21] this is NOT the case for MCL where cure is not an established concept in MCL. The uncertainty in the long-term outcomes highlights the need for cautious interpretation of the ZUMA-2 data.

Generalisability of OS

An additional area of uncertainty is the generalisability of the OS curve given the use of the subsequent therapies following progression on KTE-X19. As described in Section 3.2.1.2, the second most commonly used subsequent anti-cancer therapy in ZUMA-2 was Venetoclax (□); a treatment not currently available for MCL patients in the NHS. In response to clarification question, the company stated response data to subsequent therapy were not captured but that they expect response to subsequent targeted therapy to be low as a high proportion of patients had disease refractory to BTKi (62%). The ERG considers the likely impact on survival may well be low, however any resulting bias in the OS curves cannot be ruled out.

Minimal residual disease

Clinical advice to the ERG suggested the persistence of MRD negativity could help identify those potential long-term remitters/survivors. In addition, advice suggested the depth of negativity could provide valuable information, i.e. MRD assessed with a sensitivity of $<10^{-6}$ has a higher chance of remaining negative compared to $<10^{-4}$.

The results show a considerable difference between the sustained negative MRD assessment dependent on sensitivity. At sensitivity 10^{-4}, □ of the mITT had MRD negativity at 4 weeks, 3 months and 6 months, whereas measured at sensitivity of 10^{-6}, □ had MRD at 4 weeks, 3 months and 6 months. Although not directly included in the economic model, this analysis of MRD highlights the uncertainty regarding that KTE-X19 achieves long-term survivorship in r/r MCL patients. The ERG does, however, caution against drawing any firm conclusions from the MRD analysis as there is likely to be considerable uncertainty. This is both due to the small number of observations and the potential for selection bias given MRD analysis was conducted on only 29 of the 68 patients in the mITT population.

3.2.1.5 **HRQoL**

Health-related quality of life was assessed using the EQ-5D questionnaire at screening, week 4, month 3 and month 6. The ZUMA-2 EQ-5D scores can be seen in Table 11, pg. 47, CS.

The results broadly show a considerable drop in the EQ-5D score in week 4, followed by a gradual increase to scores approaching baseline by month 6. The mean EQ-5D visual analogue scale results show a decline in HRQoL one month after screening compared to baseline (7.5 points). By 6 months, HRQoL surpasses baseline, estimated as a small improvement (2.8 points).

The company conducted a systematic review for HRQoL evidence in adult patients with relapsed or refractory MCL (see Appendix H, CS). For further discussion, see section 4.2.8.

Points for critique

The ERG considers the use of the HRQoL data obtained from EQ-5D and measured in the mITT population to be appropriate. However, given the concerns regarding the generalisability of the ZUMA-2 trial population to the UK patient population (see Section 3.2.1.1, 3.2.1.2 and 3.2.1.3), the ERG considers there is considerable uncertainty regarding the extent to which the HRQoL data is generalisable to the NHS. In addition, the ERG cautions that owing to the lack of blinding in participants in ZUMA-2 (see Section 3.1.3 for details), the risk of bias associated with HRQoL cannot be excluded.

3.2.1.6 **Safety**

Safety results were reported for the mITT population. The CS reported almost all patients ([redacted]) had [redacted]. In addition, high levels ([redacted]) of serious adverse events (SAEs) related to KTE-X19 were reported. Only [redacted] grade 5 SAE was reported. The most frequent AEs were pyrexia (94%), neutropenia (87%), thrombocytopenia (74%) and anaemia (68%).

The CS focussed on the AEs typical of the CAR T-cell therapy class, which the company consider to be cytokine release syndrome (CRS), neurological events and B-cell aplasia (classified by neutropenia, thrombocytopenia and anaemia). The proportion experiencing at least one of these AEs is provided in Table 9 (see CS section B.2.9 for further details).

Table 9 Adverse events including cytokine release syndrome, neurological events and B-cell aplasia (adapted from Table 23, 24, 25, pg. 80-84, CS)

	KTE-X19 (n = 68)
Any CRS event, n (%) Grade ≥ 3	62 (91) 10 (15)
Any neurological event, n (%) Grade ≥ 3	43 (63) 21 (31)
Any neutropenia event, n (%) Grade ≥ 3	59 (87) 58 (85)
Any thrombocytopenia event, n (%) Grade ≥ 3	50 (74) 35 (51)

Any anaemia event, n (%) Grade ≥ 3	46 (68) 34 (50)

Abbreviation: CRS, cytokine release syndrome

Points for critique

The ERG is concerned with the high proportion of patients experiencing serious B-cell aplasia AEs. Clinical advice to the ERG detailed the frequent occurrence of cytopenia in patients and the potential for blood and platelet transfusions on a regular basis. The experience of these clinicians in using CAR T-cell therapy for DLBCL suggests that pancytopenia can be present a year after treatment.

In the company's response to clarification questions, the number of patients with the presence of cytopenia at 6 and 12 months was provided. The results show that [redacted] ([redacted]) of the mITT population had a grade ≥ 3 cytopenia at 6 months. At 12 months, this had reduced to [redacted] ([redacted]).

The long-term presence of B-cell aplasia following KTE-X19 is unknown, only long-term term follow up data will clarify this.

Given the limited evidence, the ERG have concerns regarding the precision of the AE rates in clinical practice.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Due to the lack of direct evidence comparing KTE-X19 to a 'standard of care' comparator, the company conducted an indirect treatment comparison (ITC). The ERG believe it unlikely that relevant comparative evidence will have been missed by the company's SR of comparator studies. See Section 3.1 for further details of the systematic review and identified studies. Where available, ORR, PFS and OS data were extracted from the eight studies included in the company's SR. A summary of the eight identified studies along with which data were available for extraction can be seen in Table 10.

3.3.1 **Study characteristics**

Seven of the eight identified studies are small, retrospective, observational studies; Dreyling 2016 is the only prospective RCT. Owing to the company's approach of synthesising a blended comparator due to the assumption of there being no 'true' SOC, the evidence includes a mixture of interventions. In addition, studies conducted outside of the UK were also included in the evidence. Key study characteristics can be seen in Table 10. For a full description of the studies, see Appendix D, CS.

Points for critique

Limited evidence base

As noted by the company, there are considerable limitations of the identified evidence base forming the comparator. This is a result of the evidence consisting of small, retrospective, non-comparative, observational studies. In addition, quality assessment conducted by the company showed considerable limitations in the quality of the reporting, internal validity and the generalisability of the included studies (see Section 3.1.3). The small sample size of the individual study groups is reflected in the uncertainty of the estimates. The uncertainty highlights the need for cautious interpretation of any comparative results based on the identified studies.

Table 10 Comparator studies included in the ITC (adapted from Tables 14 – 17, Appendix D, CS; and Table 14, pg. 52, CS)

Study	Intervention	Number of participants	Location	ECOG 0/1, %	No. of prior therapies, median (range)	Months on prior BTKi, median, (range)	Response to prior BTKi	MIPI Intermediate/ High, %	Prior auto stem cell transplant	Morphological variant, blastoid, %	Median OS, mo (95% CI)	Median PFS mo (95% CI)	ORR, n (%)
ZUMA-2 (mITT)	KTE-X19	68	US, Germany, France and the Netherlands	100%	3 (1-5)	7.0	38%	56%	43%	25%	n/a	n/a	n/a
Dreyling 2016	Subsequent therapy (Mixed)	40	21 countries	99%	2 (1–9)	14.4 (IQR: 15.1)	72%	Simplified MIPI 69%	-	12%	-	-	8 (20)
Epperla 2017	Subsequent therapy (Mixed)	29	US	(At diagnosis) 86%	2 (1–8)	-	45%	44%	39%	16%	-	-	14 (48)
Eyre 2019	Venetoclax	20	UK	55%	3 (2–5)	4.8 (0.7–34.8)	55%	Simplified MIPI 80%	30% (consolidation at first remission)	20%	9.4 (1.5–NR)	3.2 (1.2–11.3)	(53)
Jain 2018	Salvage therapy (Mixed)	36	US	-	3 (1–11)	8 (0.3–59)	NR	92%	-	36%	From BTKi Discontinuation 10 (Range: 0.9–52.7)	-	(27)
Martin 2016	Subsequent therapy (Mixed)	73	US, UK, Germany & Poland	-	3 (0–10)	4.7 (0.7–43.6)	51%	71%	16%	16%	5.8 (3.7–10.4)	1.9 (1.0–2.6)	18 (25)
McCulloch 2019	R-BAC	29	UK & Italy	-	2 (1–6)	-	62%	(At diagnosis) 81%	38% (post induction)	(At diagnosis) 24%	12.2	8.6	25/28 (89)
Regny 2019	RiBVD	12	France	-	-	-	-	-	-	28%	-	-	8 (66)

Wang 2017	Lenalidomide-based (Mixed)	58	US & UK	48%	4 (1–13)	4.3 (0.5–47.6)	45%	-	-	-	-	-	17 (29)

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison; IQR, interquartile range; MIPI, Mantle Cell Lymphoma International Prognostic Index; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival R-BAC, Rituximab-Bendamustine Cytarabine; RiBVD, Rituximab-Bendamustine, Velcade, Dexamethasone;

Blended comparator

The ERG understands the company's approach to generating a blended comparator based on clinical advice received by the company regarding there being no established standard of care in the post-BTKi setting. However, the ERG disagrees with the approach for a number of reasons. The approach generates OS and PFS from pools of studies, some reporting only PFS or OS. The ERG considers it inappropriate to base the economic model on PFS and OS taken from separate studies, only those identified studies providing both OS and PFS are appropriate for pooling to preserve correlation. The two studies providing these data are McCulloch 2020[1] and Eyre 2019.[11] Clinical advice to the ERG considered the majority of post-BTKi MCL patients in the NHS to be receiving R-BAC. McCulloch recently evaluated R-BAC in a UK setting and so was considered an appropriate comparator study. Eyre was not considered an appropriate study for inclusion due to the study using Venetoclax, an intervention not currently licensed in the NHS for MCL.

Of the other comparator studies, the ERG has concerns regarding the generalisability of the results of Epperla 2017,[13] Jain 2018,[14] and Regny 2019[17] given these studies were conducted entirely in countries other than the UK. The ERG considered the use of McCulloch alone to be the most appropriate, not only as a result of it being the only relevant study with appropriate survival data and it being conducted with R-BAC in the UK, but it also avoids issues around the heterogeneity of the identified studies. The company's approach results in the pooling of highly heterogeneous studies. The extent of the heterogeneity across the included interventions alone is evident in Table 10 in which studies evaluating R-BAC; Rituximab, Bendamustine, Velcade, Dexamethasone (RiBVD); Venetoclax and mixed therapies are pooled. Additional heterogeneity is evident in the locations in which the studies were conducted. The ERG does not consider this pooling to be a suitable approach given the company did not formally assess heterogeneity and subsequently combined the studies in a fixed-effects meta-analysis (see Section 3.4.1).

Allo-SCT

Allo-SCT appears to be part of the clinical pathway after R-chemotherapy, although there is limited information on the use of allo-SCT in the post-3rd line MCL setting. In McCulloch 2020, 31% received allo-SCT post-R-BAC.[1] The CS states this may not be reflective of clinical practice as allo-SCT may be saved for patients in remission to consolidate outcomes. The ERG agrees with this and considers there is uncertainty around the generalisability of McCulloch to the NHS as a result.

3.3.2 **Baseline patient characteristics**

Baseline characteristics of post-BTKi MCL patients in the included studies can be seen in Table 10. The results show considerable difference across the median number of prior therapies (range 2-4);

months on prior BTKi (range 4.3 – 14.4 months); response to prior BTKi (45-72%) and % with intermediate and high MIPI (range 44 – 92%). In addition to the differences across the pooled studies, there appear to be material differences between the baseline characteristics of the identified studies and ZUMA-2 patients. Full baseline characteristics are presented in Appendix D, CS.

As detailed in 3.3.1, the ERG considers McCulloch to best represent the patient population in the NHS. The comparison of the ZUMA-2 population to McCulloch 2019 shows McCulloch has a lower median number of prior therapies, a higher response to prior BTKi, a higher proportion of intermediate/high MIPI, and broadly similar proportion of prior ASCT and blastoid variant. In addition, following contact with the authors of McCulloch 2020, the ERG understands no patients enrolled in the McCulloch study had CNS involvement, [22] which matches ZUMA-2.

Points for critique

The pooled populations do not appear to be comparable across studies in terms of key prognostic factors such as MIPI, number of prior therapies and time on prior BTKi, which could be used as a proxy to represent time of remission in prior BTKi. The apparent heterogeneity in important baseline characteristics across studies raises issues about the validity of the results of the blended comparator particularly when considering the company's approach to using a fixed-effects meta-analysis.

There also appears to be limited overlap among the baseline characteristics, considered as effect modifiers, between ZUMA-2 and the SoC studies. A key assumption in indirect comparisons is that populations are comparable across all included studies (i.e. the consistency, or transitivity, assumption). This assumes comparators do not differ with respect to the distribution of known treatment effect modifiers. This assumption clearly does not hold when comparing the characteristics of the studies informing the blended SoC to ZUMA-2. The ERG is concerned about this lack of consistency when naïve comparisons are made between intervention and comparator. MAIC relaxes this assumption by adjusting for prognostic covariates but the extreme reduction in the ESS again shows the limited comparability of the SoC and ZUMA-2 populations (see Section 3.4.2.2 for further discussion). The baseline characteristics presented in Table 10 and the reduction in ESS in the MAIC, show McCulloch and the blended comparator both have limited overlap with the ZUMA-2 population.

Despite some uncertainty highlighted by the company's clinical advisors regarding how representative McCulloch is given the proportion of allo-SCT, the McCulloch population appears more representative of the relevant post-BTKi population due to it being a recent observational study conducted mostly in the NHS. This has implications for the indirect treatment comparison approach and the validity of the results (see Section 3.4).

3.4 Critique of the indirect comparison

The company compared the effectiveness of KTE-X19 to SoC treatments using the individual patient data from ZUMA-2 and extracted time-to-event data (PFS and OS), response data, and baseline characteristics from the identified SoC studies (see Section 3.3 for description of the studies). Extracted survival and response data of SoC studies were pooled via meta-analysis (MA). The single-arm results from ZUMA-2 and the pooled estimates for SoC were compared in unadjusted comparisons and matching-adjusted indirect comparisons (MAICs). The company's base-case for the cost-effectiveness analysis was based on the unadjusted comparison, whilst the MAIC did not inform the company's base-case or any scenario analyses. A description and critique of these methods and approaches is provided below.

3.4.1 **Meta-analysis**

In their base-case, the company fitted standard parametric models to the data of two SoC studies for PFS[11, 16] and four studies for OS.[11, 14-16]

The company's approach consisted of three steps. First, the company digitised the published Kaplan-Meier curves and recreated the individual patient-level data (IPD). Second, standard parametric models were applied to the digitised IPD. In the third step, the shape and scale parameters and correlation between the parameters which were estimated with the parametric models were synthesised in a multivariate meta-analytic framework.[23]

The company conducted fixed- and random-effects meta-analysis. The fixed-effects meta-analysis assumes that all SoC studies are estimating the exact same shape and scale parameters and any difference between them is purely due to chance. In contrast, the random effects meta-analysis accounts for the heterogeneity across the SoC studies by assuming that the study-specific shape and scale parameters are not equivalent, but only normally distributed. The variance of the normal distribution is indicative of the between-studies heterogeneity. The company rejected the random-effects analysis because the confidence intervals of the survival curves included values beyond the range of 0-1. Therefore, only results of fixed effects meta-analyses were presented in the CS.

Points for critique

Parametric model selection

The main limitation of the company's approach to combining survival data from a number of studies is that it requires that the same parametric model be used for all SoC studies, so that the same survival model parameters are subsequently meta-analysed. If one specific parametric model is the best fitting model to all of the individual studies, then this approach is reasonable. However, if the best fitting

models are different across the individual SoC studies, the company's approach implies that suboptimal models are used to extrapolate the PFS and OS for SoC. Given the small sample size, limited follow-up and heterogeneity of the individual studies, this contributes to the uncertainty in the estimates of long-term survival of SoC.

In the CS, the choice of the best fitting survival model was based on the sum of the AICs, for each survival model, across all SoC studies. The ERG considers that adding up the AICs might provide useful information for a global model fit, however in the ERG's opinion the preferred approach would be to have each curve fitting the KM data well as the individual AICs are more meaningful than their sum. Importantly, the company's approach implies that studies containing more information will be given more weight as these studies would naturally yield higher information criteria and hence drive model selection.

Fixed-effects model

The ERG considers that the company's chosen fixed-effects model is imposing the assumption that all SoC studies are estimating the same survival model parameter and any differences among them are attributed only to chance. However, this is unrealistic given the evident heterogeneity present across SoC studies, most apparent in the interventions assessed (see Section 3.3). The company dismiss the random effects models because "the 95% confidence interval (CI) around the survival curve had a lower and higher bound of 0 and 1, respectively, which was not interpretable". This could perhaps be attributed to the low number of SoC studies which prevents the between-studies heterogeneity from being appropriately estimated. In principle, the company could have tried to impose an informative prior on the heterogeneity parameter to assist its estimation.

The approach to weighting the trials in the fixed-effects model poses a number of additional issues. First, the assumption of a fixed-effect weights trials purely based on the standard error. The largest trial may not be the most reflective of the trial population or the NHS population. For instance, the CS reported 60-70% of patients are treated with R-BAC in the post-BTKi setting. The one trial assessing R-BAC is McCulloch 2020,[1] yet with a small sample size this trial will have a relatively small weighting in the MA. Second, it is unclear how the approach reflects the changing number of patients at risk over time in the individual studies. Third, studies with longer follow up will have data points beyond those with shorter follow-up, yet it is unclear how these contribute data to the MA. For example, if two studies, one of 6 months follow-up and one of 12 months follow-up are weighted equally, it appears the long study providing all of the information from 6-12 months will be weighted by 50%. The ERG considers there to be uncertainty in this approach that is not adequately reflected in the CS.

3.4.2 Indirect Treatment Comparison

Given then existence of only single-arm studies for KTE-X19 and SoC the company was unable to conduct any mixed treatment comparisons. Instead, naïve (unadjusted) comparisons and MAICs were conducted as described in Section B2.9.1, pg. 63 and Appendix D of the CS.

3.4.2.1 Naïve comparison

In their base-case, the company uses an unadjusted comparison of KTE-X19, based on ZUMA-2 data, *versus* SoC, based on the meta-analysed comparator studies. The results of the naïve comparison can be found in Section B.2.9.2.2 and B.2.9.2.3 of the CS. In summary, the HR for death (from the OS comparison) is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19. Note, this is based on the pooled results of all four studies[11, 14-16] providing OS data. The HR for progression or death (from the PFS comparison) is estimated at [redacted] (95% CI: [redacted]) in favour of KTE-X19. This is based on the pooled results of the two studies providing PFS data.

Points for critique

The ERG considers the company's approach to presenting naïve results to be understandable given the considerable uncertainties present in the results of the MAIC (see Section 3.4.2.2). However, the company's naïve comparison is subject to very strong, untestable, assumptions and should be used and interpreted with caution. Specifically, naïve comparisons assume conditional constancy of the absolute effects. This means that the absolute treatment effect between KTE-X19 and SoC is assumed constant at any given level of the effect and prognostic variables and that all effect modifiers and prognostic variables are known and accounted for. This assumption is very hard to meet and much stronger than the assumption of conditional constancy that is imposed by MAICs.[24] Therefore, the ERG considers that the naïve comparison between ZUMA-2 and the meta-analysed studies for SoC is subject to high uncertainty.

Further, in the company's response to PfC (Table 12, pg.37, PfC), the baseline characteristics of ZUMA-2 and McCulloch 2020 can be compared. Although the table does not report the % of patients with high MIPI, it can be inferred that this is the complement of the reported low and intermediate MIPI. This table implies that in ZUMA-2, 13.7% of patients had a high MIPI, compared to 57.1% in McCulloch. Given that MIPI is one of the best assessments of prognosis (see Section 2.1.2), this implies that the McCulloch patients have worse disease prognosis at baseline compared to ZUMA-2. If McCulloch patients are more representative of the NHS patients who are expected to receive KTE-X19 (see Section 3.3.1), it can be inferred that the unadjusted comparison may overestimate the relative effect of KTE vs SoC.

3.4.2.2 MAIC

The list of prognostic baseline characteristics used to re-weight the ZUMA-2 IPD were identified via a targeted literature review. The six prognostic characteristics were: number of prior therapies; prior ASCT; duration on prior BTKi; response to prior BTKi; MIPI; and morphological variant.

The company conducted several MAIC analyses, matching the ZUMA-2 baselines characteristics to the baseline characteristics of different subsets of the SoC studies (See Table 18, pg. 66 of the CS). All these analyses result in very low effective sample size (ESS) ([redacted]) for PFS and OS scenarios.

Lognormal parametric survival curves were fitted to the re-weighted ZUMA-2 data using the same method as the meta-analysis (see Section 3.4.1). OS and PFS curves were estimated up to 33 months. The MAIC results for KTE-X19 compared to SoC can be seen in full in Section B.2.9.2.2 and B.2.9.2.3 of the CS.

As the MAIC was not used to inform the company's cost-effectiveness model, the results are not discussed further in the ERG report. For details of these results, see Section B.2.9, CS.

In response to clarification questions (Question A10) the company conducted an additional MAIC against McCulloch 2020. This again resulted in a very low ESS of [redacted] (See Table 12 in the response to PfC). The results of this MAIC are presented in Table 11.

Table 11 MAIC of KTE-X19 and McCulloch 2020

	Observed ZUMA-2	Weighted ZUMA-2	McCulloch 2020
N / ESS	68	[redacted]	36
No. of prior therapies	3.3	[redacted]	2
Prior ASCT, %	42.6	[redacted]	41.7
Prior BTKi ORR, %	38.2	[redacted]	58.3
MIPI low, %	42.4	[redacted]	19.2
MIPI intermediate, %	43.9	[redacted]	23.1
Blastoid variant, %	25	[redacted]	19.4

Key: ASCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; ESS, effective sample size; MIPI, Mantle Cell Lymphoma International Prognostic Index; mITT, modified intent-to-treat; ORR, overall response rate.
Notes: Grey cells present characteristics included in the matching; a, matched on median of each scenario.

The results of the updated MAIC-adjusted and naïve ZUMA-2 PFC and OS results compared to the McCulloch 2020 data can be seen in Figure 5.

Figure 5: McCulloch et al (2020)-MAIC-adjusted ZUMA-2 mITT survival data plus digitised KM data from McCulloch 2020 (reproduced from Figure 7, PfCs)

Points for critique

Limited evidence base

The company dismisses the MAICs on the grounds of low ESS. The ERG agrees with the company's cautious interpretation of the results from the MAIC and that basing any analyses on an ESS of approximately [redacted] is extremely uncertain. However, it is important to highlight that the dismissal of the MAIC on the grounds of ESS may imply that there is a limited overlap among the baseline characteristics, considered as effect modifiers, of ZUMA-2 and the SoC studies. This argument is equally pertinent to the company's preferred naïve comparisons where it is not addressed at all.

A central judgement about the most appropriate analysis relates to the population that better reflects the UK patients expected to be eligible for KTE-X19. If this population is expected to be more similar to the ZUMA-2 patients, then MAICs are inappropriate to start with. If, however, this population is expected to be more similar to the SoC studies, then MAICs are relevant. Nonetheless, the ERG considers that the MAIC results are relevant to inform the assessment of whether and to what extent the relative effectiveness results of a naïve unadjusted comparison are at risk of bias.

MAIC of McCulloch and KTE-X19

As outlined in Section 2.1.2, the ERG considers the McCulloch data to best represent the relevant population and comparator in this appraisal. The use of survival data from McCulloch only to inform

the MAIC also circumvents the reliance on the restrictive and uncertain method of pooling survival data presented in the company's approach to meta-analysing survival data (see Section 3.4.1). In addition, the use of McCulloch only ensures PFS and OS are sourced from the same study and any correlation between them is preserved (see Section 4.2.6). Finally, this approach excludes survival data of Venetoclax, which is not currently licensed in the UK (see Section 3.3.1).

Although the ERG prefers comparisons with McCulloch et al (2020)[1] only, the ERG agrees with the company's concerns regarding the extreme reduction in the ESS and any results being highly uncertain when MAICs are considered. The results are potentially less favourable to KTE-X19 after adjustment compared to no adjustment (illustration of differences in survival outcomes between MAIC and naive using KM curves/small table), though the lack of randomised head-to-head comparison, differences in observed and unobserved prognostic factors, difference in study designs, very small sample sizes, immaturity of data means that the magnitude and direction of bias in both adjusted and naive comparisons between KTE and R-BAC are extremely uncertain.

Covariate selection

The ERG considers the company's approach to selecting covariates to be reasonable. Age and ECOG status, which are very important prognostic variables, are not included in the company's final list. This is appropriate as these variables are used to calculate MIPI which is included.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG verified the company's ITC methods and code. No additional analyses were carried out.

3.6 Conclusions of the clinical effectiveness section

- The submitted evidence reflects the decision problem defined in the final scope, although in a narrower population (subset of post-BTKi patients, as per the anticipated licence).
- The evidence for KTE-X19 is based on a cohort of a single-arm, multi-centre, non-randomised trial of 74 patients. Although the results of the ZUMA-2 trial look promising in a hard-to-treat population with poor prognosis, the ERG believes the CS is supported by very limited evidence of safety and efficacy of KTE-X19.
- The population included in the company trial is likely to be younger and fitter than the general population of r/r MCL patients, although they are likely to have undergone more prior therapies. Due to concerns about patient selection, representativeness of patient characteristics and limited evidence, the ERG have concerns regarding the generalisability of the trial population to the population who would be eligible to KTE-X19 in the NHS under the anticipated licence.

- Evidence from the only trial supporting the CS is very immature: median PFS and OS were not reached and median follow-up was [redacted] months. The long-term efficacy of KTE-X19 is highly uncertain and there is currently insufficient evidence to show a curative effect in a subset of patients.
- The limited evidence means that the precision and magnitude of effectiveness and safety outcome estimates are highly uncertain.
- The lack of randomised comparison means that the relative efficacy and safety of KTE-X19 compared with standard of care is also highly uncertain.
- Comparative evidence is very limited. Most is non-randomised and of limited relevance to the NHS. Therefore, the ERG believe that the company's approach of pooling comparative evidence as a basket standard of care is inappropriate.
- Due the limited evidence for KTE-X19 and standard of care, standard network meta-analyses were not feasible. MAIC and naïve indirect comparisons conducted by the company are significantly limited by the paucity of evidence and are subject to significant risk of bias and uncertainty.
- Overall, although promising, the evidence provided by the company for the relative efficacy and safety of KTE-X19 compared with standard of care in patients with r/r MCL with prior BTKi therapy is highly uncertain. There is insufficient evidence to support the assumption that KTE-X19 may lead to a lifetime remission in a subset of patients.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company's methods for reviewing the cost-effectiveness literature are outlined in Appendix G of the company submission. The company did not identify any studies that evaluated the use of KTE-X19 in r/r MCL. However, the company identified 12 additional studies and one NICE appraisal that evaluated alternative treatments for r/r MCL, one of which was the NICE TA502,[25] evaluating ibrutinib for treating r/r MCL. Of the 12 studies, 8 used Markov state or partitioned survival models with pre-progression, post-progression and death states, 2 studies included Markov state or partitioned survival models but did not specify the structure, 1 study used a budget impact model, and 1 did not specify the model type. The characteristics of the included studies are summarised in Tables 53 and 54 of Appendix G of the CS, while the TA502 is summarised in Table 27 of the company submission. The company only used the TA502 to guide the development of their model, citing consistency across NICE evaluations as the reason.

4.1.1 Points for critique

The ERG is satisfied with the company's review of the cost-effectiveness evidence. The searches were likely to have identified relevant cost-effectiveness studies on the treatment of r/r MCL in patients who have had at least one previous treatment. The publications are restricted to those published in English, but the ERG deems this to be acceptable. According to Table 53 of Appendix G, TA502 appears to better match the decision-making context of this appraisal (UK NHS and Personal Social Services perspective) than the remaining 11 studies, hence the ERG agrees with the company's use of TA502 to inform their submission.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	The CS is appropriate.
Perspective on costs	NHS and PSS.	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes	The CS is appropriate.

	between the technologies being compared.	Patients enter at the age of 63.2 years old and a maximum age of 100 is assumed.
Synthesis of evidence on health effects	Based on systematic review.	The CS is appropriate.
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.	The CS is appropriate. HRQoL was measured with EQ-5D-5L. The EQ-5D-5L data was mapped to EQ-5D-3L values with the van Hout et al algorithm.[26]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	The CS is appropriate. HRQoL was obtained directly from patients in the ZUMA-2 trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	The CS is appropriate.
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.	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	The CS is appropriate in the base-case. Alternative discount rates were explored in scenario analyses. However, the ERG thinks that the conditions for using lower discount rates are not met.
EQ-5D, standardised instrument for use as a measure of health outcome. HRQOL, health-related quality of life; PSS, personal social services; QALYs, quality-adjusted life years;		

4.2.2 **Model structure**

The company submitted a partitioned survival model that simulates the long-term outcomes of 3rd line r/r MCL patients (who received ibrutinib at 2nd line) over their lifetime. Patients receive either KTE-X19 or standard of care (SoC). SoC consists of multi-agent chemotherapy and is modelled as a blended comparator in the base-case. The company justified their model structure based on the progressive nature of disease (patients cannot return to a better health state once they have suffered health deterioration to further states), and on consistency with previous economic modelling of CAR T-cell therapies[27] and NICE CAR T-cell appraisals (TA559,[28] TA567[29]).

The model has three mutually exclusive health states: pre-progression, post-progression, and death (Figure 6). In partitioned survival models, the proportion of patients in each health state is determined

directly from the survival curves. All patients enter the model in the pre-progression health state. The PFS curve directly informs the proportion of patients remaining in the pre-progression state. The proportion of patients who are in the post-progression state corresponds to the difference between the proportion of patients alive (given by the OS curve) and the proportion of patients in the pre-progression state (given by the PFS curve). Each model cycle has a monthly duration. A half-cycle correction is applied for most costs and outcomes except the acquisition and administration costs of KTE-X19 and the costs and HRQoL of AEs (except intravenous immunoglobulin (IVIG)) and subsequent allo-SCT, which are all added at the start of the model.

Figure 6: Model diagram

[redacted]

[redacted]Figure adapted from the company's model,

[redacted]

The model incorporates the costs of leukapheresis and conditioning chemotherapy of the patients who received these but who did not proceed to KTE-X19 infusion (n=6) using cost multipliers. In response to PfC B1, the company submitted a scenario where the health outcomes and long-term costs of the patients who did not proceed to KTE-X19 infusion, in line with TA554[30] and TA567.[29] In this scenario, the model assumes that the patients who did not receive KTE-X19 due to manufacturing failure or ineligibility have the same health outcomes and costs as patients who received SoC (the ICER increases by £64/QALY).

Points for critique

The ERG considers that the company's model structure – a partitioned survival model including the long-term outcomes of patients who did undergo KTE-X19 infusion - is appropriate for decision making and notes that it is consistent with the previous TAs for CAR T-cell[28-30]therapies. Partitioned survival models are easy to implement and generally predict trial endpoints well for the within-trial period. The drawback is that partitioned survival models assume structural independence between OS and PFS, which implies that the extrapolation of an endpoint reflects the within-trial trend of that endpoint alone, and it may lead to logical inconsistencies between PFS and OS.[31] Furthermore, partitioned survival models may not represent uncertainty appropriately and have limited flexibility to explore alternative assumptions related to the duration of treatment effect.[31] A multi-state survival model could have potentially been more appropriate, given that these models make explicit structural links between health states, and jointly estimate transitions based on the OS, PFS and time from progression to death data. Nonetheless, both approaches share the same challenge in terms of estimating robust extrapolations over a long period of time into the future based on the immature trial data.

The ERG prefers the scenario which includes the long-term health outcomes and costs of patients who did not receive KTE-X19 over the company's base-case where these are omitted. As discussed in Section 2.1.3, the treatment pathway with KTE-X19 starts with the collection of T-cells from patients by leukapheresis. Following leukapheresis, some patients may not receive KTE-X19. In ZUMA-2, 3 patients did not proceed to infusion due to manufacturing failure, 2 due to death following disease progression and 1 patient was not treated following conditioning chemotherapy because it was found to be ineligible (i.e. 8% (6/74) of patients in ZUMA-2). In the company's base-case, the costs of leukapheresis and of conditioning therapy in patients who did not have KTE-X19 are included, while long-term health outcomes and costs were not. For consistency, and in line with the approach taken in the previous TA's for CAR T-cell therapies,[29, 30] the model should consider not only the short-term costs but also the long-term health outcomes and costs. For this reason, this is the approach implemented for the ERG's base-case (see Section 6.1.1).

item 1. The ERG considers that the model should include the outcomes and costs of all patients who were started in the KTE-X19 treatment pathway.

4.2.3 Population

The population in the decision problem is adults with r/r MCL who have previously received a BTKi, in accordance with the anticipated licensed indication for KTE-X19. In the company's model, the population corresponds to the patient population in ZUMA-2 mITT (of Cohort 1; see Figure 1). Their characteristics at model entry (that is, at treatment with KTE-X19) are summarised in Table 13.

Table 13: Population characteristics at model entry

Model parameter	Value	Source
Mean age, years	[redacted]	ZUMA-2 trial (24th July 2019)
Percentage female	[redacted]	ZUMA-2 trial (24th July 2019)
Average BSA (m^2)	[redacted]	The average body surface area is calculated using weight and height of patients enrolled in the ZUMA-2 trial (24th July 2019) based on the DuBois formula.
Average body weight (kg)	[redacted]	ZUMA-2 trial (24th July 2019)

Information obtained from the company's model, [redacted]

Points for critique

As discussed in Section 3.2.1, the ERG considers that there is uncertainty in generalisability of ZUMA-2 patients to the patients who are expected to be eligible for KTE-X19 in the UK. In the absence of additional evidence, the ERG believes it is reasonable to use the baseline characteristics of the patients in ZUMA-2 in the model. One characteristic with potentially high impact on the results is age. For example, an increase in average age by 5 years (from 63 to 68 years), [redacted] the ICER by [redacted]. This impact is driven mostly by the general population mortality risk, which is used to inform the mortality risk of the long-term survivors in the company's base-case and as a minimum bound to the mortality risk when other approaches to the extrapolation are employed. This is an area of uncertainty, the impact of which depends on to what extent the age of the patient population in clinical practice departs from the patients in ZUMA-2. This is explored in the scenario analysis to the ERG's base-case (see Section 6.1.1).

item 2. The ERG considers that there is uncertainty regarding the generalisability of the ZUMA-2 population to the UK patient population, and specifically around the age at treatment.

4.2.4 Interventions and comparators

The intervention is KTE-X19, as per the decision problem. Treatment with KTE-X19 involves leukapheresis, conditioning therapy, and infusion, with some patients requiring bridging therapy to support them until the KTE-X19 is ready for infusion. The company included retreatment with KTE-X19 given that 2 patients in ZUMA-2 were retreated. However, the company notes that retreatment is not anticipated in clinical practice.

The comparator is standard of care (SoC) in the absence of KTE-X19. Based on the BSH Guidelines and clinical expert advice, the company concluded that there is no treatment which can be considered the SoC for patients following 2nd line BTKi (ibrutinib) failure. Therefore, the company considered that SoC comprises the regimens recommended at first line in the BSH guidelines and included in the

TA502 scope. In their base-case, the company represents the SoC as a blended comparator comprising 65% RBAC, 30% R-bendamustine, and 5% R-CHOP for the calculation of treatment costs (see Section 4.2.9.2). The company based these weights on clinical expert opinion.[32]

Points for critique

The ERG considers the company's approach with respect to the intervention to be appropriate and consistent with the decision problem, with the exception of the inclusion of retreatment. Given that retreatment is not anticipated to be available in clinical practice, the ERG considers that the intervention should not include retreatment.

For the comparator, the choice of rituximab-chemotherapy as the SoC is appropriate. The ERG's clinical advisors considered that the current standard of care is R-BAC in most centres, although some may receive R-CHOP or R-Bendamustine. The ERG notes that the composition of the SoC is only relevant for costs. Since SoC treatments are relatively similar in terms of costs (Table 56 in CS), this assumption is not expected to materially impact the ICER. Given that the ERG's alternative base-case uses a study where all the patients received R-BAC to inform the outcomes of SoC (McCulloch et al,[1] see Section 4.2.6.2; item 8) and the ERG's clinical advice, the ERG base-case assumes that SoC consists of R-BAC for the purposes of costs (see Section 6.1.1).

4.2.5 Perspective, time horizon and discounting

The model adopts the NHS and Personal Social Services perspective. In the company's base-case, the model discounts costs and outcomes at 3.5%, in line with the NICE reference case, and adopts a lifetime time horizon. Sensitivity analyses use lower discount rates, and shorter time horizons. The company did not make a case for lower discount rates to be applied.

Points for critique

The ERG considers the company's approach to the perspective and time horizon to be appropriate. The discount rates in the base-case are appropriate and in line with the NICE reference case, but the scenario which uses a lower discount rate on costs and benefits was not justified. The ERG notes that the NICE Committee concluded that lower discount rates were not applicable in TA567.[33] The NICE Methods Guide recommends that a discount rate of 1.5% for costs and benefits may be considered if the treatment restores people, who would otherwise die or have a very severely impaired life, to full or near full health and when this is sustained over a very long period (normally at least 30 years) and the treatment does not commit the NHS to significant irrecoverable costs ([34]). The ERG considers that the evidence does not support lower discount rates, because (i) the evidence is not sufficiently mature to robustly demonstrate that KTE-X19 restores patients to full or near full health, (ii) the duration of health benefits is highly uncertain, and (iii) sustainability of the health benefit over at least 30 years appears unlikely given the age of the r/r MCL population who are likely to receive this treatment.

4.2.6 Treatment effectiveness and extrapolation

Table 14 provides a summary of the survival distributions and data sources used in the company's base case analysis for OS and PFS. For KTE-X19, the base-case uses mixture cure models for PFS and OS using the individual patient data from ZUMA-2 (24th July 2019 cut-off date, mITT, n=68).

For SoC, the company's base-case is based on fixed-effect multivariate meta-analyses[23] of the shape and scale parameters of the lognormal distribution of four studies for OS[11, 14-16] and two studies for PFS.[11, 16]

Table 14: Summary of survival distributions and sources applied in the company's base-case

Intervention	Overall survival	Progression-free survival
KTE-X19	Lognormal mixture cure model using the ZUMA-2 data	Lognormal mixture cure model using the ZUMA-2 data
Standard of Care	Based on a multi-variate meta-analysis of the lognormal shape and scale parameters of [11, 14-16]	Based on a multi-variate meta-analysis of the lognormal shape and scale parameters of[11, 16]

The PFS and OS curves in the model are based on naïve indirect comparisons between ZUMA-2 and the studies informing SoC. The MAIC analyses, which adjust ZUMA-2 to match the characteristics of the SoC studies at baseline (see Section 3.4.2.2), were not used to inform the model. The company justified their exclusion given the low ESS of the MAIC-adjusted ZUMA-2 (ranging between [redacted] and [redacted]) and because the survival projections of the MAIC-adjusted indirect comparison were thought to be similar to those of the naïve comparisons.

***[redacted]7 shows the original Kaplan-Meier curves for OS and PFS for KTE-X19 and their base-case extrapolation as well as the base-case OS and PFS extrapolations for SoC. Under the company's base-case, the OS and PFS curves with KTE-X19 are similar to the Kaplan-Meier curves from the ZUMA-2 trial up to the end of the trial follow-up at [redacted] months. The closest time point in the model is [redacted] months, when the cohort is [redacted] years). At this point, [redacted]% of the cohort remains in the pre-progressed state and [redacted]% has died. Of the [redacted]% who remain alive, [redacted] are in the long-term survivor fraction predicted by the lognormal mixture cure model and are only at risk of the general population mortality, adjusted with a standardised mortality ratio (SMR) – hence the change in the curve at around this point in time. For SoC, OS and PFS drop quickly; at [redacted] months from the start of treatment, [redacted]% of the patient cohort remains in the pre-progression state; [redacted]% are in post-progression and [redacted]% have died. Kaplan-Meier curves are not shown because the OS and PFS curves are based on a meta-analysis of survival models.

[redacted] 7

[redacted]

Adapted from figure 55 of the CS; pg139

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

4.2.6.1 KTE-X19

The company's base-case uses mixture cure models to inform the proportion of long-term survivors and the time to progression and time to death of the non-long-term survivors. The model assumes that, immediately after KTE-X19 treatment, the long-term survivors experience the general population mortality risk, adjusted upwards with an SMR obtained from a study in DLBCL.[35]

The company justified the use of mixture cure models given that, in their view, the standard parametric models provided poor visual fit resulting often in implausible extrapolations, and based on their belief that a proportion of the patients treated with KTE-X19 will experience a durable long-term survivorship. The company justified the belief in long-term survivorship because this assumption was accepted in the previous TAs for CAR T-cell therapies used in other indications (TA554, TA559 and TA567), and given clinical feedback that "*it is not unreasonable to expect there will be long-term survivors, although this is uncertain given it is based on early data*"[32] (p3).

In their response to PfC B2, on the plausibility of a long-term survivor fraction, the company acknowledged that currently there is no evidence of long-term survivorship in r/r MCL post-KTE-X19: "*Data on the long-term survival prospects for post-ibrutinib MCL patients who benefit from KTE-X19 infusion are absent and will only accrue with the passage of time*." (PfC p51). In the

company's view, this may be due to the efficacy of SoC rather than due to the nature of the disease: "*It could be that one type of B-cell lymphoma is, inherently, incurable and the other is not. However, this seems less plausible than the argument that the existing treatments for DLBCL are better than those for relapsed MCL, where different and better therapies are needed"* (PfC p53). Furthermore, the company argues that the CR rate (at [redacted]% of mITT patients) and the proportion of patients with no detectable disease in ZUMA-2 suggest that long-term survival is plausible.

In the original submission, the company explored only standard parametric models as an alternative to mixture cure models. In response to the PfC B4, the company implemented cubic spline models with 1 and 2 knots. The company also explored general mixture models and notes that they did not pass face validity tests, some did not converge, and some collapsed to a standard parametric model. The results of the general mixture models are reported in their response to PfC B4, but the company did not incorporate them in the cost-effectiveness model. The company did not implement landmark models because the company thought that the data were insufficient to apply them.

The company assumed that the risk of death of long-term survivors corresponds to the age- and sex-matched general population mortality risk, adjusted with a SMR of 1.09, implying that long-term KTE-X19 survivors experience a 9% higher probability of death compared to the general population. This mortality adjustment was obtained from Maurer et al, a study in DLBCL patients [35] which was used in TA559 .[28] The company used the adjustment to reflect the impact of prior lines of treatment on survival. The company conducted scenario analysis where long-term KTE-X19 survivors are not subjected to additional mortality compared with the general population, with a minor impact on the ICER. The SMR was also varied in one-way sensitivity analyses.

In response to PfC B2, on the justification for using a mortality adjustment from DLBCL, the company reemphasised that this value was used in TA559.[28] In PfC B2, the ERG asked the company to comment on whether the study by Eskelund et al,[2] on the 15-year follow-up of patients with newly diagnosed MCL who were treated with autologous SCT, could be used to inform the excess mortality risk of long-term survivors. The company responded that Maurer et al[35] was more appropriate to inform the excess mortality risk because (i) neither study was in r/r MCL patients (Maurer et al was in DLBCL and Eskelund et al was in newly diagnosed MCL following autologous SCT); (ii) Maurer et al[35] had a larger sample size (N=767 in the primary dataset and N=820 in the validation dataset compared to N=159 in Eskelund et al[2]); (iii) Maurer et al[35] reports the SMR and confidence intervals whereas Eskelund et al[2] did not report these values and deriving these from data reported in the study would require assumptions and additional analyses.

KTE X19: Progression-free survival

For PFS, the lognormal mixture cure model provided the best statistical fit to the observed PFS data in terms of AIC and BIC amongst the fitted models (Table 35; CS p116) and was therefore selected for the base case analysis. The lognormal mixture model estimated that [redacted] were long-term survivors. Among the alternative mixture cure models, the range of the estimated long-term survivor fractions was [redacted] (exponential) - [redacted] (Weibull). The company noted that all but the generalised gamma model provided a good fit and yielded similar long-term projections.

KTE-X19: Overall survival

Given that the lognormal model was selected for KTE-X19 PFS, the company selected the lognormal model for OS in their base-case for consistency. The lognormal mixture models predicted a long-term survivor fraction of [redacted] for OS. Scenario analyses explored the most optimistic (Weibull – estimated long-term survivor fraction: [redacted] and pessimistic (exponential – estimated long-term survivor fraction: [redacted] models. As with PFS, the company explored only standard parametric models and mixture cure models in their original submission and provided results of cubic spline models in response to the ERG's PfC B4. The results of all the attempted modelling approaches for OS and PFS can be found in Table 19 of the response to PfC.

Points for critique

The CS was clear in detailing the company's survival analysis to inform the OS and PFS with KTE-X19. The survival models are well implemented in the cost-effectiveness model. However, the ERG has a number of concerns regarding (1) the uncertainty in the ZUMA-2 data, (2) uncertainty regarding the long-term survivorship in r/r MCL, (3) appropriateness of mixture cure models and uncertainty in the long-term survivorship fraction, (4) uncertainty in the extrapolation of PFS and OS, and (5) appropriateness of informing the additional risk of death experienced by long-term survivors compared with the general population from DLBCL. These are discussed below in turn.

1. *Uncertainty in the ZUMA-2 data*

The ERG considers that the ZUMA-2 data are associated with considerable uncertainty. As discussed in Section 3.2.1, ZUMA-2 is a small single-arm trial (the n=68 patients who received KTE-X19 are a subset) over a short follow-up (median follow-up= [redacted] months; maximum follow-up = [redacted] months). Censoring is high; for example, at 12 months, for OS, there are [redacted]%) patients at risk; at 24 months, there were [redacted] patients at risk ([redacted]%), and from 29 months, less than [redacted] of the original sample was at risk. Median PFS and median OS have not been reached. For these reasons, the ERG considers the data immature and the long-term extrapolations subject to high levels of uncertainty.

Given the extent of censoring, the ERG considers that the plateaus in the Kaplan-Meier curves cannot be interpreted as providing robust evidence of the extent of long-term survivorship following KTE-X19. The Kaplan-Meier method assumes that the patients remaining at risk are representative of the patients who were censored. This means that the time to progression and death of the proportion of patients who are still at risk is assumed representative of the patients who were censored. However, and as Carter et al [36] highlight, the validity of this assumption requires that a large number of patients are at risk. When the risk set becomes small, as is the case in ZUMA-2, Kaplan-Meier estimates are very sensitive to single observations and may be overinterpreted.

To illustrate the uncertainty in the PFS and OS curves, the ERG asked the company to include 95% confidence intervals in the Kaplan-Meier curves (see PfC B8). Furthermore, the ERG followed suggestions by Gebski et al[37] for curtailing the Kaplan-Meier curve when less than 10% of the patients remain at risk (see ***[redacted]8). The Kaplan-Meier estimate for the proportion alive at the curtailed follow-up of [redacted] months is [redacted] (95% CI [redacted]) and for the proportion who have not progressed at the curtailed follow-up of [redacted] months is [redacted] (95% CI [redacted]), and presence of a plateau is less clear, particularly in the OS curve.

[redacted]8[redacted]

[redacted]

Progression-Free Survival (PFS) curve was curtailed at 23.95 months and Overall Survival (OS) at 28.32 months

Finally, the ERG illustrates the uncertainty by changing the status of one patient from censored to having had an event using the PFS curve.[37] As shown in ***[redacted]9, an additional event has little impact if it occurs when many patients are still at risk (panel A and panel B). In contrast, if one patient has an event at the end of the follow-up, when few patients are at risk, the impact is substantial. In panel C, one event at month 24.8 changes the Kaplan-Meier OS estimate from [redacted] to [redacted] In panel D, one event at 29.7 months, changes the Kaplan-Meier OS estimate from [redacted] to [redacted] These results illustrate the uncertainty in the Kaplan-Meier curves in general, and the fragility in the plateau and the long-term survivor fraction. For these reasons, the extrapolation beyond the trial follow-up in the ERG base-case is based on external data (see Section 6.1.1).

[redacted]9[redacted]

[redacted]

item 3. The ERG considers that the ZUMA-2 data (and any extrapolations based on these) are associated with considerable uncertainty

2. Uncertainty regarding long-term survivorship in r/r MCL

As accepted by the company, there are no data to support the assumption that KTE-X19 achieves long-term survivorship in r/r MCL: "*Data on the long-term survival prospects for post-ibrutinib MCL patients who benefit from KTE-X19 infusion are absent and will only accrue with the passage of time*." (PfC p51) and "*In short, while long-term survivorship for post-ibrutinib MCL patients following successful CAR T-cell therapy is unevidenced, in line with the mechanism of action of KTE-X19 we share the hope and anticipation of the clinical and patient community of very good long-term prospects*." (PfC p55).

The company justified the assumption of long-term survivorship, which is central to the their base-case, based on (i) the plateau in the Kaplan-Meier curves, (ii) precedent from company submissions in previous appraisals of CAR T-cell therapies (used for r/r B-cell acute lymphoblastic leukaemia and r/r DLBCL),[28-30] and (iii) on the CR rate and rate of patients with no detectable disease (according to minimal residual disease criteria). As discussed in item 3, given the extent of censoring and the short follow-up, the ERG considers that there is high uncertainty relating to the extent to which the plateau is evidence of long-term survivorship.

The ERG considered that precedent from previous TAs in CAR T-cell therapies in other conditions is insufficient to support the assumption of long-term survivorship in r/r MCL. As noted by the company, "*In DLBCL, cure is considered the treatment goal. When patients are first diagnosed in newly diagnosed MCL this is not, generally, considered a likely outcome."* (PfC p53). This is in line with the ERG clinical advisors' view, who noted that, while there is evidence of long-term remission with other non-CAR T-cell- therapies in DLBCL, similar evidence is not available in MCL. Furthermore, the ERG notes that the data on CAR T-cell therapy in r/r DLBCL (including DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma) is immature, given that the available follow-up is less than 3 years.[38, 39] Therefore, the extent of long-term remission with CAR T-cell therapies in r/r DLBCL is uncertain, as well as its generalisability to long-term remission in r/r MCL.

The ERG considered the link between the CR rate observed in ZUMA-2 (65% in mITT) and long-term survivorship to be uncertain. The study by Eskelund et al,[2] on the 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial, reports that 89.7% of patients achieved CR or unconfirmed CR after induction treatment and autologous SCT.[2] However, as reported by the authors: "*Half of all patients had either progressed or relapsed at 12.0 years (Fig 1C), and we observed a continuous pattern of relapse throughout the follow-up, including relapses later than year 10 (Fig*

1C)." and "*In conclusion, despite prolonged remissions, a continuous pattern of relapses has occurred throughout the follow-up, and there is an excess mortality among all MCL patients even after long-term remissions*." (p7).[2] This suggests that the CR rate may not fully translate to long-term survivorship for autologous SCT. The CR rate may translate to long-term survivorship after KTE-X19 treatment, but the ERG considers that ZUMA-2 is insufficiently mature to support this assumption. Furthermore, the results of Eskelund et al suggest that there is uncertainty regarding the likelihood of long-term survivorship in MCL, even in newly diagnosed patients who generally have better outcomes than those receiving third or subsequent lines of treatment, as is the case in ZUMA-2. [2]

The Eskelund et al[2] findings are consistent with Kumar et al,[40] a retrospective chart review of newly diagnosed MCL patients who were managed at Memorial Sloan Kettering Cancer Center and followed during their disease course and treatment from 2000 to 2014. Figure 10, reproduced from the original study, illustrates long-term survival patterns for MCL patients receiving non-CAR T-cell therapies at different lines of treatment. This figure suggests that durable long-term remission is not observed, for either PFS or OS, at any line of treatment. Also, time to progression and death seem to decline with subsequent lines of therapy. A plateau is not observed in the Kaplan-Meier curves, suggesting no long-term survivorship at any line of treatment (including 3rd line patients who are more similar to the patients considered in this appraisal and are shown with green colour). This may reflect the longer follow-up period and/or the nature of the treatments, which do not include CAR T-cell therapies. Overall, the evidence from Eskelund et al and Kumar et al suggest that long-term survivorship in MCL is unlikely with current therapies. Given the limited evidence in ZUMA-2 and the uncertainty in generalisability from DLBCL, the ERG considers that it is uncertain whether and to what extent KTE-X19 can lead to durable long-term remission in r/r MCL.

Figure 10:

Adopted from [40]

item 4. The ERG concludes that it is uncertain whether and to what extent KTE-X19 can lead to durable long-term remission in r/r MCL.

3. *Appropriateness of mixture cure models and uncertainty in the long-term survivorship fraction*

The ERG considers that mixture cure models may not be appropriate given the limited follow-up in the ZUMA-2 trial. Robust estimation of mixture cure models requires data from studies with long follow-up times that far exceed the anticipated time point of cure,[41] as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a long-term survivor fraction.[42, 43] To formally assess this, Maller et al[44] suggested a statistical test that evaluates the null hypothesis that the follow-up is not sufficiently long, and Zhao et al[45] developed a score test, which given a sufficiently long follow-up, tests whether a long-term survivor fraction exists. The ERG notes that the company did not implement any of these or other statistical tests to establish the existence of a cure fraction or that the existing ZUMA-2 follow-up is adequate. As the company notes, "*The use of these [mixture cure] models can be beneficial over standard parametric models where there is evidence to support that a proportion of patients have more favourable outcomes (i.e. experience long-term survivorship) following treatment, and a proportion do not"* (CS p114). However, and as stated by the company, there is no evidence of long-term survivorship: "*In short, while long-term survivorship for post-ibrutinib MCL patients following successful CAR T-cell therapy is unevidenced, in line with the mechanism of action of KTE-X19 we share the hope and anticipation of the clinical and patient community of very good long-term prospects*" (PfC p55).

The ERG considers that the estimated long-term survivorship fraction is highly uncertain. Firstly, it is estimated from mixture cure models, for which concerns are discussed above. Secondly, the parameter uncertainty in the estimation is translated into relatively large 95% confidence intervals at [redacted] for PFS and [redacted] for OS.

Thirdly, the estimated long-term survivor fractions differ between the company's base-case mixture cure PFS ([redacted]% (95%CI [redacted])) and OS ([redacted]% (95%CI [redacted])) models. This implies that approximately [redacted] of the ZUMA-2 patients relapsed and became long-term survivors following a subsequent treatment. In response to the PfC B3f, the company reported that [redacted] patients in ZUMA-2 who progressed received a subsequent anti-cancer therapy post-progression, and commented that it was plausible that the subsequent anti-cancer therapy may have led to long-term survivorship for some of these patients. If this is not clinically plausible, the discrepancy between long-term survivor fractions supports the ERG's concern that the ZUMA-2 follow-up may not be

sufficient to allow the robust estimation of mixture cure models; hence, the long-term survivorship fractions are subject to high uncertainty.

Fourthly, the point estimate for the long-term survivorship fraction in the company's submission is greater than the long-term survivorship fractions estimated for the appraisals of CAR T-cell therapies in r/r DLBCL. In TA559,[28] the use of axicabtagene ciloleucel in DLBCL was associated with a cure fraction of ~ 50% for OS and ~ 40-43% for PFS. The committee thought that significant uncertainty regarding the cure fraction remained and that the company was likely to overestimate the size of the cure fraction. Here, long-term survivorship fractions are [redacted] for OS and [redacted] for PFS. As noted by the company and the ERG's clinical advisors, in contrast with DLBCL, there is uncertainty in the extent to which r/r MCL patients who relapsed at the third line or subsequent therapies can experience long-term remission and survivorship. Therefore, the ERG finds it unlikely that the long-term survivorship fraction in r/r MCL would be higher than in r/r DLBCL.

item 5. The ERG considers that the available data may not be mature enough to robustly estimate mixture cure models and that the long-term survivor fraction is highly uncertain.

4. Uncertainty in OS and PFS extrapolations based on the ZUMA-2 data

One of the reasons given by the company to prefer mixture cure models for the base-case is their view that the parametric models did not provide good visual fit to the observed data from approximately 10 months onwards (CS p113 and p127). The ERG agrees that the parametric models do not provide plausible extrapolations in isolation because their hazard rates are generally below those of the general population (see ***[redacted]16 in Appendix B), unless a logical constraint is imposed to ensure that the maximum between the general population hazard and the parametric model is always applied, as done in the company's model. Nonetheless, the need for such a constraint highlights the uncertainty in the extrapolation.

The company also considered the spline models, which were fitted at the ERG's request, to provide a poor fit given the expectation of long-term survivorship (PfC p63). In the ERG's view, most models fit similarly well to the within-trial period, as suggested by goodness of fit criteria (see PfC Table 19 p69-70) and by their visual fit (see -***[redacted]20 in Appendix B). The ERG notes that the cubic spline models have the lowest AIC/BICs whilst having the ability to capture the heterogeneity in the long-term outcomes to some extent. This is because the spline model informs the latter part of the curve primarily from the data of the patients still at risk. The spline models are similar in fit to the within-trial period and predict similar 5-year survival estimates at [redacted]%. This is lower than the long-term survivorship fraction estimated by the mixture cure models and similar to the long-term survivorship fraction estimated in TA559 for axicabtagene ciloleucel in r/r DLBCL.[28] However, the

spline models have a similar limitation to the standard parametric models in respect to their hazard rates in the long-term, in that these are lower than the general population mortality (see ***[redacted]17 Appendix B). Furthermore, the ERG notes that the committee considered that a spline model was appropriate for the extrapolation of OS in TA567.[29]

The survival models differ considerably in their long-term extrapolations. For example, for OS, the 1-knot hazard spline yields the same AIC and BIC as the 2-knot hazard spline at (AIC: [redacted] BIC:[redacted]for both spline models) respectively, but predict considerably different proportions of patients alive at 10 years ([redacted]), 15 years ([redacted]), and 20 years ([redacted]). The best fitting spline for OS is the 2-knot normal, resulting in the lowest, yet very similar with other splines, goodness of fit criteria (AIC: [redacted]BIC: [redacted]). This spline model predicts [redacted]% alive at 10 years, [redacted]% alive at 15 years, and [redacted]% alive at 20 years (see PfC Table 19 p69-70).

***[redacted]11 shows how the long-term extrapolations differ with the example of the OS curve. Although the fit to the within-trial period is similar across mixture cure, single parametric, and spline models, the extrapolations are considerably different with the mixture cure models resulting in the most optimistic extrapolations. Therefore, the ERG concludes that there is a high level of uncertainty regarding the long-term OS and PFS following KTE-X19.

[redacted]11[redacted]

[redacted]

[redacted]Figure adapted from the company's submitted model in response to PfC.

SPM: Standard parametric model, MCM: Mixture cure model

item 6. The ERG considers that the immaturity of the ZUMA-2 data leads to high uncertainty in the extrapolation approach, and that alternative modelling approaches are plausible alternatives to mixture cure models.

5. *Appropriateness of a mortality adjustment from DLBCL for the risk of death of long-term survivors*

The ERG is concerned that the mortality adjustment from DLBCL (i.e. the SMR of 1.09) may not appropriately reflect the excess mortality risk of long-term survivors with r/r MCL compared to the general population. This is for three reasons:

First, the ERG considers that the use of the mortality adjustment obtained from a study in DLBCL patients in previous NICE appraisals in DLBCL is not a valid justification to use the same mortality adjustment in r/r MCL. The adjustment (SMR=1.09) was obtained from Maurer et al,[35] specifically in a cohort of French newly diagnosed patients with DLBCL (n=820) who were event-free at 24 months. In response to the PfC B2b (pg 52), the company maintained the position that this adjustment was appropriate and preferable to a mortality adjustment based on Eskelund et al.[2] The company provided no further evidence to support the assumption that the excess mortality risk is generalisable from DLBCL to r/r MCL.

Second, the ERG's clinical advisors considered that the excess mortality risk from DLBCL is not generalisable to r/r MCL and that the excess mortality risk compared to the general population is likely to be higher in r/r MCL than in DLBCL.

Third, evidence from Eskelund et al[2] suggests that the excess mortality risk experienced by MCL patients is substantial and likely to be higher than in DLBCL. As described earlier, Eskelund et al reports the follow-up of newly diagnosed patients with MCL (n=160) after first line treatment with chemotherapy followed by autologous SCT for up to 15 years (median follow-up = 11.4 years). Figure 12 below reproduces Eskelund et al's graphical comparison of the mortality risk of the study cohort compared to the general population, matched with respect to age, calendar year of follow-up, sex and country of origin.[2] Results were reported for (i) 159 newly diagnosed patients, (ii) 139 patients with complete remission after 1 year, (ii) 96 patients with complete remission after 5 years, and (iv) 59 patients with complete remission after 10 years. Figure 13 reproduces the OS compared to the expected survival in the French cohort from Maurer et al[35] from the evaluation of event-free survival at 24 months. A visual comparison of the Eskelund et al and of the Maurer et al curves indicates a substantial difference in excess mortality risk between MCL and DLBCL patients compared to the general population.

The ERG considers that the evidence from Eskelund et al[2] is more appropriate to inform the excess mortality risk, although considerable uncertainty remains given the data limitations and uncertain

generalisability from newly diagnosed MCL patients who mostly received autologous SCT in Eskelund et al to r/r MCL post-KTE-X19. Therefore, the ERG undertook further analyses to estimate the excess mortality risk based on Eskelund et al.[2] This is presented in Section 6.1.1.11. to inform the ERG base-case and reported in detail in Appendix C.

item 7. The ERG considers that the excess mortality risk of long-term survivors of r/r post-KTE-X19 is uncertain, but it is more appropriate to base it on data from MCL patients than from DLBCL patients.

Figure 13: Survival of the Eskelund et al study cohort compared to the general population (reproduced from Figure 3 in the original paper)

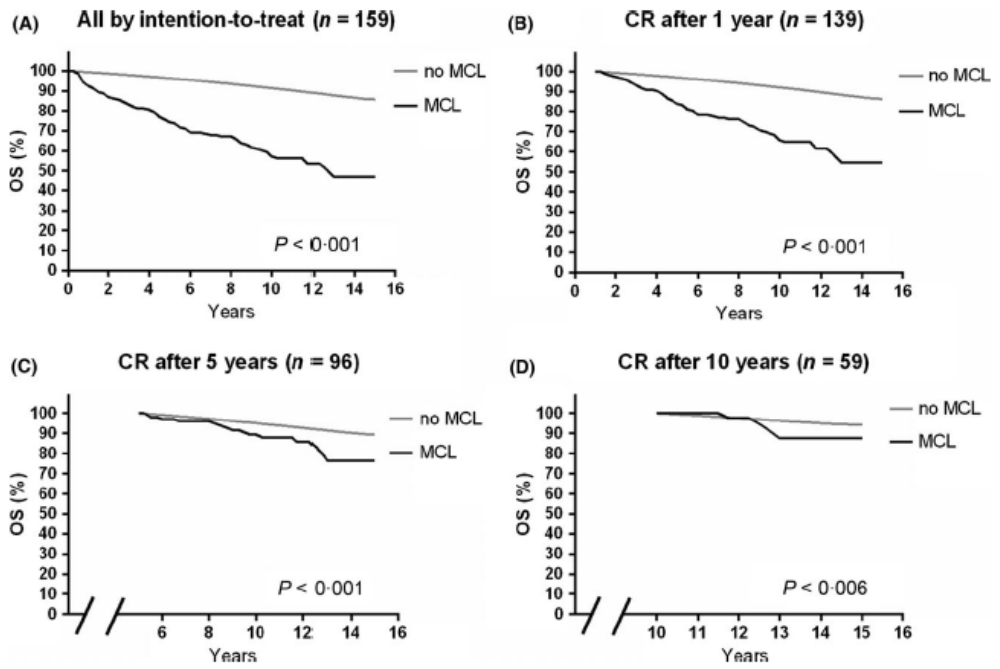


Fig 3. Conditional survival of the MCL2 patients compared to the estimated survival, had they not acquired MCL (based on data from the Human Mortality data base; http://www.mortality.org). (A) All patients. Patients in first complete remission after (B) 1 year, (C) 5 years and (D) 10 years, respectively. In (C) and (D) the *x*-axis has been adjusted to match the curves starting at 5 and 10 years, respectively. MCL, Mantle cell lymphoma; CR, complete remission; OS, overall survival.

Figure reproduced from Eskelund CW, Kolstad A, Jerkeman M, Räty R, Laurell A, Eloranta S, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. Br J Haematol. 2016;175(1365-2141 (Electronic)):410-8.

Figure 12: Survival of the Maurer et al French cohort compared to the general population (reproduced from Figure 4 in the original paper)

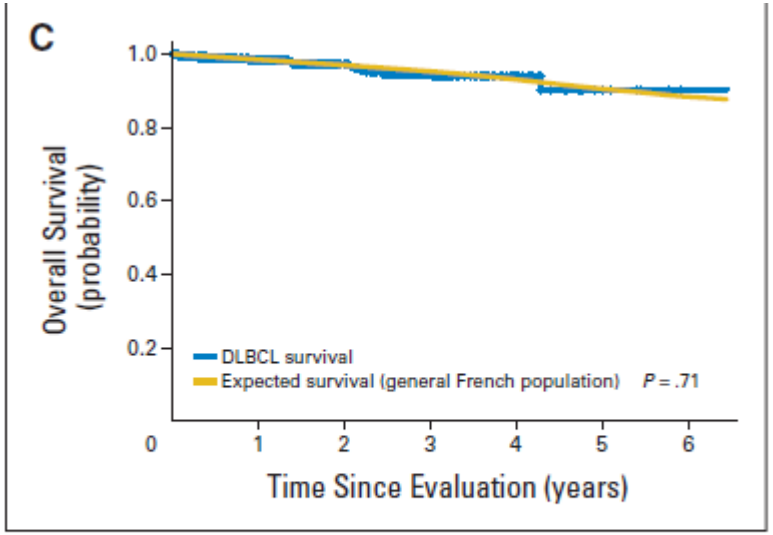


Fig 4. Overall survival versus expected survival in French cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

Figure reproduced from Maurer MJ, Ghesquieres H, Jais JP, Witzig TE, Haioun C, Thompson CA, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. J Clin Oncol. 2014;32(10):1066-73.

6. Conclusion

The ERG concludes that (1) the ZUMA-2 data (and any extrapolations based on these) are associated with considerable uncertainty given its small sample size, short follow-up and extent of censoring; (2) it is uncertain whether and to what extent KTE-X19 can lead to durable long-term remission in r/r MCL given the uncertainties in the ZUMA-2 data and the evidence suggesting that, with currently available therapies, patients with MCL are at risk of relapse in the long-term; (3) the ZUMA-2 data is not mature enough to robustly estimate mixture cure models, hence the long-term survivorship fraction estimates are highly uncertain; (4) all modelling approaches fit similarly to the within-trial data; (5) long-term extrapolation is highly uncertain given that different approaches suggest different proportion of survivors in the long-term and all approaches suggest lower hazards than the adjusted general population; (5) the excess mortality risk of long-term survivors of r/r post-KTE-X19 is highly uncertain, but to be more appropriate to base it on data from MCL patients than from DLBCL patients.

For these reasons, the ERG presents a base-case where OS and PFS is predicted by a spline model for the within-trial period and the extrapolation is based on general population mortality adjusted with a mortality adjustment estimated from Eskelund et al,[2] a study in patients with MCL (see Section 6.1.1 for details). Given the high levels of uncertainty in the extrapolation, the ERG presents plausible ranges of ICERs instead of point estimates as well as a number of scenarios with alternative assumptions.

4.2.6.2 Standard of Care (SoC)

In the company's base-case, the OS and PFS with SoC is based on meta-analysed standard parametric models fitted to the data of two observational studies for PFS[11, 16] and four studies for OS.[11, 14-16] The company's approach consisted of three steps. First, the company digitised the published Kaplan-Meier curves and recreated the IPD. Second, standard parametric models were applied to the digitised IPD. In the third step, the shape and scale parameters and correlation between the parameters which were estimated with the parametric models were synthesised in a multivariate meta-analysis model.[23] The company preferred the fixed-effect meta-analysis because the confidence intervals of the survival curves included values beyond the range of 0-1. The systematic review to inform the outcomes with SoC is discussed in Section 3.3.

As described in Section 3.4.1, the company conducted naïve (unadjusted) comparisons and MAICs between the studies on SoC and ZUMA-2. In summary, the MAIC analyses matched the ZUMA-2 baseline characteristics to the baseline characteristics of different subsets of the SoC studies (See Table 18, pg 66 of the CS). However, the company's base-case is based on a naïve comparison

between the ZUMA-2 mITT sample data and the pooled SoC studies. The company justified the use of the naïve comparison given that the conducted MAIC analyses rely on strong assumptions and result in extreme reduction of the ESS (see Table 18, pg 66 of the CS).

In response to the PfC B6, the company fitted parametric survival models to McCulloch et al (2020)[1] and included it as a scenario in the cost-effectiveness model. McCulloch et al (2020) is an update and reports a longer follow-up than McCulloch et al (2019);[16] the ICER [redacted] by [redacted] compared to the company's base-case.

In response to the PfC A10, the company conducted a MAIC between McCulloch et al (2020)[1] and ZUMA-2 (see Section 3.4.2.2). The company did not conduct survival analysis to the MAIC-adjusted ZUMA-2 data due to the small ESS.

The CS notes that further comparator data will become available during the appraisal process (CS p21). These data were not submitted by the company in its main submission nor in response to the PfC.

SoC progression-free survival

For PFS with SoC in the base-case, the company chose the meta-analysed lognormal model based on Eyre et al and McCulloch et al (2019)[11, 16] because the sum of AICs was the lowest across the set of tested parametric models. Given the median PFS in McCulloch et al (2020)[1] of 10.1 months (whereas the lognormal model predicted [redacted] months), and the company's clinical advisors expectation of 2-3% patients in PFS at 5 years (whereas the lognormal model predicted [redacted]%), the company used the generalised gamma model, which is the most optimistic, in a scenario. The generalised gamma model predicted median PFS of [redacted] months and 5-year PFS of [redacted]%; the impact on the ICER was small at [redacted] difference from the base-case).

SoC overall survival

For OS with SoC in the base-case, the company chose the meta-analysed lognormal model based on four studies.[11, 14-16] The choice was based on goodness of fit criteria, alignment with the expectations of the company's clinical advisors, and consistency with the PFS curve. Scenario analyses included projections based on each individual study instead of the meta-analysis, and based on the meta-analysed Gompertz model, which was thought to be the most optimistic. The impact on the ICER was small (between [redacted] to [redacted] compared to the base-case).

Points for critique

The approach to the identification of evidence to inform the PFS and OS with SoC is discussed in Section 3.1. Even though the company noted that further comparator data will probably be available soon, the ERG considers that the impact on the ICER is unlikely to be major given the clinical

evidence that outcomes with SoC are poor. Nonetheless, depending on the evidence presented, it might resolve some of the uncertainty if it allows for a more appropriate comparison using individual level data and matching on prognosis factors.[46]

The ERG has a number of concerns regarding some elements of the company's approach to the meta-analysis of studies of SoC. As discussed in Section 3.4.1, the ERG considers that the studies are too heterogenous to support a fixed effect meta-analysis. Secondly, the ERG notes that Eyre et al[11] included patients who received venetoclax, which is not licenced in the UK; hence, Eyre et al is unlikely to represent current SoC in the UK. Furthermore, the ERG's clinical advisors thought that the patients enrolled in Eyre et al were likely to have poorer prognosis than the patients enrolled in ZUMA-2 and patients likely to be eligible for KTE-X19 in the UK. Therefore, using Eyre et al 2019 to inform may lead to the underestimation of PFS and OS with SoC. Thirdly, the ERG is concerned that obtaining PFS and OS from different studies breaks the relationship between the two quantities and may lead to inconsistencies in the extrapolation.

The ERG's clinical advisors considered that McCulloch et al (2019)[16] and its subsequent publication McCulloch et al (2020),[1] which reports the outcomes of patients with r/r MCL following chemotherapy with R-BAC, were the most generalisable to the current SoC in the UK and to the patient population who would be eligible for KTE-X19. Given the concerns above and the feedback from the ERG's clinical advisors, the ERG considers McCulloch et al (2020)[1] to be the most appropriate source for PFS and OS for SoC and uses these data in its base-case (see Section 6.1.1.3 for the analysis informing the ERG base-case).

item 8. The ERG considers that McCulloch et al (2020) is the most appropriate source of data to inform PFS and OS under SoC.

The ERG highlights that the company's naïve comparison is subject to strong, untestable, assumptions and should be used and interpreted with caution. Specifically, naïve comparisons assume conditional constancy of the absolute effects. This means that the absolute treatment effect between KTE-X19 and SoC is assumed constant at any given level of the effect and prognostic variables and that all effect modifiers and prognostic variables are known and accounted for. This assumption is difficult to be met and much stronger than the assumption of conditional constancy that is imposed by MAICs. Furthermore, the company's MAIC analyses result in considerably reduced ESS, implying that there is a limited overlap among the baseline characteristics, considered to be effect modifiers, between ZUMA-2 and the SoC studies. This argument is equally pertinent to the unadjusted naïve comparisons. For these reasons, the ERG considers that the MAIC and the unadjusted naïve

comparison are subject to significant risk of bias and uncertainty. Given the magnitude of comparative effectiveness, this is unlikely to have a major impact on the ICER.

item 9. **The ERG considers that the company's unadjusted naïve comparison is subject to unquantifiable bias and is uncertain.**

4.2.7 Adverse events

For KTE-X19, the cost-effectiveness analysis accounted for all Grade 3 and 4 AEs occurring ≥ 10% of the ZUMA-2 mITT (N=68) cohort (total of all grades) as result of conditional chemotherapy and KTE-X19 treatment (separately). The incidence of Grade 3 and 4 AEs meeting this threshold is reported in CS Table 45 and Table 46 p145-6. No grade 3 or higher leukapheresis-related AEs occurred in ≥ 10% of subjects in ZUMA-2; hence these were not modelled. The cost-effectiveness analysis also accounted for two additional AEs considered to be of particular clinical importance for CAR T-cell therapies – all grade 3 or 4 CRS, all CRS (regardless of the grade) requiring tocilizumab treatment, and B-cell aplasia [hypogammaglobulinaemia] requiring IVIG treatment. The company accounted for uncertainty in the rate of AEs using the number of events and the sample size in the ZUMA-2 trial.

In the CS, the effect of pancytopenia (simultaneous onset of thrombocytopenia, neutropenia and anaemia) was not modelled. Following PfC B9c, the company clarified that pancytopenia had only been measured after conditioning chemotherapy (where [redacted] was recorded), and not after KTE-X19 administration. To account for the possible effect of pancytopaenia on HRQoL and costs, the company provided an additional scenario. Details of how the cost and HRQoL in pancytopenia was modelled are provided in sections 4.2.8.2 and 4.2.9.5. The ICER increased by £202/QALY compared to the company's base-case.

For SoC, adverse events are only considered in terms of their impact on HRQoL (see Section 4.2.9.2). The methods for modelling the impact of AEs on HRQoL and costs are discussed in Section 4.2.9.2 and 4.2.10.5, respectively.

Points for critique

The ERG considers the approach to include the impact of AEs in the model broadly appropriate and consistent with previous appraisals TA559[28] and TA567,[29] and well implemented in the model. The criteria of including only Grade 3 and 4 AEs which occurred the total of all grades occurred in 10% of ZUMA-2 mITT population was not justified and may exclude rarer Grade 3 and 4 AEs which have a relevant impact on health outcomes and/or costs. The ERG considers that the impact on the ICER is likely to be small.

The company only accounted for AEs related with the infusion with KTE-X19 or with conditioning chemotherapy (as in the previous CAR T-cell appraisals TA559[28] and TA567[29]); AEs related to leukapheresis were considered no Grade 3 or higher occurred in ≥ 10% of subjects in ZUMA-2; hence these were not modelled. With regards to treatment with KTE-X19, this implies that there are no AEs associated with bridging chemotherapy which have an impact on costs or HRQoL. If this is not the case, the exclusion of these AEs could underestimate the ICER. The company also excluded the cost of treating AEs in SoC, potentially overestimating the ICER (by underestimating the cost of SoC). However, the impact of either of these assumptions is likely to be negligible.

The ERG highlights one area of concern regarding the exclusion of pancytopenia from the company's base-case. Given the ERG clinical advisors' comment that pancytopenia was one of the most impactful AEs of CAR T-cell therapy in terms of costs and HRQoL, the ERG has included the scenario from PfC B9c (where pancytopenia was modelled) in their base case.

item 10. The ERG believes the impact of pancytopenia as an AE of KTE-X19 should be explicitly included in the model.

4.2.8 Health related quality of life

4.2.8.1 Health-related quality of life associated with health states

The company conducted a systematic review for HRQoL evidence in adult patients with relapsed or refractory MCL (see CS Appendix H). This systematic review originally identified five studies,[6, 47-50] and its update included an additional five studies, including ZUMA-2.[51-55] The company selected TA502 on ibrutinib for relapsed MCL as the most relevant source of HRQoL data, in addition to the data collected in ZUMA-2.

Table 15 summarises the health-related quality of life (HRQoL) data associated with health states in the company's model.

Table 15: Health-related quality of life associated with health states

Health state	Value (95% CI)	Source
Pre-progression	[redacted]	ZUMA-2, pre-progressed patients EQ-5D-5L converted to EQ-5D-3L values.[26] Mixed effect model adjusting for age, sex, and time from KTE-X19 infusion.
Post-progression	[redacted]	[redacted] 49, 56, 57 [redacted]

Health state	Value (95% CI)	Source
Pre-progression, after 5 years	0.797	Age- and sex-matched general population.[58]
Health-related quality of life is adjusted as the cohort ages in all health states.[58] CI: confidence interval, based on data in the company's model. Table adapted from CS Table 48 pg149.		

The HRQoL in the pre-progression state is based on the EQ-5D-5L data collected in ZUMA-2, mapped to EQ-5D-3L values using the van Hout et al algorithm,[26] and analysed with a mixed-effects model controlling for age, sex and time from KTE-X19 infusion. Following PfC, the company provided additional details on the results and goodness of fit of all the regression models that were explored (see PfC B11). The regression models resulted in mean HRQoL values between [redacted]. The company's scenario analysis explores using alternative HRQoL for pre-progression state, based on TA502, [49] but the impact on the ICER is small (see CS Table 73 p189).

For HRQoL in the post-progression state, the company assumed that [redacted] in each of the studies considered in TA 502 on ibrutinib for relapsed MCL. [49, 56, 57] The company justified their choice of studies on the basis of consistency with the previous appraisal. This calculation assumes that the relationship between HRQoL in the pre-progression and in the post-progression states is the same across lines of treatment and generalisable from other types of lymphoma.

After 5 years from the infusion with KTE-X19, the patients who have not yet progressed are assumed to be cured in terms of their HRQoL, and to experience the HRQoL of age- and sex-matched general population.[58] The company presented scenario analysis assuming that the cure point is at 2 years (for both HRQoL and costs), which reduced the ICER by [redacted]; and down weighting the HRQoL of long-term survivors by 0.92, which increased the ICER by [redacted] (see CS Table 73 p189). The company justified this assumption by referring to the approach taken in TA559 and TA567 on CAR T-cell therapies in r/r DLBCL. [59, 60] In TA559, patients in the pre-progression state after 2 years were assumed to have the HRQoL of the general population, which the Committee concluded to be optimistic. [20] In TA567, the HRQoL in the pre-progression state was obtained from the pre-progressed patients from the JULIET trial and adjusted over time for age-related decrements; the Committee

concluded that a cure point between 2 to 5 years was plausible but that further long-term data was needed to address this uncertainty. [33]

In response to PfC B10, the company acknowledged that there is no evidence to support the assumption that the HRQoL of pre-progression after 5 years is the same as the general population: "*The long-term health-related quality of life of post-ibrutinib MCL patients in long-term remission following KTE-X19 infusion, like the long-term survival prospects for such patients, is unevidenced.*" (p88). The company noted that the HRQoL of pre-progressed patients in ZUMA-2 was similar to that of the age- and sex-matched general population, therefore the company considered that the switch at 5 years continues an existing trend.

Points for critique

The ERG considers that informing the HRQoL in the pre-progression state from the ZUMA-2 data is appropriate and meets the NICE reference case. However, and as discussed in Section 3.2.1.5, there is some uncertainty to what extent the ZUMA-2 patient population generalises to the UK patient population, which implies some uncertainty in the generalisability of HRQoL from ZUMA-2 to UK patients. The uncertainty around generalisability is highlighted by the similar HRQoL in ZUMA-2 to the age- and sex-matched UK general population ([redacted] in ZUMA-2 at screening into the trial *versus* [redacted] in the model *versus* 0.820 for the age- and sex-matched UK general population). Furthermore, there is uncertainty on whether patients who have not progressed will continue to experience this HRQoL over the long-term.

The assumption that patients who have not yet progressed at 5 years following KTE-X19 experience the same HRQoL as the general population is a major area of uncertainty and was insufficiently justified. The ERG clinical advisors noted that HRQoL may be similar to that of the general population, but this was uncertain. As discussed in Section 4.2.6.1, the ERG considers that the evidence from ZUMA-2 is insufficient to support an assumption of long-term remission. Evidence from Kumar et al and Eskelund et al suggests that patients with MCL are at long-term risk of relapse and at higher risk of death than the general population, even after years in remission.[2, 40] Therefore, the ERG concludes that it is uncertain whether the HRQoL of long-term survivors is the same as the age- and sex-matched general population. For these reasons, the ERG explores alternative assumptions on HRQoL of long-term survivors in Section 6.1.2.

item 11. The ERG considers that it is uncertain whether long-term survivors experience the HRQoL of patients in ZUMA-2 or the HRQoL of the age- and sex-matched general population.

The approach to calculate post-progression HRQoL was not sufficiently justified. Given the relatively short period of time spent in the post-progression stage, by both the patients who received KTE-X19 and those who received SoC, this parameter has a small impact on the cost-effectiveness results (ICER increases by £[redacted]/QALY assuming that HRQoL in the post-progression stage is 50% of the HRQoL in the pre-progression state). Given the available evidence and considering the limited impact on the ICER, the ERG considers this approach to be suitable for decision-making, although subject to uncertainty.

4.2.8.2 Health-related quality of life associated with adverse events

Table 16 summarises the impact of adverse events on health outcomes in the model.

For KTE-X19, the proportion of patients who experienced CRS Grade 3 and 4 (14.7%) were assumed to have HRQoL of zero for 11 days (which corresponds to median time to CRS resolution observed in ZUMA-2). B-cell aplasia was assumed not to result in a reduction of HRQoL. Both assumptions are consistent with Hettle et al and TA559.[27, 33] For the Grade 3 and 4 adverse events which were related to KTE-X19 or with conditioning therapy, one-off HRQoL decrements were applied to the first cycle of the model, in line with TA567. [59] These HRQoL decrements were calculated assuming that the AEs were associated with 0.15 decrement if they lasted 1 year, which results in 0.0004 per day over the duration of the adverse event, and applied to the proportion of people who experienced it (from ZUMA-2, supplemented with ZUMA-1 and mean imputation in the case of missing data). As discussed in Section 4.2.7, the company's base-case does not include pancytopenia. Overall, the QALY decrement due to adverse events was 0.0713 per patient.

In response to PfC B9c, the company conducted a scenario where pancytopenia is considered by increasing the impact of Grade 3/4 thrombocytopenia on costs and HRQoL. For the impact on HRQoL, the impact was incorporated as an increase in the duration of thrombocytopenia, which translates into 0.15 QALY decrement for the 5.9% of patients who experienced this AE. The impact on the ICER is small (increase of £202/QALY).

For SoC, the patients on R-chemotherapy were assumed to experience a decrement of 0.2 per cycle during the treatment duration (which results in [redacted] QALYs in the model). This was obtained from TA502, which based it on clinical opinion. [49] Treatment duration of R-chemotherapy is detailed in Section 4.2.9.

Table 16: Impact of adverse events on health outcomes in the model

Adverse event	Value	Source
KTE-X19		
CRS	0.004 QALYs	Grade 3 and 4 CRS occurred in 10/68 (14.7%) of patients.

Adverse event	Value	Source
		HRQoL during CRS assumed to be zero, as per TA559 and Hettle et al.[27, 33] Duration of CRS corresponds to median time to CRS resolution, at 11 days.
Other KTE-X19-related adverse events	-0.0287 QALYs	Grade 3 and 4 adverse events. HRQoL decrement of 0.15 obtained from Guadagnolo et al., [61] consistent with TA567.[59] Duration of adverse event obtained from ZUMA-2, supplemented by ZUMA-1 and mean imputation.
Conditioning therapy-related adverse events	-0.0390 QALYs	
Total QALY decrement for AEs	0.0713	Includes QALY decrement for CRS, other KTE-X19 related adverse events and conditioning therapy-related adverse events.
Standard of Care		
R-chemo toxicity	[redacted] QALYs	HRQoL decrement of 0.2 per cycle over 6 treatment cycles, applied to all patients in the pre-progressed state in SoC. [49]
Table adapted from CS Table 48 pg149 and from the company's cost-effectiveness model.		

Points for critique

The ERG considered the company's approach broadly appropriate for decision-making and consistent with previous TAs, although there are some limitations. Firstly, and as discussed in Section 3.2.1.6, the ERG have concerns regarding the precision of the AE rates to clinical practice. Secondly, and as discussed in Section 4.2.7, the inclusion of only AEs which are related to conditioning therapy and to KTE-X19 infusion may not be appropriate if leukapheresis and bridging chemotherapy also have an impact on HRQoL.

The decrement of 0.15 QALYs/year, adjusted to the duration and incidence of AEs, is subject to uncertainty. As pointed out by the ERG in TA567, it is not clear how the decrement of 0.15, associated with Grade 3 and higher adverse events for KTE-X19, was calculated in the original study. [59, 61] Additionally, this assumes that all adverse events have the same impact on HRQoL per day experienced, which may not be realistic. As increasing the HRQoL impact of AEs has a small impact on the ICER (e.g. doubling the decrement increases the ICER by [redacted]), the ERG is satisfied that the approach is unlikely to bias the cost-effectiveness results.

As noted in Section 3.2.1.6 and 4.2.7 the exclusion of pancytopenia from the company's base-case may not be appropriate. Based on their experience of CAR T-cell therapies in DLBCL, the ERG clinical advisors commented that pancytopenia is the most significant AE in terms of HRQoL for the first few months after infusion, and gradually improving to resolution within 1 year. Therefore, the ERG prefers the company's scenario in response to the PfC B9 where the impact of pancytopenia in incorporated to some extent. As the company's approach required some assumptions, it is uncertain

whether it fully reflects the incidence and impact of pancytopenia in patients in UK clinical practice. Nonetheless, the ERG considers this scenario to be more reflective of the impact of AEs on HRQoL, hence it forms part of the ERG base-case.

For SoC, the 0.2 decrement associated with R-chemotherapy does not meet the NICE reference case requirements in that the source of the data for HRQoL should be patients and the HRQoL valued with a choice-based method. [62]Applying this decrement to the pre-progression health state HRQoL results in a value of 0.624, which is lower than the HRQoL in the post-progression state at [redacted]. Furthermore, and as discussed in Section 4.2.4, not all patients may receive R-chemotherapy for the full 6 treatment cycles. Nonetheless, the impact on the ICER is small (e.g. removing the 0.2 decrement increases the ICER by [redacted]). Given that suitable alternative was not identified, and the minor impact on the results, the ERG considers the company's parameterisation to be suitable to inform this decision although subject to some uncertainty.

4.2.9 Resources and costs

The resource use and costs included: treatment cost, non-treatment healthcare costs, cost of allogenic stem cell transplant (allo-SCT) and the cost of treating adverse events. The company conducted a systematic search for published cost and healthcare resource identification, measurement and valuation data in r/r MCL (see CS Appendix I). The searches initially identified 10 studies, with further 2 added following an update search. The company argued that the most relevant reference was a recent NICE single technology appraisal in r/r MCL - TA502[63] - and used this to inform healthcare cost in SoC, and in the first five years of treatment with KTE-X19. The remaining costs (treatment with KTE-X19, SoC, healthcare costs in long-term survivors, and adverse events) were based on methods employed in previous appraisals of CAR T-cell therapies (TA559[28] and TA567[29]), and data collected in ZUMA-2.

4.2.9.1 KTE-X19 treatment costs

KTE-X19 intervention costs were based on methods used in previous CAR T-cell therapy appraisals (TA559 [28] and TA567[29]) and ZUMA-2 data. KTE-X19 treatment cost incorporated the cost of leukapheresis, bridging therapy, conditioning chemotherapy, KTE-X19 acquisition, KTE-X19 infusion and monitoring costs, and the cost of retreatment. The summary of all KTE-X19 treatment costs is provided in Table 17. All treatment costs were applied as one-off costs at the start of the first cycle. As described in Section 4.2.2, cost multipliers were used to account for the 6 patients who did not have KTE-X19 but who had leukapheresis or conditioning chemotherapy.

In response to PfC B13, and given the difference in cost of the administration of conditioning chemotherapy compared to TA559,[28] the company explained that conditioning chemotherapy was expected to be delivered in outpatient setting with added hostel stay, based on input from their clinical

advisors, and that the cost of an elective stay was used to approximate those costs. The company presented a scenario where administration of conditioning chemotherapy was costed as a non-elective long-stay hospitalization (£5,679.32) rather than as an elective hospital stay (£1,382.97). The ICER increased by £752/QALY.

Table 17. Summary of all KTE-X19 treatment costs

Element of cost	Cost per patient	Adjusted cost in the model	Source/Assumption
Leukapheresis	£1,521.11	£1,655.33	NHS reference costs 2018/19,[64] weighted average of all HRGs for stem cell and bone marrow harvest (currency codes SA34Z, SA18Z), as per York study and TA559.[28] Adjusted cost estimated using a multiplier of 1.088 applied to reflect the 6 patients who underwent leukapheresis, but not KTE-X19 infusion
Bridging chemotherapy	Drug cost £1292.87 Administration cost £852.53	[redacted]	Single cycle of R-BAC (drug cost + administration in the outpatient setting) multiplied by the proportion of patients (0.37) who received bridging therapy in ZUMA-2. Adjusted cost estimated using a multiplier of [redacted] applied to reflect the [redacted] out of [redacted] patients who received bridging therapy, but not KTE-X19 infusion.
Conditioning chemotherapy	Hospital admission £1382.97 Chemotherapy acquisition £583.23	£1,995.12	Hospital admission: • NHS reference costs 2018/19,[64] weighted average of elective inpatient HRGs for malignant lymphoma, including Hodgkin's lymphoma and NHL (currency codes SA31A-F). Adjusted the length of stay from 9.4 days (mean length of stay for malignant neoplasms of lymphoid, haematopoietic and related tissue inpatient admissions in Hospital Episode Statistics, 2019[65]) to 3 days (length of treatment in the trial protocol). Chemotherapy acquisition: • 3 infusions of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 • Source of unit costs: eMIT[66] • BSA percentile from ZUMA-2 (n=69), used to estimate dose and vial combination. Assumed drug wastage. Adjusted cost estimates using a multiplier of 1.015 to reflect the 1 patient (out of 69) who underwent conditioning therapy, but not KTE-X19 infusion

Element of cost	Cost per patient	Adjusted cost in the model	Source/Assumption
Cell infusion and monitoring	£460.99 (cost per patient per day)	[redacted]	NHS reference costs 2018/19,[64] weighted average of elective inpatient HRGs for malignant lymphoma, including Hodgkin's lymphoma and NHL (currency codes SA31A-F), divided by the average length of stay (9.4 days) The cost per patient per day is multiplied by [redacted] to reflect the length of hospitalisation in patients who received KTE-X19 in ZUMA-2.
Retreatment	[redacted]	[redacted]	2.9% of the unadjusted costs of conditioning chemotherapy and cell infusion and monitoring to reflect the add on cost of the 2 patients who underwent retreatment. Acquisition of KTE-X19 assumed to incur no addition cost, as the quantity of KTE-X19 initially manufactured is sufficient for the delivery of up to two treatments.
Acquisition of KTE-X19	[redacted]	[redacted]	Company submission Assumes that cost of the drug will only be reimbursed if KTE-X19 is administered to the patient, so is only applied to patients who received KTE-X19.
Total cost excluding acquisition of KTE-X19	[redacted]	[redacted]	
Total cost in the model	[redacted]		
BSA = body surface area; eMIT = electronic market information tool; HRGs = healthcare resource groups = NA, not applicable.			

Points for critique

The methods used to estimate the cost of treatment with KTE-X19 were broadly appropriate and comparable to those used in previous CAR T-cell appraisals (TA559[28] and TA567[29]). With respect to the difference in the costs of the administration of conditioning chemotherapy compared to TA559[28] , the ERG clinical advisors commented that conditioning chemotherapy is given as an outpatient appointment, but patients may stay in a hostel if they do not reside close to the centre. Given the small impact on the ICER and the feedback from the ERG clinical advisors, the ERG believes that the approach to costing the administration of conditioning chemotherapy is reasonable.

The ERG highlights two points of concern: 1) the cost of KTE-X19 treatment (excluding drug acquisition), and 2) inclusion of retreatment in the model.

1. The cost of KTE-X19 treatment, excluding drug acquisition

The company costed KTE-X19 treatment at £[redacted] while the current NHS England tariff price for CAR T-cell therapies is [redacted].

The CS included the same costs as the previous appraisals, except the cost of training that was accounted for in appraisal TA559.[28] These costs use assumptions broadly consistent with previous appraisals of CAR T-cell therapies. The ERG notes that, in response to PfC B14, the company commented that delivery of KTE-X19 is not expected to require any additional training and infrastructure to those already in place for existing CAR-T therapies, as the treatment is expected to be provided at existing CAR-T centres, and the rare nature of MCL means additional capacity will not be needed.

[redacted] therefore the ERG is unable to assess which is the estimate that most accurately reflect the costs to the NHS. For these reasons, the ERG uses the CS estimate (updated with the preferred ERG assumptions) in its base-case, but presents a scenario using the NHS England tariff price.

item 12. The ERG considers the cost of treatment with KTE-X19, excluding KTE-X19 acquisition, to be highly uncertain.

2. Retreatment with KTE-X19

The CS included the cost of retreatment in KTE-X19. Given that retreatment is unlikely to be a plausible treatment option in the NHS setting, the ERG prefers that this cost is not included. This is comparable to previous CAR-T appraisals (TA559[28]).

item 13. The ERG considers that the cost of retreatment with KTE-X19 should be excluded from the costs of KTE-X19.

4.2.9.2 SoC cost

The cost of treatment in SoC was represented as a blended comparator of five different regimens (R-CHOP, R-BAC, R-bendamustine, R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone), and FCR (fludarabine, cyclophosphamide, rituximab)) recommended at first line in the BSH guidelines and those included in the final scope for TA502.[63] SoC cost was the average of the five chemotherapy regimens weighted by their respective distribution in clinical practice, informed by the company's clinical advisors. The cost of SoC accounted for drug acquisition and administration of six cycles of chemotherapy (5 months of treatment). The cost of SoC was applied at the start of the model.

Drug acquisition cost were estimated by multiplying dosage by drug unit costs. Dosage regimens were informed by UK hospital chemotherapy protocols.[68 6970] Drug unit costs were informed by eMIT [66] and MIMS [71] selecting the cheapest brand and pack size. The dose for all chemotherapy drugs except for prednisolone were dosed variably according to patients' BSA, derived from ZUMA-2. BSA was used to estimate the dose and vial combination, taking into account drug wastage, as vials were assumed not to be shared between patients.

The cost of administration was derived from NHS reference costs [64] for outpatient chemotherapy appointments (currency codes SB12Z and SB15Z), where only intravenous chemotherapy was assumed to incur a cost, and only on first administration of the day.

Points for critique

The ERG considers the methods for deriving the cost of SoC and incorporating it into the model to be comparable to previous appraisals, and broadly appropriate.

As discussed in Section 4.2.4, the ERG's clinical advisors considered R-BAC to be the current standard of care. Furthermore, the patients in McCulloch et al (2020), which the ERG prefers to inform the PFS and OS curves with SoC, all received R-BAC.[1] To reflect this, the ERG base-case assumed SoC to consist of R-BAC. The cost of each treatment cycles was weighted by the proportion who received each cycle in McCulloch et al.:[1] 16.7% received 2 cycles, 58.3% received 3 and 4 cycles (assumed 29.15% each), and 25% received 5 and 6 cycles (assumed 12.5% each).[1]

item 14. The ERG believes R-BAC to be the current standard of care.

4.2.9.3 State-specific healthcare costs

Healthcare resource use was assumed to depend on the patients' health state (pre or post progression, or dead), and time from starting treatment (only for KTE-X19). In the first five years pre-progression, and with progression (regardless of the time point), resource use was assumed to be identical to that in

patients receiving second line treatment r/r MCL, derived from a recent NICE single technology appraisal TA502.[63] The resource use in TA502[63] was derived from a survey completed by 52 experts (oncologists, haematologists and haematologist oncologists), about the types and frequency of medical resource use (including visits, procedures, and tests) for an average patient. These are reported in Table 62 (p169) of the CS. Healthcare costs in long-term survivors (after five years without progression) were assumed to be the same as that of the general population apart from a 6-monthly monitoring appointment with the GP, costing £6.50 per model cycle. The reduction in the cost of healthcare in long-term survivors was based on assumptions made in previous appraisals of CAR T-cell therapy in DLBCL, where long term survival implied cure (TA559[28] and TA567[29]). The need for 6 monthly GP appointments was based on the company's clinical advice.

The cost of the end of life care was £4,254 per patient, based on the end of life health care cost for breast, colorectal, lung and prostate cancers reported by Round et al.[72] The cost was applied to all patients who had died.

In response to PfC B10b, regarding the assumption that patients who remained in the pre-progressed state beyond 5 years have 6-monthly GP appointments, the company acknowledged that there is uncertainty in the follow-up care for patients who remain in remission. Therefore, the company presented a scenario where the cost of these patients comprises the cost of 6-monthly GP appointments and the cost of an annual Clinical Haematology outpatient attendance at £173.39. The ICER increases by £146/QALY.

Points for critique

The ERG considers the state-specific resource use to be uncertain, as it is based on clinicians' opinion in TA502.[63] The ERG considers this acceptable given the lack of alternative data sources.

The method for applying the cost of end of life care is commonly used in evaluations for cancer therapy. The cost represents the mean cost for breast, colorectal, lung and prostate cancers, which may be substantially different to that of r/r MCL. Nonetheless, the ERG considers that the cost of end of life care is unlikely to have significant impact on the ICER.

As discussed in Section 4.2.6.1, the ERG considers that it is uncertain whether KTE-X19 can lead to durable long-term remission in r/r MCL. Furthermore, the ERG clinical advisors felt that 6-monthly follow up with a GP was an unrealistic assumption, given that CAR-T therapy in DLBCL requires regular an annual follow up in the haematology clinic for 15 years. Therefore, the ERG prefers to apply this cost in the model rather than the 6-montly GP appointment cost.

item 15. The ERG believes that long term healthcare costs in patients with no relapse after 5 years are uncertain and include at least one clinic appointment per year.

4.2.9.4 Allogenic stem cell transplant

A proportion of patients who receive KTE-X19 and patients who receive SoC are assumed to receive an allogenic stem cell transplant (allo-SCT). The initial cost of treatment was applied as a one off at the start of the first cycle, while follow up costs were applied in 6th, 12th and 24th cycle. The initial cost of treatment (£34,728) was a weighted average of allo-SCT HRGs taken from the NHS reference costs.[64] The cost of follow up at 6 months, 12 months, and 24 were £27,519, £10,082, and £4,699, respectively, were based on the UK Stem Cell Strategy Oversight Committee Report.[73] The cost was weighted by the proportion of patients expected to receive Allo-SCT. In KTE-X19 the proportion was [redacted]% ([redacted] out of 68 patients in ZUMA-2); in SoC the proportion was 20%, based on clinical expert advice.[32] The company explored an alternative proportion, 20.69% from McCulloch et al. (2019) in sensitivity analysis.

Points for critique

The methods for deriving the cost of allogenic stem cell transplants were comparable to previous appraisals. Application of Allo-SCT costs at the start of the cycle suggests that costs are incurred within the first year following treatment (with either KTE-X19 or SoC).

The ERG believes that the proportion of patients who receive allo-SCT in SoC is uncertain. For the ERG base-case and given that the PFS and OS curves for SoC are informed from McCulloch et al, the ERG considers that the proportion of patients who receive allo-SCT is best approximated by the sample in McCulloch et al. at 31%.[1]

item 16. The ERG considers that McCulloch et al (2020) is a more appropriate source for the proportion of patients who have allo-SCT under SoC.

4.2.9.5 Adverse events costs

The company only costed AEs of KTE-X19 treatment; treatment of AEs in SoC was conservatively assumed to incur no additional cost. For KTE-X19, the following AEs were costed individually: all Grade 3 and 4 after taking KTE-X19 or after conditioning chemotherapy, grade 3 or 4 CRS, or any grade requiring treatment with tocilizumab, and B-cell aplasia [hypogammaglobulinaemia] requiring immunoglobulin treatment. All AEs except B-cell aplasia were assumed to be short term, and so their cost was applied as a one off, at the start of the first cycle.

The cost of Grade 3 or 4 events following KTE-X19 treatment, and following chemotherapy, was derived by multiplying the probability of having at least one AE (derived from ZUMA-2, as described in Section 4.2.7) by the cost of one additional hospital bed day as per NHS reference costs.[64] The

company argued that this approach, rather than costing each AE individually, would avoid double counting with those AEs which are managed during the hospitalisation period for KTE-X19 infusion and monitoring.

The cost of CRS accounted for treatment with tocilizumab and intensive care unit stay in patients with Grade 3 or 4 symptoms. Treatment with tocilizumab was derived from the proportion of patients who required treatment in ZUMA-2 (□%) and the NHS reference costs,[64] assuming one administration of tocilizumab was required for each patient. The intensive care unit (ICU) stay was assumed to comprise 4 days, as per TA559,[28] costed as per NHS reference costs.[64]

In their response to B9b, the company's clarified that the average number of doses of tocilizumab in the patients who required it in ZUMA-2 was □. In response to PfC B9a, the company highlighted that ZUMA-2 did not report the length of stay in ICU for the treatment of CRS specifically, but the average length of ICU stay for those patients who were admitted to the ICU (n=□, □%) was □ days. The company thus provided an additional scenario where the cost of treatment of CRS included □ days of ICU in □% of patients, instead of 4 days in patients who had Grade 3 or 4 CRS (15%).

In ZUMA-2, 32% of patients were treated with IVIG for B-cell aplasia. This cost is reflected in the model as a weighted average monthly cost of IVIG treatment of £667.28, which is applied in the first 12 cycles in pre-progressed state. This cost is based on the cost of a monthly administration (£183.54, NHS reference cost[64] for delivering simple parenteral chemotherapy at first attendance), an acquisition cost of IVIG of £20.90 per 0.5g dose and an estimate of the required dose (0.5g/kg; mean weight of 82 kg from ZUMA-2).

As discussed in Section 4.2.7, the cost of treating pancytopenia is not included in the company's base-case. In response to PfC B9c, the company presented a scenario where the cost of pancytopenia is included, assuming that it is associated with two additional bed days in the 5.9% of patients who are assumed to experience it, together with the impact on HRQoL. The ICER increases by £202/QALY.

Points for critique

The methods for deriving the cost of AEs and incorporating them into the model are comparable to previous CAR-T cell appraisals, and broadly appropriate. Treatment of AEs was assumed to incur one additional hospital day. The ERG highlights that this assumption is uncertain, but unlikely to have major impact on the ICER. In addition, the ERG highlights four points of uncertainty: the cost of treating pancytopaenia, the cost of tocilizumab treatment for CRS, the length of stay in ICU for CRS, and the duration of IVIG treatment for B-cell aplasia.

1. *The cost of treating pancytopaenia*

In the company's base-case, pancytopaenia was not included in the AEs considered in terms of costs and HRQoL (see Section 4.2.7). Given the ERG clinical advisors' comment that pancytopenia was one of the most impactful AEs of CAR T-cell therapy in terms of costs and HRQoL, the ERG considers that pancytopenia should be considered in the model. The ERG notes that the company's approach to the inclusion of pancytopenia in the model is subject to uncertain due to the assumptions required regarding its prevalence and impact on costs. Given the lack of empirical data on the impact of pancytopenia, the ERG incorporated these assumptions in the base-case; hence the ERG notes that some uncertainty on the impact of pancytopenia remains.

2. *The cost of treatment of CRS with tocilizumab*

The CS assumed that patients required one dose of tocilizumab in the treatment of CRS. The ERG believes that this assumption is arbitrary and inconsistent with the observed use of tocilizumab in the ZUMA-2 trial at [redacted] doses per patient who required tocilizumab. Therefore, the ERG prefers to use this estimate for its base-case.

item 17. The ERG considers that the cost of treatment with tocilizumab should be based on the observed number of doses in the ZUMA-2 trial rather than on an assumption.

3. *The duration of ICU hospitalisation due to CRS*

The company's base-case informed the duration of ICU stay for the treatment of CSR (at 4 days) was based on data from DLBCL (ZUMA-1 trial in TA559[28]). This is similar to the experience from the ERG clinical advisors, who commented that approximately 36% of DLBCL patients require ICU with an average length of stay of 2-4 days. Nonetheless, the ERG considered the alternative scenario provided in the company's response to PfC B9a ([redacted] days in ICU in [redacted]% of patients) to be more appropriate, given that it is based on the observed ICU stay in the ZUMA-2 trial, which is more relevant to this appraisal. While it is possible that not all of the ICU stay in the trial was due to CRS treatment, ICU stay was not accounted for elsewhere in the model. The ERG base-case is based on these data, although the ERG notes that the duration of ICU hospitalisation is subject to uncertainty.

item 18. The ERG considers that the ZUMA-2 data on the duration of ICU hospitalisation is more appropriate to inform the cost-effectiveness model than data from DLBLC.

4. *The duration of IVIG treatment for B-cell aplasia.*

The company's base-case assumes that duration of treatment of B-cell aplasia with IVIG is 12 months, in line with the company's assumption for TA559. As far as the ERG is aware, the duration of IVIG treatment was not collected in ZUMA-2. In TA559 and in TA567, the company assumed that the duration of IVIG treatment was 1 year, although the ERG preferred the estimate of 3 years.[28, 29] In TA567, the committee accepted the ERG's preferred assumption of 3 years.[33] For these reasons, the ERG considers that the duration of IVIG treatment to be uncertain and presents a scenario to its base-case where 3 years are tested (see 6.1.2.8).

item 19. The ERG believes that the duration of treatment of B-cell aplasia with IVIG is uncertain.

4.2.10 Summary

Overall, a summary of the key assumptions of this model is provided in Table 70 (pg. 176-177) of the CS and a comparison of the main features of this economic analysis against TA502 (Ibrutinib for r/r MCL) in Table 28 (pg. 101-102) of CS.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The cost-effectiveness results of the company's base-case are shown in Table 18. The ICER of the original base-case was £[redacted]/QALY (deterministic) and £[redacted]/QALY (probabilistic). In response to PfC B12b, the company amended their model to fix an implementation error in the way the mortality adjustment for long-term KTE-X19 survivors was implemented. The deterministic ICER changed slightly to £[redacted]/QALY. The company did not report probabilistic results for their updated base-case. Given the similar results between the original and updated base-case, it is likely that the probabilistic ICER of the updated base-case is similar to the probabilistic ICER of the original base-case. Figure 58 (p182) and Figure 59 (p183) in the CS show the cost-effectiveness acceptability curve and the probabilistic scatter plot for the original base-case, respectively. The probability that KTE-X19 is cost-effective at a cost-effectiveness threshold of £30,000/QALY is [redacted] and at a cost-effectiveness threshold of £50,000/QALY is [redacted] according to the original company's base-case. The results suggest that KTE-X19 is both considerably more costly and more effective than SoC, with the consequences of parameter uncertainty concentrated around the additional health outcomes of KTE-X19 compared to SoC.

Table 18: Company's base-case deterministic and probabilistic results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Original cost-effectiveness results (deterministic)							
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original cost-effectiveness results (probabilistic)							
SoC	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated cost-effectiveness results (deterministic)							
SoC	[redacted]	[redacted]	[redacted]				
KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not reported; QALYs, quality-adjusted life years; SoC, standard of care;

Table adapted from response to CS Table 72 pg 182 and PfC Table 33

5.2 Company's sensitivity analyses

The company conducted several scenario analyses in CS (Table 73 of the CS; pg 187) and in response to PfC (See Tables 16, 26, 25, 27 28, 36 of the response to PfC). Only scenarios exploring alternative discount rates had a material impact on the ICER. The company also conducted deterministic one-way sensitivity analyses for all model parameters that were assigned distributions by setting these parameters to their upper and lower limits of their 95% confidence intervals. A tornado diagram of the 20 most influential parameters is shown in Figure 61 of the CS. The results indicate that the pre-progression HRQoL (or utility) value and the mortality adjustment that is used to determine the excess mortality risk that long-terms survivors are subject to compared with the general population are the most influential parameters.

5.3 Model validation and face validity check

The company describes the model validation process in Section B 3.10 of the CS. The ERG undertook further validation checks and identified minor errors which were fixed in the company's response to PfC. No other face validity issues were identified with the model.

The ERG prefers alternative assumptions to those employed in the company's base-case. These are described in Section 6.1.1.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

A summary of the main issues identified and critiqued in Section 4 along with the Section where the ERG addresses each issue in its additional analyses is shown in Table 19.

Table 19: Summary of the main issues identified by the ERG

Critique item and description The ERG considers that:		Dealt with in the ERGs base case	Dealt with in the ERG Scenario analyses	Remaining uncertainty	Significant impact on ICER
1	the model should include the outcomes and costs of all patients who were started in the KTE-X19 treatment pathway.	x			
2	there is uncertainty regarding the generalisability of the ZUMA-2 population to the UK patient population, and specifically around the age at treatment.		Sc 5	x	x
3	the ZUMA-2 data (and any extrapolations based on these) are associated with considerable uncertainty.	x	Sc 1-4	x	x
4	it is uncertain whether and to what extent KTE-X19 can lead to durable long-term remission in r/r MCL.	x	Sc 3	x	x
5	the available data may not be mature enough to robustly estimate mixture cure models and that the long-term survivor fraction is highly uncertain.	x	Sc 1-4	x	x
6	immaturity of the ZUMA-2 data leads to high uncertainty in the extrapolation approach, and that alternative modelling approaches are plausible alternatives to mixture cure models.	x	Sc 1-4	x	x
7	the excess mortality risk of long-term survivors of r/r post-KTE-X19 is uncertain, but it is more appropriate to base it on data from MCL patients than from DLBCL patients.	x	Sc 1	x	x
8	McCulloch et al (2020) is the most appropriate source of data to inform PFS and OS under SoC.	x			
9	the company's unadjusted naïve comparison is subject to unquantifiable bias and is uncertain			x	
10	the impact of pancytopenia as an AE of KTE-X19 should be explicitly included in the model.	x		x	
11	it is uncertain whether long-term survivors experience the HRQoL of patients in ZUMA-2 or the HRQoL of the age- and sex-matched general population.		Sc 9	x	x
12	the cost of treatment with KTE-X19, excluding KTE-X19 acquisition, to be highly uncertain.		Sc 6	x	x
13	the cost of retreatment with KTE-X19 should be excluded from the costs of KTE-X19.	x			
14	R-BAC is the current standard of care.	x	Sc 8		
15	that long term healthcare costs in patients with no relapse after 5 years are uncertain and include at least one clinic appointment per year.	x		x	
16	McCulloch et al (2020) is a more appropriate source for the proportion of patients who have allo-SCT under SoC.	x			
17	the cost of treatment with tocilizumab should be based on the observed number of doses in the ZUMA-2 trial rather than on an assumption.	x		x	

18	the ZUMA-2 data on the duration of ICU hospitalisation is more appropriate to inform the cost-effectiveness model than data from DLBLC.	x	x	
19	the duration of treatment of B-cell aplasia with IVIG is uncertain.	Sc 7	x	

AE, adverse events; allo-SCT, allogeinic stem cell transplant; DLBCL, diffuse large B-cell lymphoma; HRQoL, health-related quality of life; ICU, intensive care unit; IVIG, intravenous immunoglobulin MCL, mantle cell lymphoma; PFS, progression-free survival; OS, overall survival; R-BAC, Rituximab, bendamustine and cytarabine; r/r, relapsed or refractory; Sc: Scenario; SoC, standard of care;

6.1 Exploratory and sensitivity analyses undertaken by the ERG

As shown in Table 19, the ERG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. The elements where the ERG felt that there was an alternative approach that was more appropriate, were modified and form part of the ERG's alternative base-case analysis (see Sections 6.1.1 for methods and 6.2.1 for results). These modifications were implemented in a cumulative manner for analyses 1 to 11; therefore, analysis 11 incorporates all changes described earlier and corresponds to the ERG's preferred base case. Given the uncertainty in the mortality adjustment (see item 7), the ERG presents a range of plausible ICERs instead of a point estimate for their base-case (see 6.1.1.11 for more details).

Elements which the ERG considered as important areas of uncertainty, but where it was unclear which approach was most appropriate, were explored in the scenario analysis (see Sections 6.1.2 for methods and 6.2.2 for results). Scenarios 1-4 address uncertainties relating to the extrapolation method, whilst Scenarios 5-9 investigate alternative assumptions regarding the average age of patients initiating treatment, the costs, and the HRQoL.

Due to the time required to run the model probabilistically, the ERG ran PSA for 5 scenarios and confirmed that the results were similar. All results shown in Table 22 and Table 23 correspond to deterministic analyses. Probabilistic results for the ERG's base-case are shown only for the ERG's preferred base-case in the last row of Table 22.

6.1.1 **Building the ERG base case**

The analyses that contributed to the ERG's base-case are described below and summarised in Table 20. The ERG base-case comprises of 11 modifications cumulatively implemented (see Appendix E for details regarding the model adaptation).

Table 20: Building the ERG base-case. Description of analyses

Analysis	Description
1. Correcting model errors	Errors corrected by the company in their response to PfC B12.

Analysis		Description
2.	Including the long-term health outcomes and costs of patients who did not receive KTE-X19	The ERG considers that, for consistency and in line with the approach taken in previous TAs for CAR T-cell therapies,[29, 30] the long-term health outcomes and costs of patients who had leukapheresis but were not infused should be included, rather than only considering the short-term costs of these patients as in the company's base-case.
3.	Using McCulloch et al[1] to inform the health outcomes of patients receiving SoC	The ERG considers that McCulloch et al [1] is the most relevant evidence for the PFS and OS of patients with r/r MCL in the absence of KTE-X19, rather than the meta-analysis of pooled studies as in the company's base-case.
4.	Excluding the costs of retreatment with KTE-X19	Given that retreatment is unlikely to be an option in the NHS, the ERG excluded the costs of retreatment; rather than including the cost of retreatment as per the company's base-case.
5.	Sourcing the number of doses of tocilizumab from ZUMA-2	The ERG considers that it is more appropriate to source the number of doses of tocilizumab from the observed tocilizumab doses in ZUMA-2 (at [redacted] per patient who had tocilizumab); rather than assuming 1 dose per patient on average.
6.	Calculating the costs of SoC based on McCulloch et al (2020)[1]	The ERG considers that the most relevant source of evidence to inform the costs of SoC is the McCulloch et al (2020) study,[1] on which the PFS and OS curves are based. Based on this study, the ERG assumes that all patients receive R-BAC, at an average of 3.75 cycles, and 31% receive allo-SCT; rather than assuming a blend of R-BAC, R-CHOP and R-benda, over 6 cycles, and 20% receiving allo-SCT.
7.	Assuming that long-term survivors have an annual haematology outpatient appointment	Given clinical advice to the ERG that patients who are long-term survivors (i.e. have not progressed for 5 years since treatment) are followed up annually in an outpatient haematology clinic, the ERG applies the cost of one outpatient appointment per year and excludes the cost of the biannual GP visit as in the company's base-case.
8.	Obtaining the number of days in ICU from ZUMA-2	The ERG considers that ZUMA-2 provides relevant evidence to inform the number of days in ICU due to the KTE-X19 infusion, and specifically due to CRS. The ERG base-case assumes that [redacted] patients stayed in ICU over an average of [redacted] days (PfC B9a); rather than [redacted]% of patients with and average ICU length of stay [redacted] days in the company's base-case (based on TA559[28]).
9.	Including pancytopenia as an adverse event in the model	Considering pancytopenia as an additional adverse event, given its impact on HRQoL and costs, as per the company's response to PfC B9c.
10.	Predicting PFS and OS with splines during the within-trial period and extrapolating beyond that based on adjusted general population mortality	Assuming that the patients who received KTE-X19 and are still alive at the end of the trial period experience a mortality risk based on the age- and sex-matched general population mortality, adjusted upwards with the company's preferred adjustment (SMR=1.09). The PFS and OS until the end of the trial period are informed by the best fitting cubic spline model.
11.	Excess mortality risk based on MCL data	The ERG considers that the mortality adjustment based on Maurer et al[35] for newly diagnosed patients with DLBCL who have been relapse-free for 24 months (SMR=1.09), is unlikely to be appropriate to reflect the additional mortality risk of long-term survivors of r/r MCL. The ERG prefers estimating HRs based on Eskelund et al data for newly diagnosed MCL patients who were in complete remission for 1 year and for 5 years.[2] Despite the uncertainty associated with the estimation, and the

Analysis	Description
	differences in the Eskelund et al population (newly diagnosed patients) with the patient population in this appraisal (r/r MCL), the ERG considers that this evidence is more likely to be generalisable to the r/r MCL patients who are long-term survivors than the evidence from Maurer et al.
ERG, evidence review group; GP, general practitioner; HR, hazard ratio; HRQoL, health-related quality of life; ICU, intensive care unit; MCL, mantle cell lymphoma; PfC, points for clarification; PFS, progression-free survival; OS, overall survival; R-BAC, Rituximab, bendamustine and cytarabine ; r/r MCL, relapsed or refractory mantle cell lymphoma; SMR, standardised mortality ratio; TA, technology appraisal.	

6.1.1.1 Analysis 1. Correcting model errors

As an initial step, the ERG implemented the two corrections to the model which were made by the company and were included as options in response to PfC B12. The first issue relates to the calculation of the undiscounted total costs and QALYs and does not impact ICER (PfC B12a). The second relates to the implementation of the mortality adjustment to the general population mortality risk, which has a minor impact on the ICER (from £[redacted]/QALY to £[redacted]/QALY). In sum, the mortality adjustment was applied to the probability of death in the company's base-case, which resulted in a probability of death over 1 when adjustment values above 2.8 were used. As the company accepted in response to PfC B12b, that the best practice is to apply the adjustment to the general population mortality rate.

6.1.1.2 Analysis 2. Considering the long-term health outcomes and costs of patients who did not receive KTE-X19

As discussed in Section 4.2.2, the company's base-case model uses cost multipliers to account for the costs of leukapheresis and conditioning chemotherapy of the patients who did not undergo KTE-X19 infusion. This approach does not capture the long-term life expectancy and QALYs, and long-term costs of those patients. For consistency, and in line with the approach taken in the previous TAs for CAR T-cell therapies,[29, 30] the model should consider not only the short-term costs but also the long-term health outcomes and costs (see item 1). The company implemented a decision tree to appropriately capture these costs and effects in response to PfC B1. This is henceforth considered in the ERG's base-case.

6.1.1.3 Analysis 3. Using McCulloch et al (2020) [1] to inform the health outcomes of patients receiving SoC

As highlighted in Section 4.2.6.2, the ERG had concerns with the meta-analysis of highly heterogeneous studies, the inclusion of Eyre et al, [11] and obtaining PFS and OS curves from different studies. Furthermore, the ERG and its clinical advisors consider that McCulloch et al (2020)[1] provides a better representation of the patients' care in NHS at present rather than the other studies selected by the company to inform the SoC. Hence, the ERG considers that McCulloch et al provides the best available evidence on the outcomes of patients who would be eligible for KTE-X19 but who received

the current SoC. Therefore, the ERG requested in the PfC B6 that McCulloch et al (2020) be considered and included in the model.[1] Using McCulloch et al (2020) as the single source of PFS and OS for SoC not only ensures consistency between PFS and OS, but also avoids the need to meta-analyse SoC studies using heterogenous SoC interventions. Given that the company did not include a MAIC of ZUMA-2 against McCulloch et al (2020) in the model in response to PfC B6b, the ERG used McCulloch et al (2020) for an unadjusted naïve comparison with ZUMA-2 mITT,[1] thereby addressing item 8.

6.1.1.4 Analysis 4. Excluding the costs of retreatment with KTE-X19

The ERG noted in Section 4.2.9.1 that retreatment is unlikely to be an option in the NHS and should not be considered in the model. In response to PfC B7, the company explained that two patients in Cohort 1, who had disease progression after having an objective response to KTE-X19, were retreated. Following retreatment, [redacted]. Ideally, to inform the cost-effectiveness model, the data from these patients would have been censored at the time of retreatment or formally adjusted using the methodology to deal with treatment switching.[74] Given the similarities between the original OS curve used to inform the cost-effectiveness model and the censored OS curve presented by the company in their response to PfC B7 (Figure 22), and the small number of patients affected (n=2), the ERG concludes that the impact on the results is minimal. Therefore, the ERG excludes the conditioning chemotherapy, cell infusion, and monitoring costs related to retreatment originally included in the company's model, thereby addressing item 13.

6.1.1.5 Analysis 5. Sourcing the number of doses of tocilizumab from ZUMA-2

As discussed in Section 4.2.9.5, the company's base-case assumes that [redacted] of patients receive, on average, 1 dose of tocilizumab. The proportion of patients was based on the ZUMA-2 data, but the number of doses was based on an assumption used in TA559.[28] In response to PfC B9b, the company reported that the average number of tocilizumab doses among the [redacted] of patients who received tocilizumab in ZUMA-2 was [redacted]. The ERG considers that it is more appropriate to use data from ZUMA-2 to inform the number of doses of tocilizumab. Therefore, this number is used in the ERG's base-case, thereby addressing item 17.

6.1.1.6 Analysis 6. Calculating the costs of SoC based on McCulloch et al (2020) [1]

As noted in Section 4.2.9.2, the company's base-case assumes that patients on SoC receive on average six cycles of a blend of R-BAC (65%), R-CHOP (5%), and R-benda (30%), and that 20% of patients receiving SoC will subsequently also receive allo-SCT based on McCulloch et al (2019).[16] However, the ERG's clinical advisors thought that it is unlikely that patients will be able to tolerate 6 cycles. Also, McCulloch et al (2020),[1] from which the PFS and OS curves for SoC were obtained for the ERG base-case, report that 16.7% received 2 cycles, 58.3% received 3 and 4 cycles, and 25% received

5 and 6 cycles. Assuming that 29.15% received 3 cycles and 29.15% received 4 cycles, and 12.5% received 5 cycles and 12.5% received 6 cycles, the weighted average is 3.75. Furthermore, McCulloch et al (2020) reports that 31% of patients received allo-SCT .[1] The ERG believes that it is more appropriate to base the costs associated with SoC from the same study which informs the PFS and OS curves with SoC. Therefore, the ERG base-case assumes that patients on SoC receive, on average, 3.75 cycles of R-BAC and that 31% of patients who received SoC subsequently had allo-SCT. Given uncertainty regarding whether R-BAC is available in all centres and regarding the number of cycles of treatment, the ERG applies the company's preferred assumptions regarding R-chemotherapy for SoC and the number of cycles for its base-case in Scenario 8, thereby addressing item 14.

6.1.1.7 Analysis 7. Assuming that long-term survivors have an annual haematology outpatient appointment

As noted in Section 4.2.9.3, the company's base-case assumes that patients who remain in the pre-progression state for more than 5 years incur the costs of a GP appointment every 6 months. However, the ERG's clinical advisors considered that these patients were more likely to be followed-up on an annual basis at an outpatient haematology clinic. In response to the PfC B10b, the company added to the biannual GP visit costs, the cost of 1 clinical haematology outpatient attendance per year costed at £173.39 according to NHS reference costs 2018-2019. For the ERG's base-case, the ERG retained the cost of the outpatient appointment but excluded the biannual GP visit cost because it considers the follow-up to take place in the outpatient clinical rather than by the GP. This modification addresses item 15.

6.1.1.8 Analysis 8. Obtaining the number of days in ICU from ZUMA-2

As noted in Section 4.2.9.5, the company's base-case assumes that [redacted] of the patients who receive KTE-X19 will require admission to ICU for the treatment of CRS, and spend on average 4 days in ICU, based on data on DLBCL (from the ZUMA-1 trial in TA559[28]). In response to PfC B9a, the company reported that in ZUMA-2, [redacted] of patients required admission to ICU where they spent on average [redacted] days, noting that this figure is not specific to patients requiring ICU stay to manage CRS. The ERG considers that the evidence from ZUMA-2 is more relevant to the current appraisal than the evidence from ZUMA-1 in DLBCL. While it is possible that not all of ICU stay in the trial was due to CRS treatment, the ERG notes that ICU stay was not accounted for elsewhere in the model apart from in the costs due to CRS. For these reasons, the ERG considers its inclusion in the costs associated with the AEs due to KTE-X19 to be appropriate and uses it to inform the ERG base-case, thereby addressing item 18.

6.1.1.9 Analysis 9. Including pancytopenia as an adverse event

As noted in Sections 4.2.7, 4.2.9.5, and 4.2.8.2, the company's base-case considers thrombocytopenia, neutropenia, and anaemia. However, it does not consider pancytopenia (i.e. the possibility of patients

suffering from all three blood cell deficiencies). The ERG clinical advisors commented that pancytopenia is the most significant AE in terms of HRQoL and costs. In response to PfC B9c, the company noted that pancytopenia was not measured after KTE-X19 infusion in ZUMA-2, but only after conditioning chemotherapy. In order to include pancytopenia in the model, the company assumed that the incidence of patients with pancytopenia is equal to the incidence of thrombocytopenia (i.e. the blood deficiency with the lowest incidence) at 5.9% of patients who received KTE-X19. The duration of pancytopenia (and so its impact on the HRQoL) was assumed to be 126 days (i.e. twice as much as the duration of thrombocytopenia which had the largest duration among the three AEs). The cost of managing pancytopenia was assumed to be that of two bed days (instead of [redacted] which was assumed for the other three AEs). The ERG and its clinical advisors believe that pancytopenia should be included in the model, given its potential impact after KTE-X19. Given the lack of empirical data on the impact of pancytopenia, the ERG incorporated these assumptions in the base-case, thereby addressing item 10.

6.1.1.10 Analysis 10. Predicting PFS and OS with splines during the within-trial period and extrapolating beyond that based on adjusted general population mortality

As noted in Section 4.2.6.1, the company's base-case uses a mixture cure model to model the ZUMA-2 PFS and OS data and extrapolate beyond the trial period. The ERG has a number of concerns regarding the extrapolation in the company's base-case, which are detailed in the Points for critique.

In light of these limitations, the ERG prefers a hybrid model where the within-trial period is informed by cubic spline models and the extrapolation is informed by general population mortality risk, adjusted for the excess mortality risk experienced by long-term survivors. The spline models have a better fit to the ZUMA-2 data (as suggested by their lower AIC/BIC). Additionally, spline models are more flexible than standard parametric models, hence can accommodate heterogeneity in the ZUMA-2 population if there is a patient group who experience remission for a longer period of time. The best-fitting spline models were the 1-knot normal for PFS and the 2-knots normal for OS, hence these models are used in the ERG base-case. Informing the extrapolation period based on adjusted general population mortality assumes that this is a reasonable proxy for the risk of relapse and death beyond the ZUMA-2 trial horizon. The advantage of the ERG's approach is that it makes use of the available data from the ZUMA-2 trial whilst retaining flexibility regarding the switch point and excess mortality risk in the long-term. To illustrate the impact of the switch point on the cost-effectiveness results, the ERG conducted a univariate sensitivity analysis to the mortality adjustment to inform the excess mortality risk (see Section 6.1.3.1) and to the switch point (see Section 6.1.3.2).

There are some important differences between the ERG's approach and the company's base-case. In the company's base-case, (i) the proportion of patients who comprise the long-term survivor fraction is estimated by the mixture cure model; (ii) the patients who comprise long-term survivor fraction are

assumed to experience the adjusted-general population mortality risk from the time of infusion with KTE-X19 (that is, time zero in the model); (iii) the patients who comprise the non-long-term cure fraction are assumed to experience a progression risk and a mortality risk informed by a standard parametric model (which is estimated jointly with the long-term survivor fraction by the mixture cure model). In the ERG's approach, all patients are assumed to experience the progression and mortality risk predicted by the same spline models up to the end of the trial follow-up. At the end of the trial follow-up, the patients who are still alive are assumed to experience the adjusted-general population mortality risk. In practice, as shown in Section 6.2.3, the company's and the ERG's approach result in similar predictions as long as the switch point in the ERG's hybrid model is at the end of the ZUMA-2 trial horizon and that the same adjustment to the general population mortality is used.

These modifications aim to address item 3, item 4, item 5, and item 6, although the ERG highlights that the extrapolation of the PFS and OS beyond the ZUMA-2 follow-up in the ERG base-case is subject to high uncertainty. This uncertainty is due to the limitations of the ZUMA-2 data and the lack of evidence regarding long-term survival in r/r MCL patients.

6.1.1.11 Analysis 11. Excess mortality risk based on MCL data

As detailed in Section 4.2.6.1 (item 7), the ERG considers that a mortality adjustment of 1.09, based on a study in DLBCL,[35] is not appropriate to reflect the long-term risk of relapse and death following KTE-X19 for r/r MCL patients compared to the age- and sex-matched general population. As the company discusses in PfC B2b and the ERG agrees, DLBCL is a different disease to MCL, with generally a better prognosis. Furthermore, the ERG's clinical advisors considered that the additional risk of DLBCL is not generalisable to r/r MCL and that the additional risk of death compared to the general population is likely to be higher in r/r MCL than in DLBCL.

The ERG prefers to use long-term data from MCL patients, based on Eskelund et al.[2] Eskelund et al provides the OS curves of patients with newly diagnosed MCL who were mostly treated with autologous SCT and of the comparable general population in terms of age, calendar year of follow-up, and country of origin (see Figure 12). The ERG derived hazard ratios (HRs) for OS by digitising the Eskelund et al[2] curves, and assuming proportional hazards and that the exponential distribution is appropriate for both curves (details in Appendix C). Two HRs were derived: based on the patients who sustained complete remission for at least 1 year (HR=4.37), and another based on the patients who sustained complete remission for at least 5 years (HR=2.36).

In the ERG base case, the switch from ZUMA-2 survival to the adjusted general population mortality happens at the end of the trial follow up, at [redacted] months. The ERG base-case uses the lower and higher HR as the lower and upper range of the mortality adjustment. This assumes that the patients who are still alive in the model at [redacted] months are patients who have been in complete remission for

1 year or will be in complete remission for 5 years. This assumption is required because the cost-effectiveness model does not explicitly consider complete remission. Nonetheless, the ERG considers that this assumption is plausible given the survival projections for SoC, which indicate that non-responders are likely to have died by this point, and estimated 12-month and 24-month OS rate in complete responders in ZUMA-2 at [redacted]% and [redacted]%, respectively (see PfC A2). While it is possible that patients still alive at [redacted] months will remain in complete remission for 5 years (60 months), the limited number of patients at risk preclude robust predictions to support this. Conversely, the 1-year HR could be seen as more consistent with the median follow-up of the ZUMA-2 trial at [redacted]months. Therefore, the ERG considers that presenting results as a range, based on the two alternative HRs, to be a pragmatic approach, and presents a univariate sensitivity analysis to the HR value (see Section 6.2.3.1) and to the timing of the switch point (see Section 6.2.3.2).

The ERG considers that the appropriate mortality adjustment is a major area of uncertainty. This is for a number of reasons: (i) the study population in Eskelund et al[2] comprises newly diagnosed MCL patients, mostly treated with autologous SCT at first line whilst the population in this appraisal is patients with r/r MCL treated with KTE-X19; (ii) Eskelund et al[2] does not report numbers at risk, hence the estimation of HR was based on the digitised points rather than on the number of patients at risk and who died over time; (iii) given the data limitations, the estimation of the HR assumes that the OS curves of the general population and the study population follow exponential distributions, (iv) it is not possible to derive valid confidence intervals given that the standard errors refer to the fit of the curves to the digitised points rather than to the original data; and (v) the estimation uses the Eskelund et al[2] comparison between patients in complete remission and the general population at 1 and 5 years, which does not directly match to the end of trial follow-up at [redacted] months. For these reasons, the ERG views these HRs as indicative of the extent of the differences in mortality risk between MCL patients in complete remission and the general population and highlights that these estimates are very uncertain. Despite the limitations and the high uncertainty, the ERG considers this approach to be more appropriate than the use of a mortality adjustment from another condition. The ERG further conducted univariate sensitivity analyses to explore the impact of the mortality-adjustment on the ICER (***[redacted]14).

6.1.2 Scenario analyses to the ERG base-case

The scenario analyses to the ERG's base-case are described below and summarised in Table 21. All except for scenario 1 were run for both adjustments to the general population mortality risk considered in the ERG base-case (HR=2.36 and HR=4.37, as per Section 6.1.1.11), and the range of plausible ICERs is shown in the results. The resulting OS and PFS curves for all extrapolation scenarios (i.e. Scenarios 1-4) are shown in Appendix D.

Table 21: Description of scenario analyses to the ERG base-case

Scenario		Description
1.	Alternative adjustments to the general population mortality for the extrapolation	This scenario explores the impact of matching the switch point to the data informing the mortality adjustment to the general population mortality risk, which informs the PFS and OS curves after the switch: (a) HR=4.37 from patients who were in complete remission for 1 year, with the switch point at 1 year; (b) HR=2.36 from patients who were in complete remission for 5 years, with the switch point at 5 years.
2.	Assuming that the long-term survivors correspond to the long-term survivor fraction estimated by the mixture cure model fitted to the PFS curve	This scenario aims to address the uncertainty regarding whether patients who have progressed can experience long-term survivorship and the uncertainty in the proportion of patients can be considered long-term survivors. In this scenario, (1) the long-term survivors are assumed to correspond to the long-term survivor fraction as estimated by the lognormal mixture cure model; (2) the long-term survivors are assumed to experience the adjusted-general population mortality risk, adjusted using the ERG's preferred HRs; (3) the non-long-term survivors are assumed to experience the progression and mortality risk as estimated by the lognormal mixture cure model for the non-long-term survivor fraction.
3.	Assuming that the ZUMA-2 data are sufficient to robustly estimate mixture cure models to inform the extrapolation	This scenario aims to address the uncertainty on whether the mixture cure models can robustly inform the extrapolation by estimating a long-term survivor fraction. This scenario corresponds to the company's preferred approach for OS and PFS with KTE-X19, although the adjustments to the general population mortality are obtained from Eskelund et al [2] as per the ERG base-case.
4.	Assuming that a standard parametric model is appropriate for the extrapolation of PFS and OS	This scenario aims to address the uncertainty regarding whether a standard parametric model is appropriate to extrapolate the PFS and OS based on ZUMA-2. It is implemented using the lognormal parametric model for both OS and PFS and for both the within-trial and the extrapolation period, including the logical constraint with the adjusted general population mortality risk.
5.	Assuming that the average age at treatment with KTE-X19 is similar to the average age at treatment in McCulloch et al (2020) [1]	This scenario aims to address the uncertainty regarding the average age of the patient population eligible for KTE-X19. Instead of the average age of patients in the ZUMA-2 trial at 63.2, this scenario assumes the average age of the patients in the McCulloch et al (2020) study at 65.2 years. [22]
6.	Assuming that the NHS England tariff for CAR T-cell therapy accurately reflects the costs of administration to the NHS	This scenario aims to address the uncertainty regarding the costs of administering KTE-X19 incurred by the NHS, by implementing the NHS England tariff in the model; rather than the company's estimated costs.
7.	Assuming that the duration of IVIG treatment for B-cell aplasia is 3 years	This scenario aims to address the uncertainty regarding the duration of IVIG treatment for B-cell aplasia, from 1 year as in the company's base-case to 3 years as in TA567[29] and TA559.[28]
8.	Cost of chemotherapy in standard of care based on the company's preferred blend and number of cycles	This scenario aims to address the uncertainty in the cost of chemotherapy used in SoC, in the absence of KTE-X19, given that R-BAC may not be used in all centres. This scenario uses the company's blended comparator which included 5% R-CHOP, 65% R-BAC, and 30% R-benda over 6 cycles.
9.	Assuming that the HRQoL of patients who remain in the pre-progression state for more than 5 years is lower than the general population	This scenario aims to address the uncertainty around the HRQoL of patients who remain in the pre-progression state for more than 5 years. It is implemented by reducing the HRQoL of these patients by 10% and by 20%.

Scenario	Description

ERG, evidence review group; GP, general practitioner; HR, hazard ratio; HRQoL, health-related quality of life; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MCL, mantle cell lymphoma; PfC, points for clarification; PFS, progression-free survival; OS, overall survival; R-BAC, Rituximab, bendamustine and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-benda, rituximab plus bendamustine; r/r MCL, relapsed or refractory mantle cell lymphoma; SMR, standardised mortality ratio; TA, technology appraisal.

6.1.2.1 Scenario 1. Using alternative adjustments to the general population mortality for the extrapolation

This scenario explores the impact of matching the switch point to the data informing the hazard ratios (HRs) adjusting the general population mortality risk, which informs the PFS and OS curves after the switch: (a) HR=4.37 from patients who were in complete remission for 1 year, with the switch point at 1 year; (b) HR=2.36 from patients who were in complete remission for 5 years, with the switch point at 5 years. For both scenarios, the PFS and OS were based on the best fitting spline model (i.e. PFS: 1-knot normal, OS: 2-knots normal) up to the time point of the switch to the adjusted general population mortality. This scenario addresses item 7.

6.1.2.2 Scenario 2. Assuming that the long-term survivors correspond to the long-term survivor fraction estimated by the mixture cure model fitted to the PFS curve

This scenario aims to address the uncertainty regarding whether patients who have progressed can experience long-term survivorship and the uncertainty in the proportion of patients can be considered long-term survivors, thereby addressing item 4 and item 5.

The long-term survivors correspond to the long-term survivor fraction as estimated by the lognormal mixture cure model fitted to the PFS curve (which was employed in the company's base-case) at [redacted]%. This assumes that the ZUMA-2 data are mature enough and provide an adequate follow-up to infer the long-term survivor fraction from the PFS curve plateaus. The patients who are not long-term survivors (i.e. the non-long-term survivors) are assumed to experience the progression risk as estimated by the lognormal mixture cure model for non-long-term survivor fraction.

The difference from the company's base-case is that the mortality risk is estimated from the best fitting spline model fitted to the OS curve up to the point where the OS and the PFS curve meet, rather than from the mixture cure model fitted to the OS curve. Therefore, in this scenario, the long-term survivor fraction is determined only by the PFS curve rather than by both the PFS and OS curves.

6.1.2.3 Scenario 3. Assuming that the ZUMA-2 data are sufficient to robustly estimate mixture cure models to inform the extrapolation

This scenario aims to address the uncertainty on whether the mixture cure models can robustly inform the extrapolation. The scenario is implemented using the company's preferred lognormal mixture cure models for both the within trial period and the extrapolation period, and for both PFS and OS, albeit

with the ERG preferred mortality adjustments based on Eskelund et al.[2] This approach assumes that the ZUMA-2 data are mature enough, and provide an adequate follow-up, to confidently infer that the observed plateaus in the PFS and the OS curves suggest that a proportion of the patients are long-term survivors, and that the long-term survivor fraction can be robustly estimated from these data. This scenario aims to address item 5.

6.1.2.4 Scenario 4. Assuming that a standard parametric model is appropriate for the extrapolation of PFS and OS

This scenario aims to address the uncertainty regarding whether a standard parametric model is appropriate to extrapolate the PFS and OS based on the ZUMA-2 data, addressing item 6. Given the immaturity of the data, it is uncertain whether a standard parametric model can be completely ruled out as implausible. This scenario uses the lognormal parametric model for both PFS and OS given its goodness of fit and predicted hazard rates (see Section 4.2.6.1. and Figure 21), but with a logical constraint on the probability of progression and death. This logical constraint takes the largest of either the probability predicted by the parametric model or the probability calculated from the adjusted general population mortality risk, adjusted with the ERG's preferred mortality adjustment based on Eskelund et al.[2] The ERG notes that, without the logical constraint, the lognormal parametric model would predict that ~[redacted]% of patients would be alive at 100 years, which is clearly implausible.

6.1.2.5 Scenario 5. Assuming that the average age at treatment with KTE-X19 is similar to the average age at treatment in McCulloch et al (2020)[1]

This scenario aims to address the uncertainty regarding the average age of the patient population eligible for KTE-X19 (see Section 4.2.3). Rather than the average age of patients in the ZUMA-2 trial at 63.2 years as in the base-case, this scenario assumes the average age of the patients in the McCulloch et al (2020) study at 65.2 years.[1, 22]

6.1.2.6 Scenario 6. Assuming that the NHS England tariff for CAR T-cell therapy accurately reflects the costs to the NHS

This scenario aims to address the uncertainty regarding the costs of administering KTE-X19 incurred by the NHS. As highlighted in Section 4.1.9.1., the ERG was made aware of an NHS England tariff being in place to reimburse centres that undertake CAR T-cell therapies which amounts to [redacted] For comparison, in the ERG's base-case these costs amount to [redacted], following a similar approach to those employed in prior TAs of CAR T-cell therapies [30]; TA559. [28] [redacted], the ERG used the NHS England tariff in this scenario. This scenario aims to address item 12.

6.1.2.7 Scenario 7. Assuming that the duration of IVIG treatment for B-cell aplasia is 3 years

As noted in Section 4.2.9, the company's base-case assumes that B-cell aplasia is treated with IVIG for the duration of 1 year. The ERG has kept this assumption in its base-case given the limited data. In

light of the uncertainty regarding the duration of IVIG treatment, the ERG implemented the preferred assumptions of TA567 as a scenario. This scenario aims to address item 19.

6.1.2.8 Scenario 8. Cost of chemotherapy in SoC based on the company's preferred blend and number of cycles

This scenario aims to address the uncertainty in the cost of chemotherapy used in SoC, in the absence of KTE-X19. As described in 6.1.1.6, the ERG base-case assumes that patients have R-BAC over 3.75 cycles on average, as per McCulloch et al . [1] However, there is uncertainty regarding whether all centres use R-BAC as the preferred chemotherapy. Therefore, in this scenario, the ERG used the company's preferred blended comparator which included 5% R-CHOP, 65% R-BAC, and 30% R-benda over 6 cycles. This scenario aims to address item 14.

6.1.2.9 Scenario 9. Assuming that the HRQoL of patients who remain in the pre-progression state for more than 5 years is lower than the general population

This scenario aims to address the uncertainty around the HRQoL of patients who remain in the pre-progression state for more than 5 years. The company's base-case assumes that the HRQoL of these patients corresponds to the HRQoL of the age- and sex-matched UK general population. However, the assumption was insufficiently justified and the ERG clinical advisors noted that it was uncertain. In the absence of additional evidence, the ERG has maintained this assumption for its base-case but recognises that it is an important area of uncertainty. To explore the impact on the results, the ERG reduces the HRQoL by 10% and 20%, although these are arbitrary reductions for illustrative purposes. This scenario aims to address item 11.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.2.1 Results of analyses building the ERG base-case

A summary of results for the analyses that led to the ERG's preferred base-case (i.e. analyses 1-11) is shown in Table 22 in a cumulative manner; analysis 11 corresponds to the ERG's preferred base-case.

Analysis 1 to 10 had limited impact on the ICER. Overall, the ICER changed from £[redacted] in the company's base-case to [redacted]/QALY in analysis 10, an increase of £[redacted]/QALY. This increase is primarily due to the use of McCulloch et al (2020) [1] as the ERG's preferred source of data to inform PFS and OS with SoC (analysis 3, Section 6.1.1.3). Analysis 10 shows that using a spline model for the within-trial period and extrapolating thereafter based on external adjusted general population mortality data, instead of using a mixture cure model for both the within-trial period and the whole of the extrapolation period, does not lead to a substantially different ICER compared with the company's base-case if the same mortality adjusted to the general population mortality risk is used.

The analysis with the largest impact on the ICER was analysis 11 (Section 6.1.1.11), where the ERG uses alternative mortality adjustments to the general population mortality for the patients who are alive at the end of the trial follow-up. As discussed in Section 6.1.1.11, the ERG estimated mortality adjustment values as a HR based on the Eskelund et al's[2] comparison of survival of patients with newly diagnosed MCL following first line treatment including autologous SCT, after 1 year in complete remission (HR=4.37) and after 5 years in complete remission (HR=2.36), with the general population. Given the uncertainty in the estimation of these HRs and in their generalisability to the r/r MCL patients who received KTE-X19, the uncertainty in the ZUMA-2 data and the limited evidence on the long-term survival in r/r MCL, the ERG presents a range of plausible ICERs using the lowest and highest adjustment values which were estimated from the Eskelund et al data.[2] In the ERG's base-case, deterministic results suggest that KTE-X19 compared with SoC is associated with an ICER of [redacted] per QALY gained. The probabilistic ICER is [redacted]/QALY.

6.2.2 Results of the scenario analyses to the ERG base-case

In general, most analyses resulted in similar ICERs to the ERG base-case. Alternative extrapolation approaches resulted in ICERs around or above [redacted] per QALY. The lowest ICER range was estimated in Scenario 3 which used the company's preferred extrapolation approach (i.e. based on the lognormal mixture cure model) with the ERG's preferred mortality-adjustment for long-term survivors [redacted]. The highest ICER range was estimated in Scenario 4 where a single parametric lognormal model is used for extrapolation in conjunction with the ERG's preferred mortality-adjustment ([redacted]).

Alternative costing assumptions with regards to the duration of IVIG treatment or the composition SoC did not materially impact the ICER. However, increasing the average age by 2 years from 63.2 years as per ZUMA-2 to 65.2 years as per McCulloch et al [1, 22] increases the ICER to [redacted] (Scenario 5). Using the NHS England tariff of [redacted] as an estimate of all costs associated with KTE-X19, except for treatment acquisition (Scenario 6), resulted in an ICER range of [redacted]. Finally, assuming that patients who remain progression-free for more than five years do not experience the HRQoL of age-adjusted general population HRQoL, but instead a HRQoL reduced by a factor of 20%, [redacted] the ICER by around [redacted] per QALY.

Table 22: ERG's preferred assumptions (ERG base-case)

	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs SoC)
	KTE-X19	SoC	KTE-X19	SoC	
CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Changes without substantial impact on ICER					
1. Correcting model errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. 1+ Including the long-term health outcomes and costs of patients who did not receive KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. 2+ Using McCulloch et al [1] to inform the health outcomes of patients receiving SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. 3+ Excluding the costs of retreatment with KTE-X19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. 4+ Sourcing the number of doses of tocilizumab from ZUMA-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. 5+ Calculating the costs of SoC based on McCulloch et al (2020) [1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. 6+ Assuming that long-term survivors have an annual haematology outpatient appointment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. 7+ Obtaining the number of days in ICU from ZUMA-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. 8+ Including pancytopenia as an adverse event in the model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. 9+ Predicting PFS and OS with splines during the within-trial period and extrapolating beyond that based on adjusted general population mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Changes that materially impact ICER					
11. Excess mortality risk based on MCL data [2] Ranges are presented based on the two HRs. Probabilistic results are shown in parentheses **ERG's PREFERRED BASE-CASE**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All analyses were run deterministically. Probabilistic results are shown only for the ERG's base case in parentheses.

Table 23: ERG scenario analyses

Scenario analysis	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs SoC)
	KTE-X19	SoC	KTE-X19	SoC	
ERG's preferred base-case (i.e. analysis 11)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative extrapolations					
1. Alternative adjustments to the general population mortality for the extrapolation a) 1 year following KTE-X19 treatment (rather than at 2.5 years as in the ERG base-case) and informing the mortality adjustment from the comparison of patients who had complete remission at 1 year with age- and sex-matched general population (i.e. HR = 4.37)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) 5 years following KTE-X19 treatment rather than at 2.5 years as in the ERG base-case and informing the mortality adjustment from the comparison of patients who had complete remission at 5 years with age- and sex-matched general population (i.e. HR = 2.36)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Assuming that the long-term survivors correspond to the long-term survivor fraction estimated by the mixture cure model fitted to the PFS curve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Assuming that the ZUMA-2 data are sufficient to robustly estimate mixture cure models to inform the extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Assuming that a standard parametric model is appropriate for the extrapolation of PFS and OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative average age at treatment					
5. Assuming that the average age at treatment with KTE-X19 is similar to the average age at treatment in McCulloch et al (2020) [1] at 65.2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative cost assumptions					
6. Assuming that the NHS England tariff for CAR T-cell therapy at £[redacted] accurately reflects the costs of administration to the NHS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Assuming that the duration of IVIG treatment for B-cell aplasia is 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Cost of chemotherapy in standard of care based on the company's preferred blend and number of cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Impact of late relapses on HRQOL					
9. Assuming that the HRQoL of patients who remain in the pre-progression state for more than 5 years is lower than the general population a) 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b) 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.3 Univariate sensitivity analysis

6.2.3.1 Univariate sensitivity analysis to the mortality adjustment for long-term survivors

***[redacted] 14 shows the results of the univariate sensitivity analysis to the mortality adjustment; that is, the HR which aims to reflect the excess mortality risk experienced by r/r MCL patients who are long-term survivors compared to the age- and sex-matched general population. As discussed in Sections 4.2.6.1 and 6.1.1.11, and stated in item 7, the ERG considers that the excess mortality risk of long-term survivors of r/r post-KTE-X19 to be uncertain, but to be more appropriate to base it on data from MCL patients than from DLBCL patients. This analysis explores the consequences of this uncertainty for the cost-effectiveness results.

For both the company's and the ERG's base-case, the ICERs are approximately [redacted]/QALY if mortality adjustment for long-term survivors is based on the DLBCL evidence derived in Maurer et al [35] (specifically [redacted] for the company's base-case and [redacted] for the ERG's base-case). As the adjustment increases, so do the ICERs and for a HR of 5, ICERs exceed [redacted]/QALY (specifically [redacted] for the company's base-case and [redacted] for the ERG's base-case). Overall, conditional on the mortality adjustment, the company's and the ERG's ICERs are similar.

[redacted] 14 [redacted]

[redacted]

6.2.3.2 Univariate sensitivity analysis to the switch point to adjusted general population mortality risk

***[redacted] 15 shows the results of the univariate sensitivity analysis to the switch point; that is, the time at which the probability of death in the model is based on only the adjusted general population mortality risk. As discussed in Sections 4.2.6.1, 6.1.1.10 and 6.1.1.11, the appropriate switch point is uncertain. In the ERG base case, the switch from ZUMA-2 survival to the adjusted general population mortality happens at the end of the trial follow up, at [redacted] months.

The upper line in red uses the higher HR at 4.37, estimated from the Eskelund et al comparison between MCL patients in complete remission for 1 year compared to the general population; the lower line in blue uses the lower HR at 2.36, estimated from the Eskelund et al comparison between MCL patients in complete remission for 5 years. The results suggest that earlier switch point at 1-year result in lower ICERs at £[redacted]/QALY for HR=2.36 and £[redacted]/QALY for HR=4.37. The ICERs increase up to approximately 5 years, where the ICERs plateau at approximately £[redacted]/QALY for HR=2.36 and £[redacted]/QALY for HR=4.37. The difference in the ICERs between the two HRs is similar irrespective of the changes in the switch point at approximately £[redacted]/QALY.

[redacted] 15 [redacted]

[redacted]

6.3 *Conclusions of the cost effectiveness section*

The company submitted a *de novo* partitioned survival cost-effectiveness model which was largely consistent with the models submitted in previous NICE appraisals of CAR T-cells. The ERG deems that the submitted evidence reflects the decision problem defined in the final scope and meets the requirements of the NICE reference case.

There are, however, areas of uncertainty and limitations with some of the company's assumptions and model inputs. The main area of uncertainty relates to the long-term PFS and OS of the patients who receive KTE-X19. The company's base-case uses a mixture cure model to inform the OS and PFS of patients receiving KTE-X19 from infusion to the longer term. This mixture cure model assumes that there are two groups of patients, the long-term survivors who, after treatment with KTE-X19, experience the general population mortality risk, adjusted upwards with an adjustment obtained from newly diagnosed patients in DLBCL who were progression-free for 24 months;[35] and the non-long-term survivors who experience progression and mortality risk estimated from the trial data.

The ERG is concerned that the company's base-case may not accurately reflect the cost-effectiveness of the use of KTE-X19 for the treatment of r/r MCL patients and is subject to high uncertainty. The major sources of uncertainty are the generalisability of the ZUMA-2 trial population to the UK population, and specifically around the age at treatment (item 2); the long-term PFS and OS of r/r MCL patients after KTE-X19 (items 3 to 6); the excess mortality risk experienced by long-term survivors (item 7); the generalisability to the UK NHS and comparability with ZUMA-2 of the observational studies informing the PFS and OS for SoC (items 8 and 9); the HRQoL of durable survivors in the long-term (item 11); and the administration costs of KTE-X19 (item 12). In particular, and as discussed in Section 4.2.6.1, the ERG considers that the company's approach, using mixture cure models which rely on the assumption that a proportion of patients are long-term survivors immediately after KTE-X19 treatment and experience an adjusted general population mortality risk, not to be sufficiently evidenced; and the adjustment to the general population mortality risk from DLBCL patients to be unlikely to generalise to the r/r MCL population.

Other areas of uncertainty and limitations, which have a smaller impact on the results, are summarised in Table 11 and include the exclusion of the long-term costs and health outcomes of the patients who had leukapheresis but who did not receive KTE-X19 (item 1), the approach to the inclusion of adverse effects due to KTE-X19 (items 10, 17, 18, 19), and some aspects of the approach used to parameterise costs with KTE-X19 and with SoC (items 13, 14, 15, 16).

To address these issues, the ERG made a number of changes to the company's base-case (see Section 6.1). Given the uncertainty in the estimation of the mortality adjustments from Eskelund et al[2] to inform the excess mortality risk and in their generalisability to the r/r MCL patients who received

KTE-X19, the uncertainty in the ZUMA-2 data and the limited evidence on the long-term survival in r/r MCL, the ERG presents a range of plausible ICERs using the lowest and highest adjustment values which were estimated from the Eskelund et al data.[2] The ERG's base-case estimated an ICER range of [redacted] per QALY gained.

Despite the ERG's attempt to address the key uncertainties, limitations in the evidence base meant that some of these uncertainties could not be fully explored (see Table 19). First, and as discussed in Sections 3.2.1.3 and 4.2.3, the ERG considers that the generalisability of the ZUMA-2 population to the UK patients who may have KTE-X19 is uncertain and notes that age at treatment has a large impact on the results (Scenario 5).

Second, given the immaturity of the ZUMA-2 trial and the lack of evidence of durable long-term remission in r/r MCL with other therapies, the ERG concludes that there is uncertainty regarding whether and to what extent KTE-X19 can lead to durable long-term remission (items 3 and 4). The ERG base-case employs a spline model for the within-trial period with a switch to an adjusted general population mortality beyond this. The advantage of the ERG's approach is that it makes use of the available data from the ZUMA-2 trial whilst retaining flexibility regarding the switch point and excess mortality risk in the long-term. Nonetheless, substantial uncertainty remains, which has a considerable impact on the ICER. The ERG explored alternative extrapolation assumptions in scenarios 1-4 and alternative switch points in a univariate sensitivity analysis (see Section 6.2.3). Addressing this uncertainty around the long-term outcomes requires longer-term follow-up of the ZUMA-2 trial and/or long-term observational evidence of r/r MCL patients post-KTE-X19 treatment.

Third, there is uncertainty around the mortality adjustment to the general population mortality risk to reflect the excess mortality risk of long-term survivors. As discussed in Section 6.1.1.11, the ERG's preferred mortality adjustment, estimated from the Eskelund et al data,[2] is subject to uncertainty due to the mismatch between the Eskelund et al study population (newly diagnosed MCL patients mostly treated with autologous SCT and who achieved complete remission for 1 or 5 years) and the population in this appraisal (r/r MCL patients after KTE-X19 therapy) and uncertainty related to the available data and methodology used to derive the mortality adjustments. To explore the consequences of the uncertainty around the mortality adjustment, the ERG presents a univariate sensitivity analysis where the adjustment is varied between the values of 1 and 5 (see ***[redacted]14). The ERG highlights that without long-term data from r/r MCL patients sustaining complete remission after KTE-X19, it is difficult to accurately infer the excess mortality risk that long-term r/r MCL survivors after KTE-X19 are subject to, compared with the general population.

Fourth, the cost-effectiveness estimates are based on an uncontrolled naïve comparison, hence the results are affected by unquantifiable bias and are uncertain (item 9). However, given the magnitude of comparative effectiveness of KTE-X19, this is unlikely to have a major impact on the ICER.

Fifth, the HRQoL of patients who have not progressed in the long-term is uncertain. The ZUMA-2 data suggests that patients who have not progressed have similar HRQoL to the age- and sex-matched general population. After 5 years in the pre-progressed state, the model assumes that the HRQoL corresponds to the age- and sex-matched general population. No evidence was submitted to support this assumption. Given the excess mortality risk experienced by MCL patients as suggested by Eskelund et al,[2] it is uncertain whether the HRQoL of r/r MCL who are long-term survivors is the same as the age- and sex-matched general population as assumed in the model. In light of the limited evidence, the ERG employs this assumption in its base-case, but highlights its uncertainty and impact on the cost-effectiveness results (see Scenario 9).

Lastly, the administration costs of KTE-X19 are subject to uncertainty. The company followed a similar approach to previous appraisals of CAR T-cell therapies in their estimation of the costs, which was broadly carried over to the ERG base-case. Using the NHS England's tariff [redacted] the ICER by around £[redacted]/QALY. Whether the current NHS England's tariff is more appropriate depends on whether it more accurately reflects the costs to the NHS. [redacted], the ERG was unable to make an assessment. Therefore, the ERG presents these costs as a scenario and notes the administration costs as an area of uncertainty which has not been fully resolved.

In sum, none of the analyses conducted by the ERG resulted in ICERs below or around [redacted] per QALY. The ERG highlights that conclusions are tentative, primarily due to the uncertainty associated with the long-term PFS and OS of patients after KTE-X19 and lack of evidence to enable the estimation of the excess mortality risk that long-term r/r MCL survivors are subject to compared with the general population. The long-term follow-up of the patients in ZUMA-2 has the potential to address the uncertainties relating to the PFS and OS extrapolation and around the excess mortality risk, depending on the maturity of the data. These longer-term data could be supplemented with observational data on the long-term survival and HRQoL of r/r MCL patients in long term remission compared to the general population. Furthermore, data on the characteristics of patients eligible for KTE-X19 in the UK would help address the uncertainty specifically around the average age of patients at treatment and more generally around the generalisability of ZUMA-2 patient population to the UK patient population.

7 END OF LIFE

The CS (Table 26, p93 CS) presents evidence to support KTE-X19 as an end-of-life therapy, arguing that it satisfies both criteria that 1) the treatment is indicated for patients with a short life expectancy, normally less than 24 months; and 2) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

The CS based their expected survival without KTE-X19 on the SoC survival estimated from MAIC (mean survival [redacted] months), reported survival post-BTKi (mean survival 3.6 to 12.5 months), and the 'standard of care' survival estimates from economic modelling (mean survival [redacted] months, 24 months survival [redacted]%). All three support the assertion that third line treatment patients with r/r MCL have a life expectancy less than 24 months (see Table 26 in CS B for details). The ERG found that the assumption also holds in the ERG base case (lognormal distribution used to extrapolate OS in McCulloch et al. (2020)[1]), where mean expected survival is [redacted] years, and mean survival after 24 months is [redacted]%.

In the CS, the effect of KTE-X19 on the length of life was based on KTE-X19 survival estimates from MAIC modelling (mean survival with KTE-X19 is [redacted] months, compared to [redacted] months with SoC), from ZUMA-2 (where median survival was not reached), and from the economic model (mean survival [redacted] months, life years gained with KTE-X19 vs SoC was [redacted]). The ERG found that the assumption holds in the ERG base case, where KTE-X19 led to additional [redacted] life years compared to SoC.

For these reasons, and notwithstanding the uncertainty in the estimates presented, the ERG agrees that the end of life criteria apply to this appraisal.

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APPENDICES

APPENDIX A – QUALITY ASSESSMENT OF ZUMA-2 AND MCCULLOCH 2020

Downs and Black Checklist

DESCRIPTION OF CRITERIA	ZUMA-2	McCulloch 2020
Is the hypothesis/aim/objective of the study clearly described? Must be explicit	Yes	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no. ALL primary outcomes should be described for YES	Yes	No (for PFS & CR)
Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. Single case studies must state source of patient	Yes	Yes
Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes	Yes
Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided. YES = age, severity	N/A	N/A
Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported	Yes	Yes
Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events (COMPLICATIONS BUT NOT AN INCREASE IN PAIN).	Yes	No
Have the characteristics of patients lost to follow-up been described? If not explicit = NO. RETROSPECTIVE – if not described = UTD; if not explicit re: numbers agreeing to participate = NO. Needs to be >85%	No	No
Have actual probability values been reported (e.g. 0.035 rather than?	Yes	Yes
Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected.	UTD	UTD
Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated.	UTD	UTD
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. Must state type of hospital and country for YES.	UTD	UTD
Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which	No	No

intervention they received, this should be answered yes. Retrospective, single group = NO; UTD if > 1 group and blinding not explicitly stated		
Was an attempt made to blind those measuring the main outcomes of the intervention? Must be explicit	No	No
If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective = YES	Yes	No
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? Where follow-up was the same for all study patients the answer should yes. Studies where differences in follow-up are ignored should be answered no. Acceptable range 1 yr follow up = 1 month each way; 2 years follow up = 2 months; 3 years follow up = 3months.....10years follow up = 10 months	Yes	Yes
Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do = NO	Yes	UTD
Was compliance with the intervention/s reliable? Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. Surgical studies will be YES unless procedure not completed.	Yes	UTD
Were the main outcome measures used accurate (valid and reliable)? Where outcome measures are clearly described, which refer to other work or that demonstrates the outcome measures are accurate = YES. ALL primary outcomes valid and reliable for YES	Yes	Yes for OS. No for PFS and CR.
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? Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients	N/A	N/A
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time? For a study which does not specify the time period over which patients were recruited, the question should be answered as UTD. Surgical studies must be 10 years then NO	N/A	N/A
Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation.	N/A	N/A
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	N/A	N/A
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? In nonrandomised studies if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as no. If no significant difference between groups shown then YES	No	No
Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported = unable to determine.	Yes	UTD
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes	UTD

APPENDIX B – SUPPORTING MATERIAL FOR SECTION 4

16 [redacted]

[redacted]

SPM: Standard Parametric Model, HR: Hazard ratio

17 [redacted]

[redacted]

HR: Hazard ratio

[redacted] 18 [redacted]

[redacted]

KM: Kaplan-Maier

[redacted] 20 [redacted]

OS: Overall Survival, MCM: Mixture Cure Model, KM: Kaplan-Maier

[redacted]

APPENDIX C – DERIVING THE MORTALITY ADJUSTMENT FOR R/R MCL PATIENTS IN COMPLETE REMISSION

Methods

A hazard ratio (HR) was derived from long term data on survival in MCL, reported by Eskelund et al. (2016[2]). Eskelund et al report the 15-year follow-up of the Nordic Mantle Cell Lymphoma 2 (MCL2) Study. In this study, 160 newly diagnosed MCL patients received at the Nordic MCL2 regimen at first line, which includes chemotherapy and autologous SCT. Of the 160 patients, 145 (91%) proceeded to autologous SCT and 130 (89.7%) achieved complete remission or unconfirmed complete remission after autologous SCT. Median follow-up was 11.4 years.

The authors graphically compared survival of the study cohort compared to the general population, matched with respect to age, calendar year of follow-up, sex and country of origin. Results were reported for (i) 159 newly diagnosed patients, (ii) 139 patients with complete remission after 1 year, (ii) 96 patients with complete remission after 5 years, and (iv) 59 patients with complete remission after 10 years.

The graphs were digitised using the WebPlotDigitiser,[75] assuming 10px interpolation. The proportional hazard assumption was assessed using standard log-cumulative hazard plots (as the plot of: log (-log of the survivor function) against log (time)).[76] Given that Eskelund et al do not report the number of patients at risk over time, it was not possible to recreate the individual level data.

Two options were explored for estimating the hazard ratios: assuming that survival in the general population and in the MCL patient follows an exponential distribution (see Equation 1), or that it followed a Weibull distribution. These distributions were selected given that they could be fitted without the need to recreate the individual patient data, albeit with uncertainty.

$$S(t) = e^{-\lambda t} \qquad \text{Equation 1}$$

where $S(t)$ = survival at time t, and λ = hazard rate.

From Equation 1, $\ln S(t) = -\lambda t$, hence the hazard rate was estimated by regressing $\ln S(t)$ on time, where the time coefficient is $-\lambda$. The regression was run in R version 4.0.1, restricting the intercept to 0[1] to ensure predicted survival is constrained to be no greater than 1 and given that an intercept different from zero would not be consistent with the exponential distribution.

[1] R function: lm (log(survival) ~ 0 + time)

The HR was derived using Equation 2.

$$HR = \frac{\lambda_{MCL}}{\lambda_{GP}} \qquad \text{Equation 2}$$

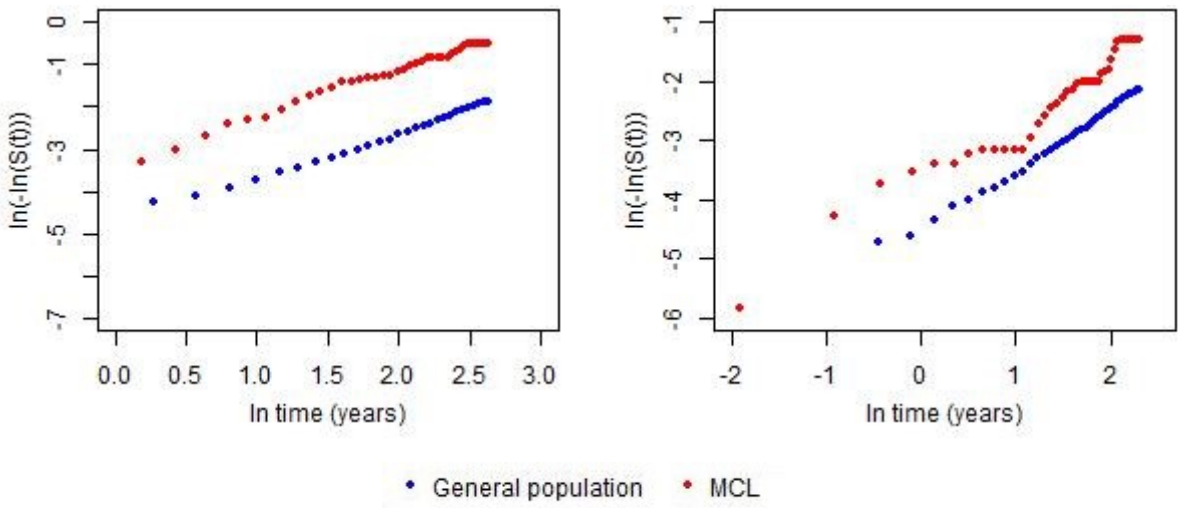
where λ_{MCL} and λ_{GP} are the hazard rate in MCL and the general population, respectively.

Results

Figure 21 shows the standard log-cumulative hazard plots. The log-cumulative hazard plots suggest that the comparison between the general population survival and the survival of MCL patients who were in complete remission at 1 year meets the proportional hazards assumption, as the two lines are fairly parallel. The comparison with patients who were in complete remission at 5 years suggests that there is some change in the hazard over time. The stepwise change in the log hazard could be due to the smaller sample size (N=96 at 5 years v. N=139 at 1 year) and numbers at risk, as the smaller number of patients at risk makes the curve more sensitive to change. However, the non-linear log hazard could also reflect changes in the hazard rate over time.

Figure 21. Log cumulative hazard plots

a) Patients in complete remission after 1 year **b) Patients in complete remission after 5 years**



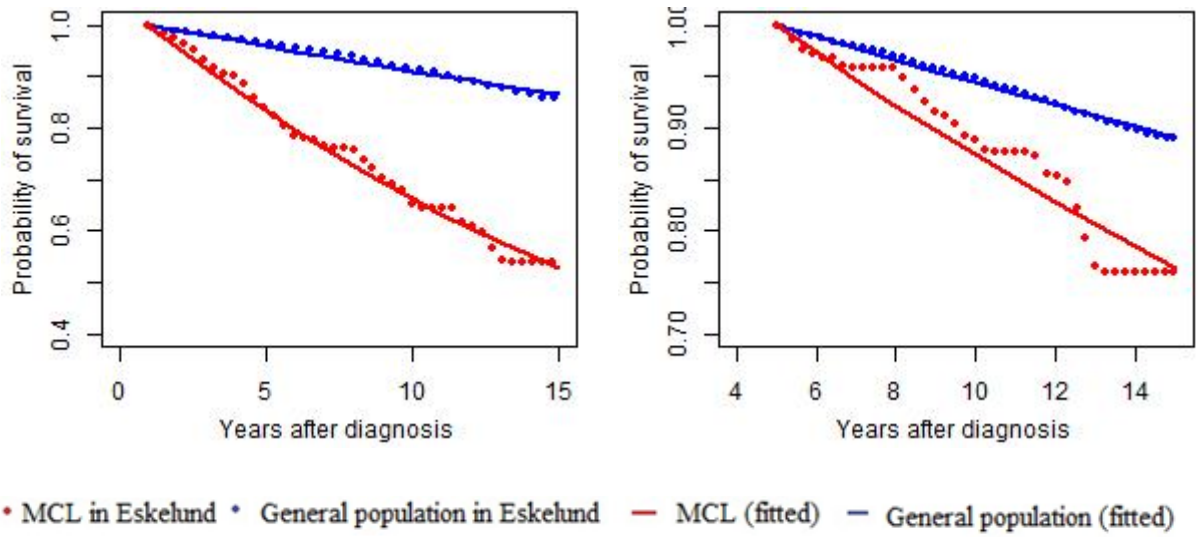
The digitised points and fitted survival models are shown in

Figure 22. On visual inspection, the exponential curve fits well to the general population survival data. The exponential curve provides a reasonable fit for the survival of patients with complete remission after 1 year, although less so for the survival of patients in complete remission at 5 years. The poorer fit for the survival of patients in complete remission at 5 years may indicate that the

exponential distribution is less adequate to the data, although it may be related to the sample size and the numbers at risk over time (unknown given that Eskelund et al do not report numbers at risk).

Figure 22. Survival in patients with complete remission, with fitted exponential distribution

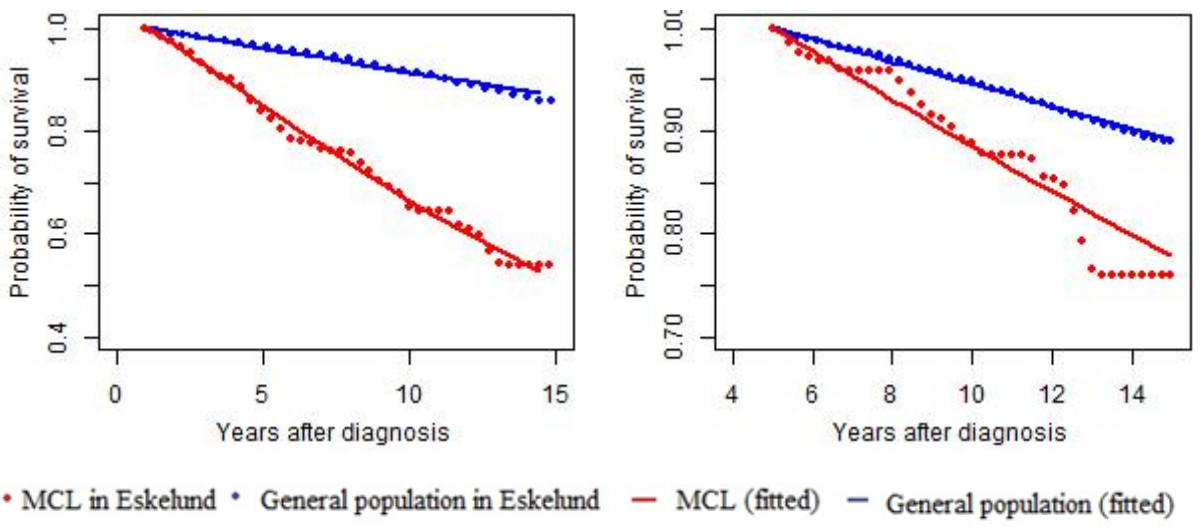
a) Patients in complete remission after 1 year b) Patients in complete remission after 5 years



The Weibull distribution was explored by assuming a linear relationship between $\ln(-\ln S(t))$ and $\ln(t)$, but the fit was not substantially improved (see Figure 23).

Figure 23. Survival in patients with complete remission, with fitted Weibull distribution

a) Patients in complete remission after 1 year b) Patients in complete remission after 5 years



Assuming an exponential distribution for the survival of MCL patients and comparable general population, the derived HR in patients in complete remission after 1 year, and in complete remission after 5 years is shown in Table 24.

Table 24. HR in MCL in patients with CR.

	Patients in complete remission after 1 year	Patients in complete remission after 5 years
HR	4.37	2.36

The ERG notes that the estimation of the HR for mortality between MCL patients and the general population is subject to high uncertainty. This is for a number of reasons: (i) the study population in Eskelund et al comprises newly diagnosed MCL patients, mostly treated with autologous SCT at first line; (ii) Eskelund et al does not report numbers at risk, hence the estimation of HR was based on the digitised points rather than on the number of patients at risk and who died over time; (iii) given the data limitations, the estimation of the HR assumes that the OS curves of the general population and the study population follow exponential distributions, (iv) it is not possible to derive valid confidence intervals given that the standard errors refer to the fit of the curves to the digitised points rather than to the original data; and (v) the Eskelund et al comparison between patients in complete remission and the general population is done at zero, 1, 5 and 10 years, which does not directly match to the end of the trial follow-up at [redacted] months. For these reasons, the ERG views these HRs as indicative of the extent of the differences in mortality risk between MCL patients in complete remission and the general population and highlights that these estimates are very uncertain.

APPENDIX D – SUPPORTING MATERIAL FOR ERG'S SCENARIO ANALYSES

All redacted.

APPENDIX E – IMPLEMENTATION NOTES FOR THE ERG'S BASE-CASE

Analysis	[redacted]
1. Correcting model errors	[redacted]
2. Including the long-term health outcomes and costs of patients who did not receive KTE-X19	[redacted]
3. Using McCulloch et al[1] to inform the health outcomes of patients receiving SoC	[redacted]
4. Excluding the costs of retreatment with KTE-X19	[redacted]
5. Sourcing the number of doses of tocilizumab from ZUMA-2	[redacted]
6. Calculating the costs of SoC based on McCulloch et al (2020)[1]	[redacted]
7. Assuming that long-term survivors have an annual haematology outpatient appointment	[redacted]
8. Obtaining the number of days in ICU from ZUMA-2	[redacted]
9. Including pancytopenia as an adverse event in the model	[redacted]
10. Predicting PFS and OS with splines during the within-trial period 11. and extrapolating beyond that based on adjusted general population mortality	[redacted]

	[redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 9 July 2020** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Comparison of McCulloch et al.[1] and ZUMA-2 baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG reply
Page 53 - conclusion that patients in McCulloch et al [1] study have worse disease prognosis at baseline compared to ZUMA-2 patients.	Please remove the conclusion that McCulloch et al [1] patients have worse disease prognosis at compared to ZUMA-2 patients.	There are some key differences that could affect prognosis between the baseline characteristics of patients in the ZUMA-2 and McCulloch et al [1] paper. These were acknowledged in the response to ERG clarification question A10c and encompass MIPI risk and treatment history. Although consideration of MIPI risk alone, as currently detailed on page 53 of the ERG report, implies that the McCulloch et al patients have worse disease prognosis at baseline compared to ZUMA-2, consideration of treatment history alone would imply that the ZUMA-2 patients have worse disease prognosis at baseline. As detailed in Table 12 of the response to ERG clarification question A10c, the median number of prior therapies was 3.3 in ZUMA-2 (with 81% of patients having received 3 or more lines of therapy) compared to 2 in the McCulloch et al study (with only 11% of patients having 3 or more lines of therapy). Furthermore, only 38% of patients in ZUMA-2 had responded to prior BTKi treatment compared to 58% of patients in the McCulloch et al study. Both number	This is not a factual accuracy issue, but a matter of interpretation. The ERG did acknowledge differences in treatment history between the ZUMA-2 and McCulloch et al[1] populations (p50), but believe that, on balance, the McCulloch population have worse prognosis than the ZUMA-2 population at baseline.

		of prior therapies and response to prior therapy have been shown to be prognostic in MCL.[2-4] The current ERG critique on page 53 does not account for differences in treatment history. If it did, a fairer conclusion would be that there are likely to be differences in prognosis between the patient groups but that it is difficult to make any firm conclusions on whether one patient group has a worse prognosis than the other.	

Issue 2 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG reply
Page 26 – systematic review summary limited to update search results	Systematic review summary to include original and update search results: "A total of 3,285 potentially relevant titles or abstracts were identified for the review. After primary and secondary screening, 306 unique studies were identified."	Clarification	Edited.
Page 35 – summary of patients recruited in the US	Not clear what data this summary is based on (please reference as not taken from company submission). The list of investigators and study sites provided in the supplementary appendix of the ZUMA-2 publication (Wang et al. 2020)	Clarification	Table 14.1.1.3a., pg. 264, ZUMA-2 CSR states 92% of the FAS were recruited in the US. ERG report edited to include

	shows 91% of patients treated with KTE-X19 were recruited in the US. Please check calculation and description if these are the source data for this summary.		reference.
Page 35 – reporting of timing of new manufacturing facilities	As the ERG report, new manufacturing facilities are being developed in Amsterdam. The ERG report indicates that these are expected to go live in July; however, this is not expected until Q2 2022 for KTE-X19. Please update the text to reflect this.	Clarification / correction.	Edited.
Table 10 (page 47) – labelling misleading and data clarification / correction needed	Please confirm if outcome data reported in the included studies are to be provided in the final three columns and if so (i) update labelling (ii) add median PFS data for Martin et al 2016 [5] (see Table 18 of Appendix D of CS). Data clarifications: • Descriptor of 'Simplified MIPI' to be entered above MIPI data presentation (as per Dreyling et al 2016 [2] summary in the same table) for Eyre et al 2019 [6] • Descriptor of 'From BTKi Discontinuation' to be entered above median OS data presentation for Jain et al 2018 [7] Data corrections: • Location to be corrected to US, Germany, France and the Netherlands for ZUMA-2	Median OS and PFS data presented was not extracted for ITC as currently labelled; KM curves were used to inform the MAIC, not median data. Data clarifications / corrections.	Edited.

Page 64 – it is not clear where the values reported in the last paragraph of page 64, marked academic-in-confidence, have been taken from. These are not reported in the company submission and we failed to trace these values back using our original company submitted model.	Please check these values and clarify how these have been derived	Clarification	Our understanding is that this comment refers to the last paragraph in page 65, which is about Figure 7. Thank you for pointing these values out, which we have now corrected. We would like to clarify how these values were obtained from the company's model: the model cycle closest to the end of the trial follow-up is at [redacted] months; according to the tab 'Patient distribution – KTE-X19' cell W45, [redacted]% of the cohort is in the pre-progressed state and [redacted]% is alive (cell Y45: 100-[redacted]%)). According to 'Survival KTE-X19 MCM' cell Y83, at this point, [redacted]% of the long-term survivorship fraction is alive. By multiplying it with the long-term survivorship fraction ([redacted]% in cell AD46), we obtain the proportion of the cohort who is alive and is in the long-term survivorship fraction at [redacted]%. Of the patients who are alive, the proportion who is in the long-term survivorship fraction is the ratio between the proportion of patients who are alive and in the long-term survivorship fraction ([redacted]%)

			by the proportion of patients who are alive ([redacted]%, cell AD83) at [redacted]%. According to 'Patient distribution – SoC', [redacted]% (cell W45) are in the pre-progressed state, [redacted]% (cell X45) are in the post-progression state and [redacted]% (cell Y45) are dead at [redacted] months. We have now corrected the incorrect values in the report.
Page 88 – systematic review summary reports number of studies not limited to r/r MCL population only. This is inconsistent with the reporting of the summaries provided for the cost-effectiveness and HRQL searches.	Systematic review summary to report the numbers of studies identified that meet the decision problem (r/r MCL population only). For example: "The company conducted a systematic search for published cost and healthcare resource identification, measurement and valuation data in r/r MCL (see CS Appendix I). The searches initially identified 10 studies in r/r MCL, with a further 2 added following an update search."	Clarification	Thank you for the correction. The original sentence referred to the PRISMA diagram (Figure 48 page 179 of Appendix). We have now corrected the sentence as suggested.
Table 17 (page 89) – cost per patient per day reported as cost per patient.	The figure in row 5, column 2 is the cost per patient <u>per day</u> used for cell infusion and monitoring; the column 2 heading reports it as the cost per patient. The text in row 5, column 4 could be amended slightly to clarify this.	Clarification	We have now edited row 5 column 2 to include "(cost per patient per day)" and have edited row 5 column 5 to state "The cost per patient per day is multiplied by [redacted] to …"

Page 93 – the ERG report that they could not validate the resource use assumptions applied in the analysis; stating "TA502 report appears to report similar but not identical numbers, and Table 81 in Appendix I in this CS matches those from TA502 rather than their own analysis." The resource use used in the company analysis was derived from the TA502 Committee papers (1), page 217. Specifically, the frequencies reported for stable disease (SD) and post-progression survival (PPS) were used to inform our pre-progression and post-progression health states, respectively. The difference in the frequencies reported in TA502 (and the company submission appendices) and those used in the company analysis is that we have converted the annual frequencies reported in TA502 (Committee papers, Appraisal Committee Meeting 1, page 217 [8]) to frequency per month. For example, the full blood count annual frequency in SD reported in TA502 is 6. In the company submission, we have assumed this translates to 0.5 full blood counts per month.	If this explanation provides the ERG with clarity, please reconsider page 93 text.	Clarification	Edited. Thank you for the clarification. The calculation is now clear. We have now deleted the following sentences from the report: "*However, the ERG could not validate the resource use used in the analysis (reported in Table 62 of the CS). The TA50263 report appears to report similar but not identical numbers, and Table 81 in Appendix I in this CS matches those from TA502 63 rather than their own analysis*."

Issue 3 Minor edits

Description of problem	Description of proposed amendment	Justification for amendment	ERG reply
Page 13 – patient numbers for ZUMA-2 (n=74) marked as academic-in-confidence	Data to be unmarked	Data published and thus not marked as academic-in-confidence in company submission	Edited.

<table>
<tr>
<td>Page 17 and 113 – ICER increase reported (£[redacted]) is incorrect and potentially misleading.
The table below shows the impact of assuming McCulloch et al {McCulloch, 2020 #69} baseline age, upon summary cost-effectiveness (ICER) results. Across company submission (CS), ERG lower bound (ERG LB) and ERG upper bound (UB) base case analyses, this change increases the ICER by <£[redacted] in each case.
<table>
<tr><th></th><th>Base case ICER</th><th>McCulloch et al baseline age ICER</th><th>Change from base case</th></tr>
<tr><td>CS</td><td>[redacted]</td><td>[redacted]</td><td>£4,150</td></tr>
<tr><td>ERG LB</td><td>[redacted]</td><td>[redacted]</td><td>£6,465</td></tr>
<tr><td>ERG UB</td><td>[redacted]</td><td>[redacted]</td><td>£9,480</td></tr>
</table>
In addition, on page 17, the text refers to (ERG) “Scenario 6” when the ERG Scenario in question in Scenario 5.</td>
<td>Please reword text to either report exact ICER increases, or to state that the ICER increase was <£[redacted].
Please reword “(Scenario 6)” to “(Scenario 5)” on page 17.</td>
<td>Edit can avoid incorrect and potentially misleading reporting</td>
<td>Edited.
We have now removed the text stating the specific increase in the ICER in both page 17 and page 113.
We have now corrected the scenario number in page 17 from Scenario 6 to Scenario 5, as pointed out.</td>
</tr>
<tr>
<td>Page 18 – missing comma in list of prognostic factors presented</td>
<td>Comma to be added in between ‘Ki67’ and ‘response to previous line of therapy’</td>
<td>Edit will avoid potential misunderstanding that these are not separate prognostic factors</td>
<td>Edited.</td>
</tr>
<tr>
<td>Page 35 – time range from leukapheresis to infusion of KTE-X19 ([redacted]) not marked up</td>
<td>Data to be marked as academic-in-confidence</td>
<td>Data not published and thus marked as academic-in-confidence</td>
<td>Edited.</td>
</tr>
</table>

		in company submission	
Page 41 – reported that 25 of 29 patients in whom MRD could be assessed had no detectable disease	Data to be corrected to report that 24 (83%) had no detectable disease at week 4	Data correction	Edited.
Page 43 – proportion of patients receiving venetoclax (▇) not marked up	Data to be marked as academic-in-confidence	Data not published and thus marked as academic-in-confidence in company submission	Edited.
Page 44 – treatment-related serious adverse event rate data does not match the description	Option one: data to be corrected to report that 41% of patients had a serious adverse event, classed as grade 3 or higher, related to KTE-X19 Option two: description to be corrected to report that ▇ of patients had a serious adverse event related to KTE-X19	Data correction	Edited.
Page 54 – ESS range reported limited to PFS and OS scenarios	Further detail to be added e.g. "All these analyses result in very low effective sample size (ESS) for PFS and OS scenarios (▇▇▇▇▇▇).	Data clarity	Edited.
Page 58 – the following is stated: "However, the company identified 12 additional studies and one NICE appraisal that evaluated alternative treatments for r/r MCL" "According to Table 53 of Appendix G, TA502 appears to better match the decision-making context of this appraisal (UK NHS and Personal Social Services perspective) than the remaining 12 studies, hence the	Please reword the two sentences to correct for this. For example: "However, the company identified 12 studies, one of which was a NICE appraisal, that evaluated alternative treatments for r/r MCL" "According to Table 53 of Appendix G, TA502 appears to better match the decision-making context of this appraisal (UK NHS and Personal Social Services	Proposed rewording provided to correct for incorrect reporting	Edited. Thank you for the correction, which we have now incorporated.

ERG agrees with the company's use of TA502 to inform their submission." The literature review of cost-effectiveness studies in r/r MCL identified a total of 12 studies. Currently, text reads as though the NICE appraisal (TA502) was additional to the 12 studies (i.e. 13 in total).	perspective) than the remaining 11 studies, hence the ERG agrees with the company's use of TA502 to inform their submission."		
Page 64 – patient numbers for ZUMA-2 mITT group (n=68) marked as academic-in-confidence	Data to be unmarked	Data published and thus not marked as academic-in-confidence in company submission	Edited as suggested.
Page 66 – the ERG state that the Eskelund[3] study is a "15-year follow-up of patients with newly diagnosed MCL who were treated with allo-SCT" and suggest its use to inform the excess mortality risk of long-term survivors. The Eskelund[3] study follows patients after autologous SCT rather than allogeneic SCT.	Please reword text as follows: "15-year follow-up of patients with newly diagnosed MCL who were treated with autologous SCT"	Addressing factual and potentially misleading error	Edited as suggested, in this page and in subsequent pages where relevant.
Page 67 – the following is stated: "Censoring is high; for example, at 12 months, there are [redacted] ([redacted]%) patients at risk; at 24 months, there were [redacted] patients at risk ([redacted]%), and from 29 months, less than [redacted] of the original sample was at risk."	Please state that the example reported is specific to OS.	Data clarity	Edited; the sentence now states: "*Censoring is high; for example, at 12 months,* ***for OS,*** *…"*
Page 82 – number of patients experiencing pancytopenia ([redacted]) not marked up	Data to be marked as academic-in-confidence	Data not published and thus marked as academic-in-confidence in company clarification responses	Edited as suggested.
Page 82 and 83 – the following is stated:	As reported on page 144 of the company	Edit will avoid potential	Edited as suggested. Page

"The company only accounted for AEs related with the infusion with KTE-X19 or with conditioning chemotherapy (as in the previous CAR T-cell appraisals TA559 and TA567). With regards to treatment with KTE-X19, this implies that there are no AEs associated with leukapheresis and bridging chemotherapy which have an impact on costs or HRQoL."	submission, no grade 3 or higher leukapheresis-related AEs occurred in ≥ 10% of subjects in ZUMA-2; hence these were not modelled. Please add text to clarify that leukapheresis-related AEs were considered but were not included in the economic model as they did not meet the threshold applied to determine which AEs to include.	misinterpretation that leukapheresis-related adverse events were not considered in the submitted economic analysis.	83 (paragraph under 4.2.7 Adverse events) now states: "***No grade 3 or higher leukapheresis-related AEs occurred in ≥ 10% of subjects in ZUMA-2; hence these were not modelled***." Page 84 1st paragraph now states: "***AEs related to leukapheresis were considered no Grade 3 or higher occurred in ≥ 10% of subjects in ZUMA-2; hence these were not modelled***. *With regards to treatment with KTE-X19, this implies that there are no AEs associated with bridging chemotherapy which have an impact on costs or HRQoL*."
Page 84 – the following is stated: "The company presented scenario analysis assuming that the cure point is at 2 years, which reduced the ICER by [redacted];"	This sentence is reported in the health-related quality of life (HRQL) section. Please clarify that the scenario analysis assuming a 'cure point' at 2 years was used to adjust both HRQL and resource use after this point. The impact of changing the 'cure point' for HRQL only would be smaller.	Edit will provide clarity on the impact of the company scenario analysis	Edited as suggested. The sentence now states: "The company presented scenario analysis assuming that the cure point is at 2 years (**for both HRQoL and costs**), …"
Page 93 – typographical error	Second and fifth paragraphs: "lunch" written; "lung" intended	Spelling correction	Edited as suggested.

Page 95 – the following is stated: “This differs to other appraisals of CAR-T cell therapy (specifically TA559), where no additional costs were added for the treatment of AE, under the assumption that all hospitalisation would have been captured in the trial that informed the treatment effect.” This is not true. In the TA599 committee papers, page 226, the following is stated: “Also, consistent with the York study, all AEs, barring CRS and B-cell aplasia, assume the cost of one excess bed day.”	Please remove the sentence referred to on page 95 as this is not true.	Correction	Edited as suggested.
Page 105 – assumed duration (126 days) and number of bed days (two) required to manage pancytopenia marked as academic-in-confidence	Data to be unmarked	Based on published evidence used to inform assumptions	Edited as suggested.
Page 107 – end of trial follow-up ([redacted] months) not marked up	Data to be marked as academic-in-confidence	Data not published and thus marked as academic-in-confidence in company submission	Edited as suggested.
Page 108 and 110 – mean patient age in ZUMA-2 (63.2) marked as academic-in-confidence	Data can be unmarked	Data not marked as academic-in-confidence in company submission	Edited as suggested.
Page 121 – typographical error	First paragraph: “forth” written; “fourth” intended	Spelling correction	Edited as suggested.
Page 122 – life years gained marked as	Data to be marked as commercial-in-	Data could impact on commercial interests and thus marked as	Edited as suggested.

academic-in-confidence	confidence	commercial-in-confidence in company submission	
Figure 22 and 23 (page 135) – key colouring appears to be incorrect. In addition, the figure 23 caption is incorrect.	Red and blue colouring used in the figure keys should be switched (i.e. the blue curve and KM are used for general population survival, the red curve and KM are used for MCL survival). Please correct figure 23 caption, changing the word “exponential” to “Weibull”.	Edit will avoid potential misinterpretation of the digitised survival plots from Eskelund et al.	Edited as suggested.

References

1. McCulloch R, Visco C, Eyre TA, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. *Br J Haematol*. 2020.
2. Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet*. 2016; 387(10020):770-8.
3. Epperla N, Hamadani M, Cashen AF, et al. Predictive factors and outcomes for ibrutinib therapy in relapsed/refractory mantle cell lymphoma-a "real world" study. *Hematol Oncol*. 2017; 35(4):528-35.
4. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *Br J Haematol*. 2017; 179(3):430-8.
5. Martin P, Maddocks K, Leonard JP, et al. Postibrutinib outcomes in patients with mantle cell lymphoma. *Blood*. 2016; 127(12):1559-63.
6. Eyre TA, Walter HS, Iyengar S, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. *Haematologica*. 2019; 104(2):e68-e71.
7. Jain P, Kanagal-Shamanna R, Zhang S, et al. Long-term outcomes and mutation profiling of patients with mantle cell lymphoma (MCL) who discontinued ibrutinib. *Br J Haematol*. 2018; 183(4):578-87.

8. National Institute for Health and Care Excellence (NICE). TA502: Company submission - Ibrutinib for treating relapsed or refractory mantle cell lymphoma 2018. (Updated: 18 August 2016) Available at: https://www.nice.org.uk/guidance/ta502/documents/committee-papers. Accessed: 19 March 2020.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

KTE-X19 for treating relapsed or refractory mantle cell lymphoma

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
Issues related to the clinical evidence		
1. Generalisibility of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice	• The evidence for the clinical effectiveness of KTE-X19 comes from a single-arm, multi-centre, non-randomised trial called ZUMA-2(n=74) which provides limited evidence of safety and efficacy of KTE-X19.There are no randomised trials for KTE-X19. • ZUMA-2 was conducted in 33 centres in the US, France, Germany and the Netherlands, with 92% of the full analysis set (FAS) being recruited in the US. As KTE-X19 has not been tested in the UK, the applicability of trial results to the NHS setting is uncertain. • The **ERG** noted that the population included in ZUMA-2 is likely to be younger and fitter than people in NHS clinical practice with relapsed or refractory (r/r) mantle cell lymphoma (MCL) that have received previous Bruton Tyrosine Kinase (BTKI) therapy, although they are likely to have undergone more prior therapies. People with r/r MCL that are older and less fit are known to have poorer prognosis. NHS patients will also likely have had 2 prior lines of therapy before treatment with KTE-X19. As there is worsening prognosis with each subsequent treatment line, the **ERG** considers that a negative bias in survival estimates may have been introduced. Due to concerns about patient selection and patient characteristics (see pages 31-34 and 36-38 of the ERG report) , the **ERG** notes that there is a risk that the trial population may have a more favourable prognosis than people who would be eligible for KTE-X19 under the anticipated marketing authorisation. • Despite these limitations, the clinical advisors to the **ERG** consider the ZUMA-2 population to be broadly representative of the population informing the company's decision problem.	• The precision and magnitude of effectiveness and safety outcome estimates from ZUMA-2 are highly uncertain and there is a risk that the trial population may have a more favourable prognosis than people who would be eligible for KTE-X19.
2. Blended SoC comparator	• The **company** considers rituximab-chemotherapy as standard of care (SoC) in the absence of KTE-X19. Its clinical experts noted that there is no SoC for	• The **company's** approach of pooling comparative

	patients whose MCL progresses following a BTK inhibitor and that treatment options at later lines are limited, not well- established and may depend on therapies received earlier. It therefore produced a " blended comparator" on the assumption of there being no 'true' SoC. • There are considerable limitations of the identified evidence base forming the SoC blended comparator. This is because the evidence consists of small, retrospective, non-comparative, observational studies, some of which were not conducted in the UK and therfore are not directly relevant to the NHS. In addition, the blended comparator evidence includes a mixture of interventions. • The **ERG** believe that the company's approach of pooling comparative evidence as a basket SoC is inappropriate as it results in the pooling of highly heterogeneous studies. In addition to the differences across the pooled studies, material differences between the baseline characteristics of the identified studies and ZUMA-2 population exist. • Based on clinical expert opinion, the **company** considered SoC comprising of 65% rituximab-bendamustine cytarabine (R-BAC), 30% rituximab plus bendamustine (R-bendamustine), and 5% rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) as representative of clinical practice in the UK.The **ERG's** clinical advisors considered that although there is uncertainty regarding chemotherapy regimens in clinical practice, the current SoC is R-BAC for the post-BTKi MCL population in most centres, although some people may receive R-CHOP or R-Bendamustine. The composition of the SoC is only relevant for costs • The blended comparator approach generates OS and PFS from pools of studies, some reporting only PFS or OS. The **ERG** considers it inappropriate to base the economic model on PFS and OS taken from separate studies and considers that only studies providing both OS and PFS are appropriate for pooling. The two studies providing these data are McCulloch et al. 2020 and Eyre et al. 2019. • The **ERG** considers the use of McCulloch et al. 2020 alone instead of the **companys** approach of a blended comparator is more appropriate as the study best represents the patient population in the NHS. The study reports	evidence as a basket SoC is inappropriate. Using the results of the single study McCulloch et al. 2020 to inform the comparison is preferred as it better represents the patient population in the NHS. • SoC treatments are relatively similar in terms of costs, so the composition of SoC is not expected to materially impact the ICER.

	appropriate survival data, was conducted with R-BAC in the UK and avoids issues around the heterogeneity of the identified SoC studies.	
3. Indirect treatment comparison	• Due to lack of direct evidence comparing KTE-X19 to a SoC comparator, the **company** conducted an indirect treatment comparison. • Due the limited evidence for KTE-X19 and SoC, standard network meta-analyses are not feasible.Individual patient data (IPD) from ZUMA-2 were compared with extracted time-to-event data (PFS and OS), response data, and baseline characteristics from 8 SoC studies. Extracted survival and response data of identified studies were pooled via meta-analysis. The single-arm results from ZUMA-2 and the pooled estimates for SoC were compared in unadjusted comparisons and matching-adjusted indirect comparisons (MAICs). • The **company** uses an unadjusted comparison of KTE-X19, based on ZUMA-2 data, versus SoC, based on the meta-analysed comparator studies in its base-case analysis. The MAIC analyses, which adjust ZUMA-2 to match the characteristics of the SoC studies at baseline were not used to inform the cost-effectiveness analyses. • The **ERG** agrees with the **company's** dismissal of the MAIC results as they are highly uncertain and notes that results are potentially less favourable to KTE-X19 after adjustment compared to no adjustment. However, it considers that both the MAIC and naïve indirect comparisons conducted by the **company** are significantly limited by the paucity of evidence and are subject to significant risk of bias and uncertainty. • The **ERG** prefers comparison with McCulloch et al. (2020) only. • Patients in McCulloch et al. have worse disease prognosis at baseline compared to ZUMA-2 (13.7% of patients had a high MIPI, compared to 57.1% in McCulloch). If the McCulloch study population is more representative of the NHS population expected to receive KTE-X19, the **ERG** infers that the unadjusted comparison may overestimate the relative effect of KTE-X19 compared to SoC.	• Observed baseline imbalances between KTE-X19 and relevant SoC evidence, and results of MAIC analyses suggest unadjusted comparisons supporting the **company** model are inappropriate. • Comparison with McCulloch et al. (2020) is a more appropriate approach. • The company's unadjusted comparison may overestimate the relative effect of KTE-X19 compared to SoC.

4. Long term survival data from ZUMA-2	• PFS and OS data from ZUMA-2 is immature. Median PFS and OS were not reached and median follow-up was [redacted] months. • The **compan**y considers that results show an extension to life for patients experiencing a complete response (CR) to KTE-X19 treatment compared to patients with partial response (PR). The assumption of long-term survivorship is based on (i) the plateau in the Kaplan-Meier (KM) curves, (ii) precedent from company submissions in previous appraisals of CAR T-cell therapies (used for r/r B-cell acute lymphoblastic leukaemia and r/r DLBCL), and (iii) on the CR rate and rate of patients with no detectable disease (according to minimal residual disease criteria). • However, given the extent of censoring and immaturity of the data, the **ERG** considers that the plateaus in the KM curves cannot be interpreted as providing robust evidence of the extent of long-term survivorship following KTE-X19. Similar uncertainties in long-term effectiveness were discussed in the NICE appraisal of the CAR T-cell therapy, axicabtagene ciloleucel, for the treatment of diffuse large b-cell lymphoma (DLBCL) [TA559].Although there is evidence of long-term remission/cure with non-CAR T-cell treatments for other lymphoma's such as DLBCL, this is not the case for MCL where cure is not an established concept	• The long-term efficacy of KTE-X19 is highly uncertain and there is currently insufficient evidence to show a curative effect in a subset of patients.
Issues related to cost effectiveness		
5. Age at treatment of patient population	• A major source of uncertainty in the cost effectiveness analysis is whether the the ZUMA-2 patient population is reflective of patients likely to receive KTE-X19 in terms of age(see Section **Error! Reference source not found.** and item 2 of the ERG report) • The **ERG** notes there is a considerable difference in age between those in ZUMA-2 (median age 65 years) and the age of MCL patients at diagnosis in the UK (median age 72.9 years). The mean age of patients in ZUMA-2 (used in the economic analysis) is even lower at 63.2 years. This may have an impact on the generalisability of the ZUMA-2 results, as people who are older and less fit with r/r MCL are known to have poorer prognosis. • This impact is driven mostly by the general population mortality risk, which is used to inform the mortality risk of the long-term survivors in the **company's**	• The age at treatment has a large impact on cost effectiveness results, for example, an increase in average age by 5 years (from 63 to 68 years), [redacted] the ICER by [redacted]. • The **ERG** considers that there is uncertainty regarding how reflective the age at treatment of the ZUMA-2 population is to the UK patient population

	base-case and as a minimum bound to the mortality risk when other approaches to extrapolation are used (see point 8 later). This is an area of uncertainty, the impact depends on the extent to which the age of the patient population in clinical practice departs from the patients in ZUMA-2. • The age at treatment of the patient population further impacts age adjustment to health-related quality of life (HRQoL), and to the generalisability of the HRQoL data from ZUMA-2 (see point 9)	
6. Long-term PFS and OS of patients with r/r MCL after treatment with KTE-X19	• The **company's** base-case uses a mixture cure model to inform the OS and PFS of people receiving KTE-X19. This mixture cure model assumes that there are two groups of patients, the long-term survivors who, after treatment with KTE-X19, experience the general population mortality risk, adjusted upwards with an adjustment obtained from newly diagnosed patients with DLBCL who were progression-free for 24 months; and the non-long-term survivors who experience progression and mortality risk estimated from ZUMA-2. • The **ERG** is concerned that the mixture cure model approach is not sufficiently supported by evidence due to the limited follow-up of ZUMA-2 (See section 4.2.6, items 3, 4,5 and 6 of the ERG report) and notes that survival modelling is the primary driver of cost effectiveness. Robust estimation of mixture cure models requires data from studies with long follow-up times that far exceed the anticipated time point of cure as well as sufficient numbers of patients at risk at the end of follow-up in order to estimate a long-term survivor fraction. • The estimated long-term survivor fractions differ between the **company's** base-case mixture cure models, PFS ([redacted])) and OS ([redacted]). This implies that approximately [redacted] of the ZUMA-2 population relapsed and became long-term survivors following a subsequent treatment.The **company** noted that [redacted] patients in ZUMA-2 who progressed received a subsequent anti-cancer therapy post-progression, and that it was plausible that the subsequent anti-cancer therapy may have led to long-term survivorship for some of these patients. If this is not clinically plausible, the discrepancy between long-term survivor fractions supports the **ERG's** concern that the ZUMA-2 follow-up may not be sufficient to allow the	• Immature trial data do not allow robust estimations of mixture cure models and lead to high uncertainty in the extrapolation approach and long-term survivor fraction. • Alternative modelling approaches such as spline or parametric models with switch points to an adjusted general population mortality risk are plausible alternatives to mixture cure models.

	robust estimation of mixture cure models; hence, the long-term survivorship fractions are subject to high uncertainty. • The point estimates for the long-term survivorship fraction in the **company's** model is greater than the long-term survivorship fractions estimated for the appraisals of CAR T-cell therapies in r/r DLBCL. In TA559, the use of axicabtagene ciloleucel in DLBCL was associated with a cure fraction of ~ 50% for OS and ~ 40-43% for PFS. For KTE-X19, long-term survivorship fractions are ~[redacted]% for OS and ~[redacted]% for PFS. As noted by the **company** and the **ERG's** clinical advisors, there is uncertainty in the extent to which people with r/r MCL who relapsed at the third line or subsequent therapies can experience long-term remission and survivorship in contrast with DLBCL. Therefore, the **ERG** finds it unlikely that the long-term survivorship fraction in r/r MCL would be higher than in r/r DLBCL. • Alternative extrapolation approaches, such as spline or parametric models with switch points to an adjusted general population mortality risk, are more plausible, make use of available data from ZUMA-2 and offer more flexibility regarding the timing of the switch point to an adjusted general population mortality risk. The **ERG** noted that if a proportion of patients are cured making the patient group heterogenous, spline models have the capacity to model this heterogeneity.Therefore, the **ERG's** base-case employs a spline model for the within-trial period with a switch to an adjusted general population mortality beyond this. Substantial uncertainty still remains, which has a considerable impact on the ICER. Addressing this uncertainty around the long-term outcomes requires longer-term follow-up of the ZUMA-2 trial and/or long-term observational evidence from people with r/r MCL post-KTE-X19 treatment. • The company considered that parametric models did not provide good visual fit to the observed data from approximately 10 months onwards.The ERG agrees that the parametric models do not provide plausible extrapolations in isolation because their hazard rates are generally below those of the general population unless a logical constraint is imposed to ensure that the maximum between the general population hazard and the parametric model is always applied (as in the company's model). The need for such a constraint only highlights the uncertainty in the extrapolation.	

	• The company also considered that spline models provided a poor fit given the expectation of long-term survivorship. The ERG noted that spline models are similar in fit to the within-trial period and predict similar 5-year survival estimates at [redacted]%. This is lower than the long-term survivorship fraction estimated by the mixture cure models and similar to the long-term survivorship fraction estimated in TA559 for axicabtagene ciloleucel in r/r DLBCL. However, spline models have a similar limitation to standard parametric models in respect to their hazard rates in the long-term, in that these are lower than the general population mortality.	
7. Excess mortality risk experienced by long-term survivors	• The excess mortality risk experienced by long-term survivors is a key uncertainty related to the long-term PFS and OS of patients with r/r MCL after KTE-X19 treatment (see Section 4.2.6 and item 7 of the ERG report) • The **company** assumed that the risk of death of long-term survivors corresponds to the age- and sex-matched general population mortality risk, adjusted with a SMR of 1.09, implying that long-term KTE-X19 survivors experience a 9% higher probability of death compared to the general population. This mortality adjustment was obtained from Maurer et al, a study in people with DLBCL which was used in TA559. The **company** used the adjustment to reflect the impact of prior lines of treatment on survival. • The **ERG** considers that it is more appropriate to base the adjustment on data from people with MCL such as from the study by Eskelund et al. (newly diagnosed patients mostly treated with autologous SCT and who achieved complete remission for 1 or 5 years (n=160)) rather than on data from people with DLBCL. The **company's** adjustment was based on Maurer et al., a study in a cohort of French people with newly diagnosed DLBCL (n=820) who were event-free at 24 months. The **ERG's** clinical advisers considered that the excess mortality risk from DLBCL is not generalisable to r/r MCL and that the excess mortality risk compared to the general population is likely to be higher in r/r MCL than in DLBCL. The **ERG** also noted that Eskelund et al. provides evidence from a therapy that allowed people with MCL to achieve CR and sustain it. They considered that it was possible that excess mortality for people treated with KYE-X19 is similar for people with MCL who achieved and sustained CR, regardless of whether this was aacheieved through autologous	• Excess mortality risk of long-term survivors of r/r post-KTE-X19 is uncertain, but it is more appropriate to base it on data from MCL patients than from DLBCL patients

	SCT or a CAR-T cell therapy. Evidence from Eskelund et al. also suggests that the excess mortality risk experienced by people with MCL is substantial and likely to be higher than in DLBCL. A visual comparison of the survival cures from Eskelund et al. and Maurer et al. indicates a substantial difference in excess mortality risk between MCL and DLBCL compared to the general population (see figure 12 and 13, page 78 of the ERG report) • Given the data limitations, the **ERG** estimated an upper and lower estimate of the mortality adjustment and uses both to inform the **ERG** base-case results as a range. The **ERG** highlights that this is a key driver of the cost-effectiveness results with the largest impact on the ICER (sees section 6.1.1.11 of the ERG report) • The **ERG** notes that its preferred mortality adjustment, estimated from the Eskelund et al data is subject to uncertainty due to the mismatch between the Eskelund et al. study population and the population in this appraisal (r/r MCL patients after KTE-X19 therapy) and uncertainty related to the available data and methodology used to derive the mortality adjustments.The **ERG** highlights that without long-term data from r/r MCL patients sustaining complete remission after KTE-X19, it is difficult to accurately infer the excess mortality risk that long-term r/r MCL survivors after KTE-X19 are subject to, compared with the general population.	
8. HRQoL of long-term survivors	• HRQoL of patients who have not progressed in the long-term is uncertain. The **company** model assumes that patients who have not yet progressed at 5 years following treatment with KTE-X19 experience the same HRQoL as the general population. The **ERG** considers trial data from ZUMA-2 insufficient to support an assumption that patients who have not progressed have similar HRQoL to the age- and sex-matched general population and considers this to be a significant area of uncertainty. • Given the excess mortality risk experienced by people with MCL as suggested by Eskelund et al., it is uncertain whether the HRQoL of people with r/r MCL who are long-term survivors is the same as that of the age- and sex-matched general population as assumed in the company's model. Due to limited evidence,the ERG employs this assumption in its base-case but explores assuming that the HRQoL of patients who remain in the pre-progression state	• It is uncertain whether long-term survivors experience the HRQoL of patients in ZUMA-2 or the HRQoL of the age- and sex-matched general population.

	for more than 5 years is lower than the general population in scenario analyses (range of ICERs increases)	
9. Administration costs of KTE-X19	• Administration costs of KTE-X19 are subject to uncertainty. The ERG notes that there is a [redacted] between the administration costs estimated by the **company**, which follow a similar approach to previous appraisals of CAR T-cell therapies, and the NHS England tariff, which is based on [redacted] (see Section 4.2.9 and item 12 of the ERG report). • Using the NHS England's tariff [redacted] the ICER by around £[redacted]/QALY. Whether the current NHS England's tariff is more appropriate depends on whether it more accurately reflects the costs to the NHS. [redacted], the ERG was unable to make an assessment. Therefore, the ERG presents these costs as a scenario and notes the administration costs as an area of uncertainty which has not been fully resolved.	• Administration costs are an important driver of cost-effectivness. Clinical opinion is sought to determine which are more reflective of NHS clinical practice.

2 Questions for engagement

Generalisibility of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice

1. Question for clinical expert: Are the results of ZUMA-2 (conducted in people with a mean age of 63 years, median number of 3 prior therapies, 100% with an ECOG 0/1 and 43% having received a stem cell transplant) generalisable to people who would be eligible to receive KTE-X19 in NHS clinical practice?

2. Question for clinical expert: What is the natural history of this disease? is relapsed or refractory mantle cell lymphoma considered curable?
    - Is there evidence of long-term remission/cure for people with relapsed or refractory mantle cell lymphoma as there is for people with diffuse large b-cell lymphoma treated with non-CAR T-cell treatments?
    - How likely is it that patients that have received a stem cell transplant or a CAR T-cell therapy are cured of disease?
3. If people are long term survivors following treatment with KTE-X19, are they expected to live as long as the general population, that is have a similar mortality risk as the general population?
    - If long term survivors have a lower life expectancy than the general population, what are the leading causes of mortality in this group?

Figure 1: key baseline characteristics of patients in mITT (modified intent-to-treat) group

	All treated patients (ml
Median age, years (range) Mean age, years	65 (38-79) 63
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
ECOG 0/1, n (%)	68(100)
Intermediate/high-risk s-MIPI, n (%)	38 (56)
Median no. of prior therapies (range)	3 (1-5)
Prior auto-SCT, n (%)	29 (43)
Prior BTKi, n (%) Ibrutinib Acalabrutinib Both	68 (100) 58 (85) 16 (24) 6 (9)
Received bridging therapy, n (%) Ibrutinib	25 (37) 14 (21)

Acalabrutinib	5 (7)
Dexamethasone	12 (18)
Methylprednisolone	2 (3)
Ibrutinib plus steroid	4 (6)
Acalabrutinib plus steroid	2 (3)
Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; MIPI, Mantle Cell Lymphoma International Prognostic Index; mITT, modified intent-to-treat; SCT, stem cell transplant	

Source: Table 6, page 36 of the ERG report

Blended standard of care comparator

4. Question for clinical expert: What is the composition of standard of care used in clinical practice in the NHS? Is the company's composition of 65% R-BAC, 30% R-bendamustine, and 5% R-CHOP representative of current standard of care for the post-bruton's tyrosine kinase inhibitor mantle cell lymphoma population?
   OR
   is R-BAC representative of standard of care in most centres in the UK as favoured by the ERG?

5. Do stakeholders agree with the company's approach of pooling comparative evidence using a meta-analysis of comparator studies as a basket standard of care on the assumption that there is no 'true' standard of care for patients whose mantle cell lymphoma progresses following a BTK inhibitor to inform the comparison of KTE -X19 with established clinical management
   OR

   the ERG's preferred approach of using the results of the single retrospective cohort study McCulloch et al. 2020 to inform the comparison. McCulloch et al. 2020 was conducted in the UK and Italy, included people with median number of 2 prior therapies, 42% of patients with prior autologous stem cell transplant and 6% with with previous allogenic stem cell transplant. It provided comparator evidence for R-BAC which the ERG considered best representative of clinical practice in the UK.

   Both approaches have limitations. Are the results of the company's meta-analysis approach plausible?

Figure 2: Comparator studies included in the Company's ITC

Study	Intervention	Number of participants	Location	ECOG 0/1, %	No. of prior therapies, median (range)	Months on prior BTKi, median, (range)	Response to prior BTKi	MIPI Intermediate/ High, %	Prior auto stem cell transplant	Morphological variant, blastoid, %	Data extracted for ITC		
											Median OS, mo (95% CI)	Median PFS mo (95% CI)	ORR, n (%)
ZUMA-2 (mITT)	KTE-X19	68	US, Germany, France and the Netherlands	100%	3 (1-5)	7.0	38%	56%	43%	25%	n/a	n/a	n/a
Dreyling 2016	Subsequent therapy (Mixed)	40	21 countries	99%	2 (1–9)	14.4 (IQR: 15.1)	72%	Simplified MIPI 69%	-	12%	-	-	8 (20)
Epperla 2017	Subsequent therapy (Mixed)	29	US	(At diagnosis) 86%	2 (1–8)	-	45%	44%	39%	16%	-	-	14 (48)
Eyre 2019	Venetoclax	20	UK	55%	3 (2–5)	4.8 (0.7–34.8)	55%	80%	30% (consolidation at first remission)	20%	9.4 (1.5–NR)	3.2 (1.2–11.3)	(53)
Jain 2018	Salvage therapy (Mixed)	36	US	-	3 (1–11)	8 (0.3–59)	NR	92%	-	36%	From BTKi Discontinuation 10 (Range: 0.9–52.7)	-	(27)
Martin 2016	Subsequent therapy (Mixed)	73	US, UK, Germany & Poland	-	3 (0–10)	4.7 (0.7–43.6)	51%	71%	16%	16%	5.8 (3.7–10.4)	-	18 (25)
McCulloch 2019	R-BAC	29	UK & Italy	-	2 (1–6)	-	62%	(At diagnosis) 81%	38% (post induction)	(At diagnosis) 24%	12.2	8.6	25/28 (89)
Regny 2019	RiBVD	12	France	-	-	-	-	-	-	28%	-	-	8 (66)
Wang 2017	Lenalidomide-based (Mixed)	58	US & UK	48%	4 (1–13)	4.3 (0.5–47.6)	45%	-	-	-	-	-	17 (29)

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison; IQR, interquartile range; MIPI, Mantle Cell Lymphoma International Prognostic Index; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival R-BAC, Rituximab-Bendamustine Cytarabine; RiBVD, Rituximab-Bendamustine, Velcade, Dexamethasone;

Source: Table 10, page 46 of the ERG report

Figure 3: survival estimate summary of fixed-effects meta-analysis (log normal model) of OS curves

	All included studies (mixed ST, venetoclax or R-BAC)	All included studies with Time 0 set at time of ST	Mixed ST studies	Mixed ST or R-BAC studies	Mixed ST or R-BAC studies with Time 0 set at time of ST
Mean survival, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median survival, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival rate, % (95% CI)					
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; R-BAC, rituximab, bendamustine and cytarabine; ST, subsequent therapy.

Source: Table 15, page 59 of the company submission

Figure 4: progression-free survival estimate summary of fixed-effects meta-analysis (log normal model) of progression-free survival curves

	All included studies (venetoclax or R-BAC)
Mean survival, months (95% CI)	[redacted]
Median survival, months (95% CI)	[redacted]
Survival rate, % (95% CI) 6 months 12 months 18 months 24 months 30 months	[redacted]
Key: CI, confidence interval; R-BAC, rituximab, bendamustine and cytarabine.	

Source: Table 16, page 61 of the company submission

Figure 5: Response estimate summary of fixed-effects meta-analysis

	All included studies (mixed ST, venetoclax, R-BAC, RiBVD or LEN-based)	Mixed ST studies	All included studies with OS and ORR data (mixed ST, venetoclax or R-BAC)	Mixed ST studies with OS and ORR data
ORR, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
CR rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PR rate, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 17, page 62 of the company submission

Indirect treatment comparison

6. Do stakeholders consider that the company's approach of using an unadjusted indirect comparison of KTE-X19 (based on ZUMA-2 data) versus standard of care (based on the meta-analysed comparator studies) more appropriate?

   OR

   the ERG's preferred approach of using the results of the study McCulloch et al. 2020 to inform the comparison of KTE-X19 to a standard of care comparator?

   Both approaches have limitations. Are the results of the company's approach comparing KTE-X19 with standard of care plausible and in line with what is seen in clincal practice?

Figure 6: PFS comparison of SoC studies used in the company's meta-analysis and McCulloch 2020

Source: ERG response to technical query on hazard ratios

Figure 7: OS comparison of SoC studies used in the company's meta-analysis and McCulloch 2020

Source: ERG response to technical query on hazard ratios

Long term survival data from ZUMA-2

7. Question for clinical expert: In clinical practice what is the average extension to life you would expect to see for a patient who experiences a complete response. Do results from ZUMA-2 below reflect what is seen in clinical practice?

8. Can the plateaus in the Kaplan-Meier survival curves be interpreted as providing robust evidence of a "cure" i.e people suriving long term? What is the anticipated "cure" point based on your experience in clinical practice and is the length of follow- up of ZUMA-2 (median follow-up of [redacted] months) sufficient to provide an estimation?

9. Question for clinical expert: How do you interpret the high complete response rate in the ZUMA-2 trial?

    - Is a cure/long-term remission possible without a complete response for patients with relapsed or refractory mantle cell lymphoma?
    - How many people with a complete response do you think can considered to be long-term survivors/cured in clinical practice?

10. Question for clinical expert: Can people who do not achieve a complete response go on to be be considered long term survivors?

Figure 8: Progression-free survival using central assessment (IRRC) per IWG Lugano classification

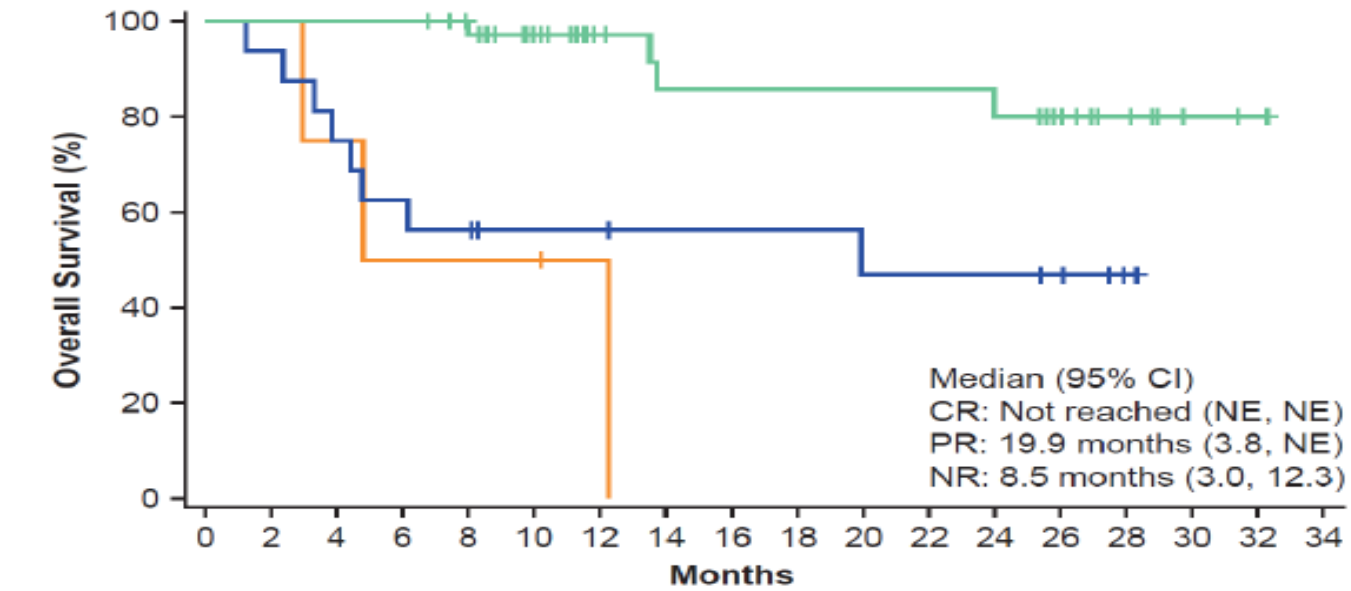
(Cohort 1; modified intent-to-treat group)

Key: CI, confidence interval; CSR, Clinical Study Report; IRRC, Independent Radiology Review Committee; NE, not estimable
Source: Figure 10, page 43 of company submission

Figure 9: Overall survival (Cohort 1; modified intent-to-treat group)

Source: Figure 13, page 46 of company submission

Figure 10: Overall survival by best objective response using central assessment (IRRC) per Lugano classification (inferential analysis set)



Source: Figure 12, page 46 of company submission

Age at treatment of patient population

11. Question for clinical expert: Is the median age of 65 years in the ZUMA-2 population reflective of the age of patients with relapsed or refractory mantle cell lymphoma that are likely to be treated with KTE-X19 in NHS clinical practice?

Long-term PFS and OS of patients with relapsed or refractory mantle cell lymphoma after KTE-X19 treatment

12. The estimated long-term survivor fractions in the company's base-case mixture cure models are PFS ([redacted])) and OS ([redacted])). The ERG's preferred spline models predict 5-year survival estimates at [redacted]%. This is lower than the long-term survivorship fraction estimated by the mixture cure models and similar to the long-term survivorship fraction estimated in previous NICE appraisal for a CAR T-cell therapy for axicabtagene ciloleucel in relapsed or refractory diffuse large B-cell lymphoma (TA559). Which model produces cure fractions that are clinically plausible?

13. The estimated long-term survivor fractions differ between the company's base-case mixture cure, PFS (~[redacted]) and OS (~[redacted]) models. This implies that approximately [redacted] of ZUMA-2 patients relapsed and became long-term survivors following a subsequent treatment. [redacted] patients in ZUMA-2 who progressed received a subsequent anti-cancer therapy post-progression. Is it clinically plausible for subsequent anti-cancer therapy given to patients post-progression to lead to long-term survivorship in some patients?

14. In TA559, the use of axicabtagene ciloleucel in diffuse large B-cell lymphoma was associated with a cure fraction of ~ 50% for OS and ~ 40-43% for PFS. There is uncertainty in the extent to which relapsed or refractory mantle cell lymphoma patients who relapsed at the third line or subsequent therapies can experience long-term remission and survivorship compared with patients with diffuse large B-cell lymphoma. Is it clinically plausible that the long-term survivorship fraction in relapsed or refractory mantle cell lymphoma is higher than in relapsed or refractory diffuse large B-cell lymphoma?

Excess mortality risk experienced by long-term survivors

15. The company's approach assumes that long-term KTE-X19 survivors experience a 9% higher probability of death compared to the general population. This moratality adjustment was sourced from Maurer et al. in a cohort of French newly diagnosed patients with DLBCL (n=820) who were event-free at 24 months:

    - Is the death rate of patients with relapsed or refractory diffuse large B-cell lymphoma comparable to patients with relapsed or refractory mantle cell lymphoma?

    - Would you expect the death rate observed in the general population to be higher in patients with relapsed or refractory mantle cell lymphoma than in relapsed or refractory diffuse large B-cell lymphoma?

16. The ERG considers that it is more appropriate to base the mortality adjustment on data from patients as in Eskelund et al. (newly diagnosed patients with mantle cell lymphoma mostly treated with autologous stem cell transplant and who achieved complete remission for 1 or 5 years (n=160)) rather than in data from patients with diffuse large B-cell lymphoma. Which data source is appropriate and likely to produce more clinically plausible results?

Figure 11: Survival of the Eskelund et al study cohort compared to the general population (reproduced from Figure 3 in the original paper)

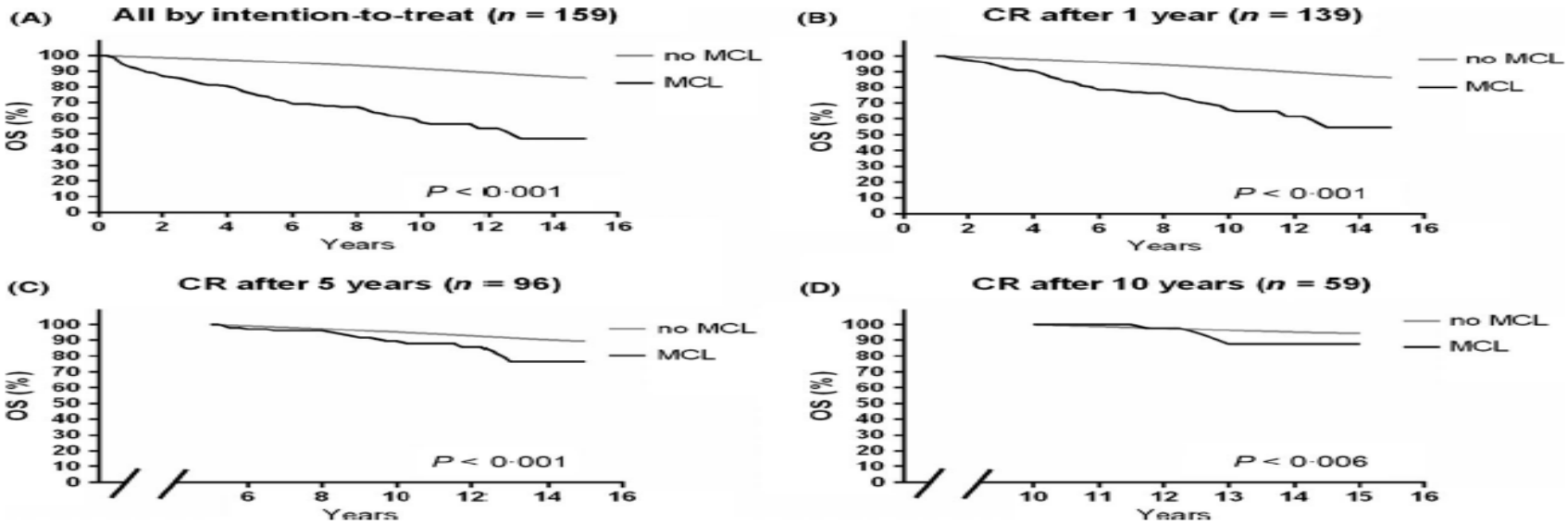


Fig 3. Conditional survival of the MCL2 patients compared to the estimated survival, had they not acquired MCL (based on data from the Human Mortality data base; http://www.mortality.org). (A) All patients. Patients in first complete remission after (B) 1 year, (C) 5 years and (D) 10 years, respectively. In (C) and (D) the *x*-axis has been adjusted to match the curves starting at 5 and 10 years, respectively. MCL, Mantle cell

Source: Figure 12, page 78 of ERG report

Figure 12: Survival of the Maurer et al French cohort compared to the general population (reproduced from Figure 4 in the original paper)

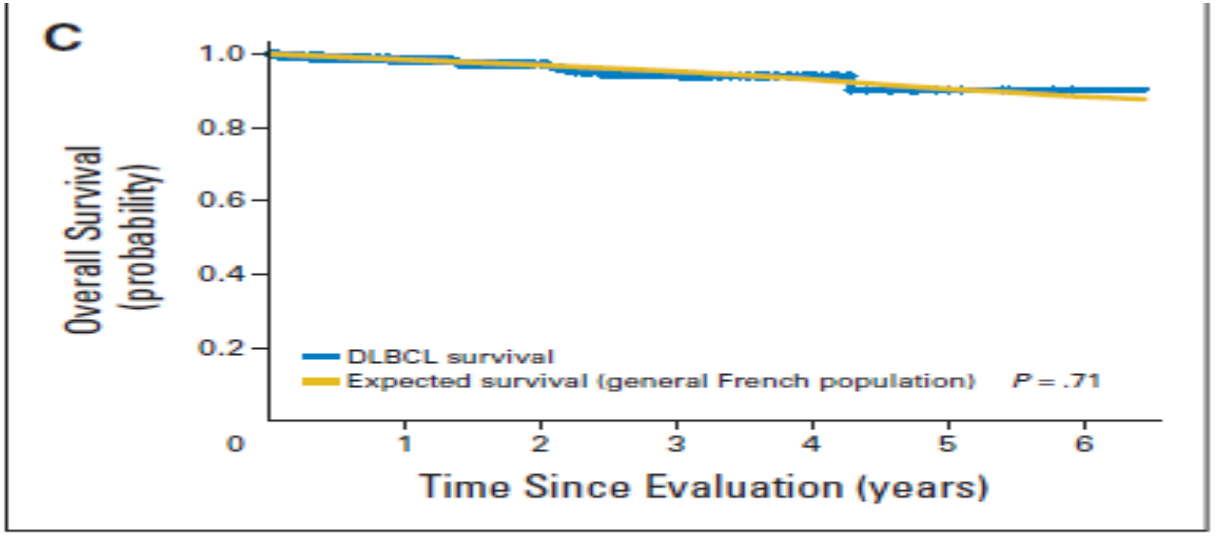


Fig 4. Overall survival versus expected survival in French cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

Source: Figure 13, page 78 of ERG report

Health related quality of life of long-term survivors

17. Do stakeholders agree with the company's view that if a patient survives 5 years without progressing following treatment with KTE-X19, they will experience the same health related quality of life as the the age-and sex-matched general population i.e they would be considered cured and to have the same mortality risk as the general population?

Administration costs of KTE-X19

18. The company costed KTE-X19 treatment at £[redacted] (included the same costs as the previous appraisals, except the cost of training that was accounted for in appraisal TA559) while the current NHS England tariff price for CAR T-cell therapies is considerably more at £[redacted].

    [redacted]

    [redacted] The ERG was unable to assess which estimate most accurately reflect the costs to the NHS. The ERG uses the company estimate (updated with the preferred ERG assumptions) in its base-case, but presents a scenario using the NHS England tariff price. Can stakeholders comment on which costing is appropriate to be used in the cost-effectiveness analysis? Are the treatment costs used by the company and ERG in Figure 15 below reflective of costs to the NHS?

Figure 13: Summary of all KTE-X19 treatment costs

Element of cost	Cost per patient	Adjusted cost in the model	Source/Assumption
Leukapheresis	£1,521.11	£1,655.33	NHS reference costs 2018/19,[64] weighted average of all HRGs for stem cell and bone marrow harvest (currency codes SA34Z, SA18Z), as per York study and TA559.[28] Adjusted cost estimated using a multiplier of 1.088 applied to reflect the 6 patients who underwent leukapheresis, but not KTE-X19 infusion
Bridging chemotherapy	Drug cost £1292.87 Administration cost £852.53	[redacted]	Single cycle of R-BAC (drug cost + administration in the outpatient setting) multiplied by the proportion of patients (0.37) who received bridging therapy in ZUMA-2. Adjusted cost estimated using a multiplier of [redacted] applied to reflect the [redacted] out of [redacted] patients who received bridging therapy, but not KTE-X19 infusion.
Conditioning chemotherapy	Hospital	£1,995.12	Hospital admission: • NHS reference costs 2018/19,[64] weighted average of elective inpatient

Element of cost	Cost per patient	Adjusted cost in the model	Source/Assumption
	admission £1382.97 Chemotherapy acquisition £583.23		HRGs for malignant lymphoma, including Hodgkin's lymphoma and NHL (currency codes SA31A-F). Adjusted the length of stay from 9.4 days (mean length of stay for malignant neoplasms of lymphoid, haematopoietic and related tissue inpatient admissions in Hospital Episode Statistics, 2019[65]) to 3 days (length of treatment in the trial protocol). Chemotherapy acquisition: • 3 infusions of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 • Source of unit costs: eMIT[66] • BSA percentile from ZUMA-2 (n=69), used to estimate dose and vial combination. Assumed drug wastage. Adjusted cost estimates using a multiplier of 1.015 to reflect the 1 patient (out of 69) who underwent conditioning therapy, but not KTE-X19 infusion
Cell infusion and monitoring	£460.99 (cost per patient per day)	[redacted]	NHS reference costs 2018/19,[64] weighted average of elective inpatient HRGs for malignant lymphoma, including Hodgkin's lymphoma and NHL (currency codes SA31A-F), divided by the average length of stay (9.4 days) The cost per patient per day is multiplied

Element of cost	Cost per patient	Adjusted cost in the model	Source/Assumption
			by [redacted] to reflect the length of hospitalisation in patients who received KTE-X19 in ZUMA-2.
Retreatment	[redacted]	[redacted]	2.9% of the unadjusted costs of conditioning chemotherapy and cell infusion and monitoring to reflect the add on cost of the 2 patients who underwent retreatment. Acquisition of KTE-X19 assumed to incur no addition cost, as the quantity of KTE-X19 initially manufactured is sufficient for the delivery of up to two treatments.
Acquisition of KTE-X19	[redacted]	[redacted]	Company submission Assumes that cost of the drug will only be reimbursed if KTE-X19 is administered to the patient, so is only applied to patients who received KTE-X19.
Total cost excluding acquisition of KTE-X19	[redacted]	[redacted]	
Total cost in the model	[redacted]		
BSA = body surface area; eMIT = electronic market information tool; HRGs = healthcare resource groups = NA, not applicable.			

Technical engagement response form

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Thursday 10 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Kite a Gilead company**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Introduction

Gilead would like to thank the NICE technical team for reviewing the company submission for KTE-X19, for preparing their technical report, and for providing us with the opportunity to engage in the technical engagement process, both in the technical engagement call on 27th August, and in written stakeholder response.

Our response comprises three separate parts:

1) Details of the revised company base case
2) Our responses to the questions for engagement
3) Additional supportive evidence

1. Revised company base case

Following discussions during the technical engagement call regarding the plausible cost-effectiveness of KTE-X19, Gilead is pleased to confirm that a patient access scheme (PAS) discount has been submitted as part of the possible CDF agreement. [redacted] It is hoped that this submitted discount can enable a positive recommendation in the 13 October 2020 Committee A meeting, avoiding any unnecessary delay in patient access to this innovative treatment that is anticipated to transform the clinical outlook of a small patient group with high unmet need.

In Table 22 of the Evidence Review Group (ERG) Report, the ERG set out their preferred amendments that lead from the company submitted (CS) base case to the ERG's preferred base case, in a cumulative manner. Table 1 of this response follows the ERG Table 22 approach in describing how the estimated base case incremental cost-effectiveness ratio (ICER) changes from (i) CS base case, through (ii) those ERG amendments we do not wish to contest, to (iii) the revised company base case ICER, which includes the proposed confidential price discount to KTE-X19.

Note that we have accepted all but one of the ERG's suggested amendments. The only suggested amendment not incorporated into the revised company base case is the increased mortality risk for patients who experience long-term survival (ERG amendment #11). Our rationale for this is discussed in greater detail in response to 'Issue 7: Excess mortality risk experienced by long-term survivors'.

Table 1: Revised company base case, KTE-X19 for treating relapsed or refractory mantle cell lymphoma (adapted from ERG report, Table 22)

ERG-preferred amendments to CS base case (#in ERG report Table 22 | description in ERG report Table 22) included in revised company base case		**ICER**
0	Company submitted base case	[redacted]
1	0+ Correcting model errors	[redacted]
2	1+ Including the long-term health outcomes and costs of patients who did not receive KTE-X19	[redacted]
3	2+ Using McCulloch et al (2020) to inform the health outcomes of patients receiving SoC	[redacted]
4	3+ Excluding the costs of retreatment with KTE-X19	[redacted]
5	4+ Sourcing the number of doses of tocilizumab from ZUMA-2	[redacted]
6	5+ Calculating the costs of SoC based on McCulloch et al (2020)	[redacted]
7	6+ Assuming that long-term survivors have an annual haematology outpatient appointment	[redacted]
8	7+ Obtaining the number of days in ICU from ZUMA-2	[redacted]
9	8+ Including pancytopenia as an adverse event in the model	[redacted]
10	9+ Predicting PFS and OS with splines during the within-trial period and extrapolating beyond that based on adjusted general population mortality	[redacted]
Inclusion of confidential PAS discount in revised company base case (# change in this table | description)		
11	10+ [redacted]; **Revised company base case**	[redacted]
Key: CS, company submission; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; ICU, intensive care unit; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; SoC, standard of care.		

The final ICER, considering the [redacted] applied to the list price of KTE-X19, is £[redacted]. This revised base case ICER is below the NICE decision-making threshold limit, given end-of-life weighting. Gilead believes KTE-X19 transforms the long-term outlook for relapsed or refractory mantle cell lymphoma (r/r MCL) patients where there is currently no ‘standard of care’ due to a lack of effective treatment options, and the revised base case ICER presents a compelling case for KTE-X19 as a candidate for CDF approval.

2. Responses to questions for engagement

Issue 1: Generalisibility of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice	
Question for clinical expert: Are the results of ZUMA-2 (conducted in people with a mean age of 63 years, median number of 3 prior therapies, 68% with an ECOG 0/1 and 43% having received a stem cell transplant) generalisable to people who would be eligible to receive KTE-X19 in NHS clinical practice? Please see Figure 1 in the technical report.	The company would like to note that UK clinicians are now fully cognizant of the need for strict patient selection when determining who is eligible for CAR T-cell treatment, and all treatment decisions are made by a National CAR-T clinical panel (NCCP). The median age of patients (with relapsed or refractory diffuse large B cell lymphoma (R/R DLBCL)) approved for CAR T-cell therapy up to July 2019 was 57 (range 18-75), and all patients with performance score data were recorded as having an ECOG score of 0-1.[1] This is not reflective of the expected disease status in the general R/R DLBCL population, but of the careful evaluation, assessment and established processes to determine who would benefit from these (CAR T-cell) treatments. So while, the company agrees that a mean age of 63 years is younger than you might expect in the general relapsed or refractory mantle cell lymphoma UK population (R/R MCL), it is likely reflective of those who would be determined to be *eligible* for this CAR T-cell treatment in clinical practice. Conversely, due to the treatment pathway, with ibrutinib as the standard of care in second line, it is likely that patients will have received less prior treatments before KTE-X19 in the real world setting. In addition, while there remains uncertainty regarding these differences in baseline characteristics (such as age/MIPI score and prior therapies), the overall response rate in ZUMA-2 was consistent between these sub-groups (see Appendix E of the company submission [CS]).
Question for clinical expert: What is the natural history of this disease? is relapsed or refractory mantle cell lymphoma considered curable? • Is there evidence of long-term remission/cure for people with relapsed or refractory mantle cell lymphoma as there is for people with	When interpreting responses to this question, please note that any disease is considered incurable until a cure is found. This is central to the unmet need that this appraisal can address and although there are no currently available options that offer cure, this does not mean the disease cannot be curable with novel treatment options such as CAR T-cell therapy.

diffuse large b-cell lymphoma treated with non-CAR T-cell treatments? • How likely is it that patients that have received a stem cell transplant or a CAR T-cell therapy are cured of disease?	
If people are long term survivors following treatment with KTE-X19, are they expected to live as long as the general population, that is have a similar mortality risk as the general population? • If long term survivors have a lower life expectancy than the general population, what are the leading causes of mortality in this group?	
Issue 2: Blended standard of care comparator	
Question for clinical expert: What is the composition of standard of care used in clinical practice in the NHS? Is the company's composition of 65% R-BAC, 30% R-bendamustine, and 5% R-CHOP representative of current standard of care for the post-bruton's tyrosine kinase inhibitor mantle cell lymphoma population? **OR** is R-BAC representative of standard of care in most centres in the UK as favoured by the ERG?	For the sake of clarity, please note that the original company base case assumed R-BAC was representative of standard of care in most centres (65%) whereas the ERG base case assumes all patients receive R-BAC. When interpreting responses to each Issue 2 question, please note that in the revised company base case, we have aligned with ERG preference on this issue in the spirit of expediated decision making in the presence of variability and uncertainty, when uncertainty around this issue - to paraphrase section 6.2 of the ERG report - does not have substantial implications for cost-effectiveness conclusions.
Do stakeholders agree with the company's approach of pooling comparative evidence using a meta-analysis of comparator studies as a basket standard of care on the assumption that there is no 'true' standard of care for patients whose mantle cell lymphoma progresses following a BTK inhibitor to	

inform the comparison of KTE -X19 with established clinical management **OR** the ERG's preferred approach of using the results of the single retrospective cohort study McCulloch et al. 2020 to inform the comparison. McCulloch et al. 2020 was conducted in the UK and Italy, included people with median number of 2 prior therapies and 38% with prior stem call transplant. It provided comparator evidence for R-BAC which the ERG considered best representative of clinical practice in the UK. Both approaches have limitations. Are the results of the company's meta-analysis approach plausible? Please see Figures 2-5 of the technical report	
Issue 3: Indirect treatment comparison	
Do stakeholders consider that the company's approach of using an unadjusted indirect comparison of KTE-X19 (based on ZUMA-2 data) versus standard of care (based on the meta-analysed comparator studies) more appropriate? OR the ERG's preferred approach of using the results of the study McCulloch et al. 2020 to inform the comparison of KTE- X19 to a standard of care comparator? Both approaches have limitations. Are the results of the company's approach comparing KTE-X19 with standard of care	When interpreting responses to each Issue 3 question, please note that in the revised company base case, we have aligned with ERG preference on this issue (as is the case for Issue 2) in the spirit of expediated decision making in the presence of variability and uncertainty, when uncertainty around this issue - to paraphrase section 6.2 of the ERG report - does not have substantial implications for cost-effectiveness conclusions.

plausible and in line with what is seen in clincal practice? Please see figures 6-7 in the technical report.	
Issue 4: Long term survival data from ZUMA-2	
Question for clinical expert: In clinical practice what is the average extension to life you would expect to see for a patient who experiences a complete response. Do results from ZUMA-2 below reflect what is seen in clinical practice? Please see figures 8-9 of the technical report	There are no routine clinical practice data on outcomes for post-BTKi MCL patients who are then treated with CAR T-cell therapy. This is again central to the unmet need that this appraisal can address; there are no currently available options for which the implications of complete response are comparable to those from CAR T-cell therapy. With this in mind, it would be impossible for clinical experts to comment on whether results from ZUMA-2 reflect what is seen in clinical practice, unless they have been involved in the ZUMA-2 trial itself.
Can the plateaus in the Kaplan-Meier survival curves be interpreted as providing robust evidence of a "cure" i.e people surviving long term? What is the anticipated "cure" point based on your experience in clinical practice and is the length of follow- up of ZUMA-2 (median follow-up of [redacted] months) sufficient to provide an estimation? Please see figures 8-9 of the technical report	Considering the immunotherapeutic nature of CAR T-cell therapy, it is expected that at least a proportion of patients will experience long-term survivorship following KTE-X19 treatment. In the broader NHL setting, CAR T-cell therapy survival curves are starting to show an observed plateau with no downward tail, representing long-term survivorship.[2] In recently reported 3-year survival data from ZUMA-1, only four deaths were observed since the 2-year follow-up (patients at risk, n=51).[2] No such survival curve plateau is observed with conventional immunochemotherapy treatment. In the Follow-up analyses (data cut-off 31 December 2019) section of this response, we provide updated ZUMA-2 data that have become available since the original CS (median follow-up in the mITT group of [redacted] months). These data show that, for the mITT group, median OS has still not been reached, and the estimated 36-month OS rate of [redacted]% (compared to the estimated 24-month OS rate of [redacted]% in the primary analyses used in the CS) results in an extended Kaplan-Meier plateau and further supports the belief of long-term survivorship. The estimated 24-month PFS rate slightly reduced from [redacted]% to [redacted]% and the estimated 33-month PFS rate was [redacted]%.

	In addition, the Follow-up analyses (data cut-off 31 December 2019) section reports outcomes for those patients in the inferential analysis set with at least 30 months follow-up at data cut off (n=28) and further validate the above findings.
Question for clinical expert: How do you interpret the high complete response rate in the ZUMA-2 trial? • Is a cure/long-term remission possible without a complete response for patients with relapsed or refractory mantle cell lymphoma? • How many people with a complete response do you think can considered to be long-term survivors/cured in clinical practice? Please see figure 10 of the technical report	
Question for clinical expert: Can people who do not achieve a complete response go on to be considered long term survivors?	
Issue 5: Age at treatment of patient population	
Question for clinical expert: Is the median age of 65 years in the ZUMA-2 population reflective of the age of patients with relapsed or refractory mantle cell lymphoma that are likely to be treated with KTE-X19 in NHS clinical practice?	Due to the side effect profile and manufacturing time, CAR T-cell treatments are generally only suitable for fitter patients. We would expect that patients treated with KTE-X19 would undergo the same rigorous selection criteria as they do for currently available CAR T-cell treatments, resulting in a younger population. This is reflective of the UK real world evidence to date, where of 183 patients with R/R DLBCL treated with currently commercially available CAR T-cell treatments the median age is only 57. This was consistent with the median ages of patients in the ZUMA-1 (for axicabtagene ciloleucel) and Juliet (for tisagenlecleucel) pivotal studies, where the median ages

	were 58 and 56 respectively. Given this experience of the consistency between trial populations and real world patient selection, we believe a median age of 65 is reflective of patients who are determined to be eligible for KTE-X19.
Issue 6: Long-term PFS and OS of patients with relapsed or refractory mantle cell lymphoma after KTE-X19 treatment	
The estimated long-term survivor fractions in the company's base-case mixture cure models are PFS ([redacted])) and OS ([redacted])). The ERG's preferred spline models predict 5-year survival estimates at [redacted]%. This is lower than the long-term survivorship fraction estimated by the mixture cure models and similar to the long-term survivorship fraction estimated in previous NICE appraisal for a CAR T-cell therapy for axicabtagene ciloleucel in relapsed or refractory diffuse large B-cell lymphoma (TA559). Which model produces cure fractions that are clinically plausible?	In the revised company base case, we include the ERG preference for a hybrid approach to survival modelling (cubic splines followed by SMR-adjusted age- and sex-matched general population mortality), as described in the Revised company base case section of this response. The ERG's preferred approach provides a good fit to the trial data and plausible long-term progression-free survival and overall survival projections. For clarity, the 5-year survival estimates of [redacted]%, predicted by the ERG's preferred spline models do not reflect the 5-year survival estimates from their preferred base case model. As described above, the ERG's base case uses a hybrid approach whereby SMR-adjusted age- and sex-matched general population mortality is used from the end of the ZUMA-2 trial follow up ([redacted] months). As a technical note, spline models do not produce cure fractions so the phrasing of this question may be a little misplaced.
The estimated long-term survivor fractions differ between the company's base-case mixture cure, PFS (~[redacted]) and OS (~[redacted]) models. This implies that approximately 8.5% of ZUMA-2 patients relapsed and became long-term survivors following a subsequent treatment. 17/20 patients in ZUMA-2 who progressed received a subsequent anti-cancer therapy post-progression. Is it clinically plausible for subsequent anti-cancer therapy given to patients post-progression to lead to long-term survivorship in some patients?	

In TA559, the use of axicabtagene ciloleucel in diffuse large B-cell lymphoma was associated with a cure fraction of ~ 50% for OS and ~ 40-43% for PFS. There is uncertainty in the extent to which relapsed or refractory mantle cell lymphoma patients who relapsed at the third line or subsequent therapies can experience long-term remission and survivorship compared with patients with diffuse large B-cell lymphoma. Is it clinically plausible that the long-term survivorship fraction in relapsed or refractory mantle cell lymphoma is higher than in relapsed or refractory diffuse large B-cell lymphoma?	In the absence of longer-term clinical evidence, it is difficult to comment on the 'long-term survivorship fraction' following different CAR T-cell therapies across diseases. The approach taken to modelling the potential long-term survivorship benefit of KTE-X19 was based on observations from the ZUMA-2 data which provide the most robust data available to inform such potential benefit at this time. In the latest data cut of ZUMA-2 presented in the Follow-up analyses (data cut-off 31 December 2019) section of this response, the estimated 33-month PFS rate was [redacted]% and the estimated 36-month OS rate was [redacted]%. In a group of patients with at least 30 months follow-up at data cut off (n=28), [redacted]% are still alive and the longest observed survival to date is [redacted] months. These data help to validate the potential for long-term survivorship modelled in the CS base case.
Issue 7: Excess mortality risk experienced by long-term survivors	
The company's approach assumes that long-term KTE-X19 survivors experience a 9% higher probability of death compared to the general population. This moratality adjustment was sourced from Maurer et al. in a cohort of French newly diagnosed patients with DLBCL (n=820) who were event-free at 24 months: • Is the death rate of patients with relapsed or refractory diffuse large B-cell lymphoma comparable to patients with relapsed or refractory mantle cell lymphoma? • Would you expect the death rate observed in the general population to be higher in patients with	There is currently a lack of evidence informing the excess mortality risk for r/r MCL patients following KTE-X19 CAR T-cell therapy infusion. In NICE TA559 (Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies), there was similarly a lack of evidence on the excess mortality risk following axicabtagene ciloleucel CAR T-cell therapy infusion. Yet, data from Maurer et al. were used to inform an assumption that long-term CAR T-cell survivors experience a 9% higher probability of death compared to the general population in this appraisal. Such an assumption supported the Committee C recommendation for interim patient access to axicabtagene ciloleucel via the CDF, as discussed in Section 3.17 and 3.20 of the final appraisal determination.[3] In TA559, it was unclear how evidence from patients with event-free survival 24 months after frontline rituximab-chemotherapy (as provided by Maurer et al.) translated to prospects for refractory patients with good initial outcomes after CAR T-cell infusion, shown in limited follow-up

relapsed or refractory mantle cell lymphoma than in relapsed or refractory diffuse large B-cell lymphoma?	from the Phase I/II ZUMA-1 study for axicabtagene ciloleucel. Similarly, for this appraisal, there are no long-term data for the step-change CAR T-cell therapy. It is yet to be seen how long-term survival prospects following CAR T-cell therapy would compare between different lymphoma types. In this appraisal, as in TA559, assumptions in the absence of any robust data are required. Longer-term data from ZUMA-2, reported in the Follow-up analyses (data cut-off 31 December 2019) section, further support the notion of long-term survivorship for patients who, before CAR T-cell therapy, would have had a poor prognosis. Further ZUMA-2 data collection via the CDF can better inform assumptions for this issue as well as others, while allowing interim access to KTE-X19: a novel treatment with the potential to change the lives of patients with an urgent unmet medical need.
The ERG considers that it is more appropriate to base the mortality adjustment on data from patients as in Eskelund et al. (newly diagnosed patients with mantle cell lymphoma mostly treated with allogeneic stem cell transplant and who achieved complete remission for 1 or 5 years (n=160)) rather than in data from patients with diffuse large B-cell lymphoma. Which data source is appropriate and likely to produce more clinically plausible results? Please see figures 11-12 of the technical report	For the sake of clarity, the Eskelund et al. study investigates long-term prospects for newly diagnosed MCL patients who are treated with intensified first-line regimens containing cytarabine, rituximab and consolidation with high-dose-therapy, followed by ***autologous*** (not allogeneic) stem cell transplantation (auto-SCT). The analyses conducted included comparisons versus general population survival data, for (i) all ***159*** patients from baseline, (ii) the ***139*** patients with complete response (CR) after 1 year, (ii) the ***96*** patients with CR after 5 years and (iv) the ***59*** patients after 10 years. There are limitations to using the Eskelund et al. study to inform decision making, from both clinical and technical perspectives, as described in the June 2020 company response to ERG Priority question B2. Most notably (and as noted above), patients in Eskelund et al. were treated with auto-SCT, rather than CAR T-cell therapy. Auto-SCT involves collecting and freezing stem cells from the patient and treating the patient with chemotherapy before reinfusing stem cells back into the patient.[4] The purpose of cell collection and reinfusion in auto-SCT is to allow dose escalation of cytotoxic chemotherapy – escalation that is required because of the accepted insensitivity of MCL to cytotoxic drugs. Reinfused cells play no direct part in attacking the underlying disease. CAR T-cell therapy involves collecting T-cells from the patient, which are engineered ex vivo to target and kill

	cancer cells when they are returned to the patient. CAR engagement with target cells not only kills cancer cells but also starts a signaling process that stimulates proliferation of the CAR T-cells such that the patient builds up a personalized immune system to their cancer. The potential for durable remission and long-term survivorship with CAR T-cell therapy is therefore much higher than the potential for such benefits with auto-SCT. From a technical perspective, the ERG's method for deriving estimates for long-term excess mortality also has limitations. Appendix C of the ERG's report details the ERG's methods for estimating hazard ratios based on Eskelund et al. In brief, Kaplan-Meier curves from Figures 3b and 3c were first digitized and subsequently, a regression analysis was performed to estimate the hazard rate (λ). Hazard ratios were calculated from the hazard rate in the population with the disease, and the hazard rate in the general population. The final hazard ratios derived by the ERG were 4.37 for patients who sustained a complete remission for at least 1 year, and 2.36 based on the patients who sustained complete remission for at least 5 years. The quality of the Kaplan-Meier curves from which the hazard ratios have been produced is poor. Censoring points are not shown, nor are changes in the number remaining at risk over time. Furthermore, the Kaplan-Meier curve is not stepped, further increasing uncertainty in relation to the specific time point that each death event occurred. To assess the impact of these limitations, the ERG's analysis was reproduced independently by two analysts. The two analysts derived hazard ratios for patients who sustained a complete remission for at least 1 year of 4.34 and 4.45, and the hazard ratios derived for patients who sustained complete remission for at least 5 years were 2.09 and 2.07. These can be compared to the ERG's hazard ratios of 4.37 and 2.36. The differences between the estimates highlights the inherent uncertainty due to analyst inference when using data from this source.
Issue 8: Health related quality of life of long-term survivors	

Do stakeholders agree with the company's view that if a patient survives 5 years without progressing following treatment with KTE-X19, they will experience the same health related quality of life as the age-and sex-matched general population i.e they would be considered cured and to have the same mortality risk as the general population?	We would like to note that it is unclear what this question is asking: whether it is feasible for patients who have survived 5 years without progressing to have health related quality of life equal to that of the age- and sex-matched general population, or whether these patients have the same mortality risk as the age- and sex-matched general population? If the latter, we would like to clarify that the original company base case did not assume that those patients who had survived 5 years without progressing would have the same mortality risk as the general population. Rather, it was assumed that long-term KTE-X19 survivors experience a 9% higher probability of death compared to the general population (i.e. an SMR of 1.09 was applied to the age- and sex-matched general population survival), as discussed in Issue 7. We believe that the assumption of equivalent survival or health related quality of life are two separate but related issues; please interpret stakeholder responses with the phrasing of the question in mind.
Issue 9: Administration costs of KTE-X19	
The company costed KTE-X19 treatment at £[redacted](included the same costs as the previous appraisals, except the cost of training that was accounted for in appraisal TA559) while the current NHS England tariff price for CAR T-cell therapies is considerably more at £[redacted]	We would like to emphasize that if NHS England would not provide a detailed breakdown of the tariff currently used, there will be a significant risk of double counting some of the costs already included in the company model. For example, the tariff currently used in the company model doesn't include ICU bed days, while these might be included in the NHS England tariff. In addition, we would like to note that, as mentioned by the ERG, this tariff was derived prospectively at the beginning of the hospital CAR-T journey, when the experience on treating patients with commercial CAR-T and the management of associated side effect was minimal. The tariff will be retrospectively estimated next year, and we don't think that a prospectively derived tariff without a detailed breakdown and confirmed used of the resource included should be used to assess KTE-X19.

[redacted] The ERG was unable to assess which estimate most accurately reflect the costs to the NHS. The ERG uses the company estimate (updated with the preferred ERG assumptions) in its base-case, but presents a scenario using the NHS England tariff price. Can stakeholders comment on which costing is appropriate to be used in the cost-effectiveness analysis? Are the treatment costs used by the company and ERG in Figure 15 below reflective of costs to the NHS? Please see figure 13 of the technical report	

3. Additional supportive evidence

Gilead acknowledges the uncertainties highlighted by the NICE technical team in relation to the limited duration of follow-up in ZUMA-2 and the lack of direct evidence comparing KTE-X19 to standard of care. Previously unavailable supportive evidence is provided here; this evidence may alleviate the concerns of the NICE technical team.

Additional data comprise:

- Efficacy data for standard of care – overall survival data based on the National Cancer Registration and Analysis Service (NCRAS) dataset
- Efficacy data for KTE-X19 – data from the ZUMA-2 trial with an additional 6 months' follow-up

New evidence is provided for validation purposes; the data introduced here have not been incorporated into cost-effectiveness model calculations, as noted in the 27 August Technical Engagement call. However, with poorer survival outcomes in clinical practice than reported in McCulloch et al. (see Figure 3), should the NCRAS data have been incorporated they would have reduced the ICER estimates for KTE-X19.

Overall survival data based on the National Cancer Registration and Analysis Service (NCRAS) dataset

To further investigate post-BTKi treatment outcomes in UK clinical practice, a retrospective cohort review of patients diagnosed with MCL who failed BTKi and were initiated on a subsequent treatment was conducted (herein referred to as patients who failed BTKi). For clarity, analyses presented have been conducted by a third-party vendor; Gilead do not have access to these data and have not informed the analytical process.

Patients diagnosed with MCL in England between January 2010 to December 2017 were identified from the NCRAS: a population-based registration service which routinely collects, quality assures and analyses data on all people living in England who are diagnosed with malignant and pre-malignant neoplasms. Patients recorded as receiving BTKi and a subsequent therapy were selected for analysis.

Survival analysis was conducted based on Kaplan-Meier methods. No covariates were considered, and censoring was applied to patients who had not died at the end of the period of observation. The starting point for tracking was at the start of treatment initiated subsequently to BTKi and the end point for tracking was death (as per NCRAS vital status information).

Patient numbers

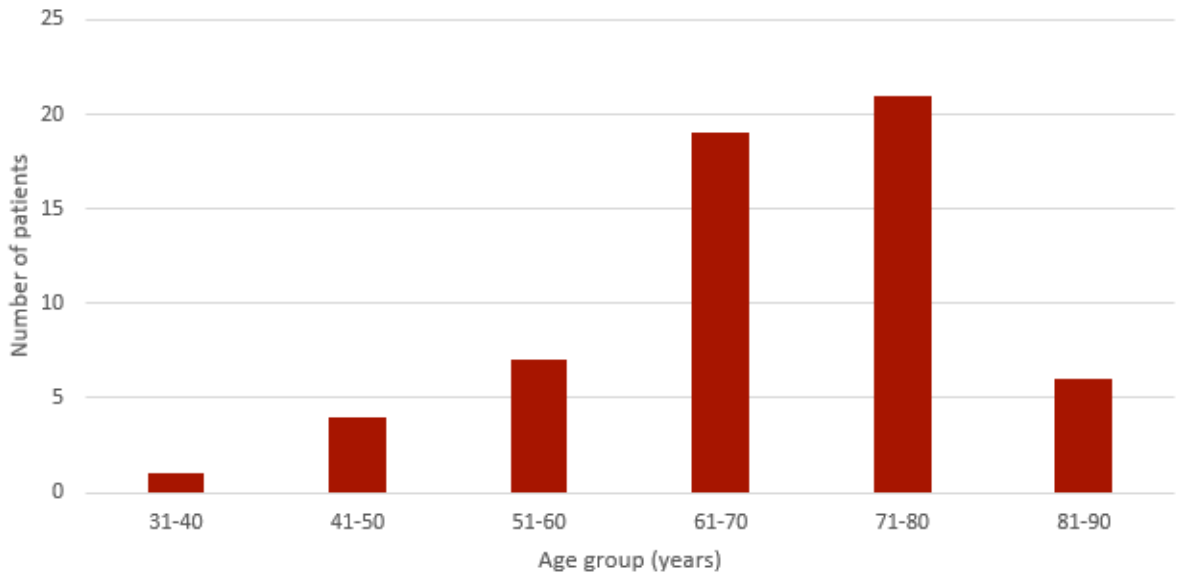
There were 4,031 MCL patients identified in total, of whom 372 (9.2%) were reported as having been treated with a BTKi at some point during their care: 70 (18.8%) at first-line; 133 (35.8%) at second-line and 169 (45.4%) at third- or later-line.

Among patients treated with a BTKi (n=372), 58 (15.6%) had been initiated on a subsequent treatment. Of these patients: 8 (13.8%) had been treated with BTKi at first-line; 25 (43.1%) at second-line and 25 (43.1%) at third- or later-line. For the remaining 314 patients, 195 (61.5%) had died while receiving BTKi and 121 (38.5%) were alive and still receiving BTKi at the time of data cut-off.

Patient demographics

The mean and median age of patients in the BTKi failure cohort (n=58) was 67 and 70 years, respectively with the majority of patients aged between 61 and 80 years, as depicted in Figure 1.

Figure 1: Age group of patients in the BTKi failure cohort (n=58)



The majority of patients in the BTKi failure cohort were male (77.6%) and Caucasian (93.1%); most were diagnosed with Stage III or IV disease (60.3% and 17.2%, respectively) and all were reported to have at least one comorbidity. Despite this, almost all patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (96% of those for whom data were available [n=50]).

Patient outcomes

All patients in the BTKi failure cohort

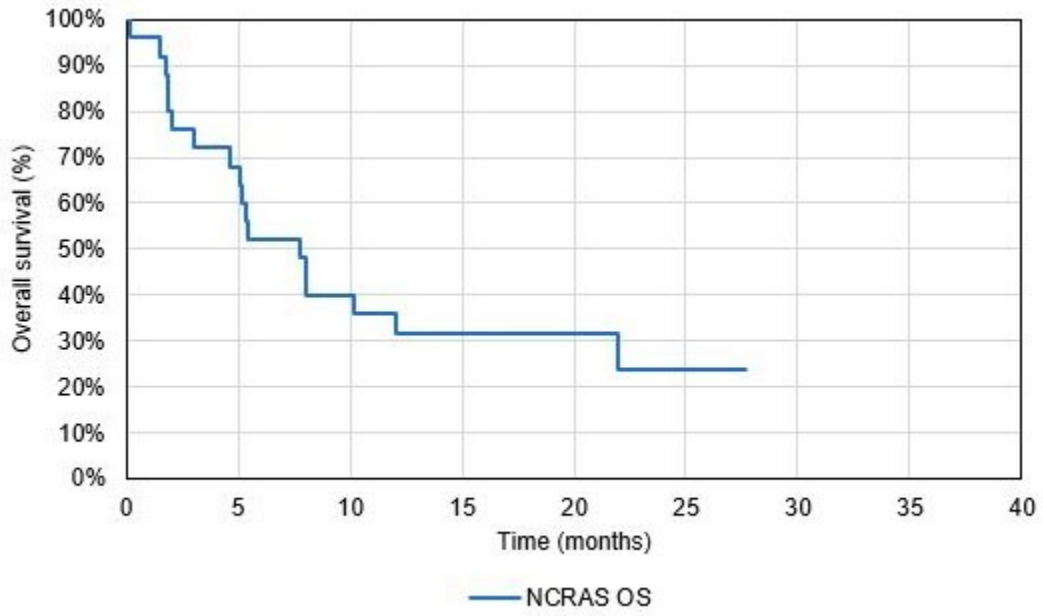
Of the 58 patients in the BTKi failure cohort, 36 (62.1%) died during the study period. The median OS was 8.1 months (243 days) and the 1-year OS rate was 42.1%.

Patients in the BTKi failure cohort who received BTKi at second line

Of the 25 patients in the BTKi failure cohort who received BTKi at second line, 18 (72.0%) died during the study period. The median OS was 7.8 months (235 days) and the 1-year OS rate was 36.0%.

The Kaplan-Meier curves for OS is presented in Figure 2.

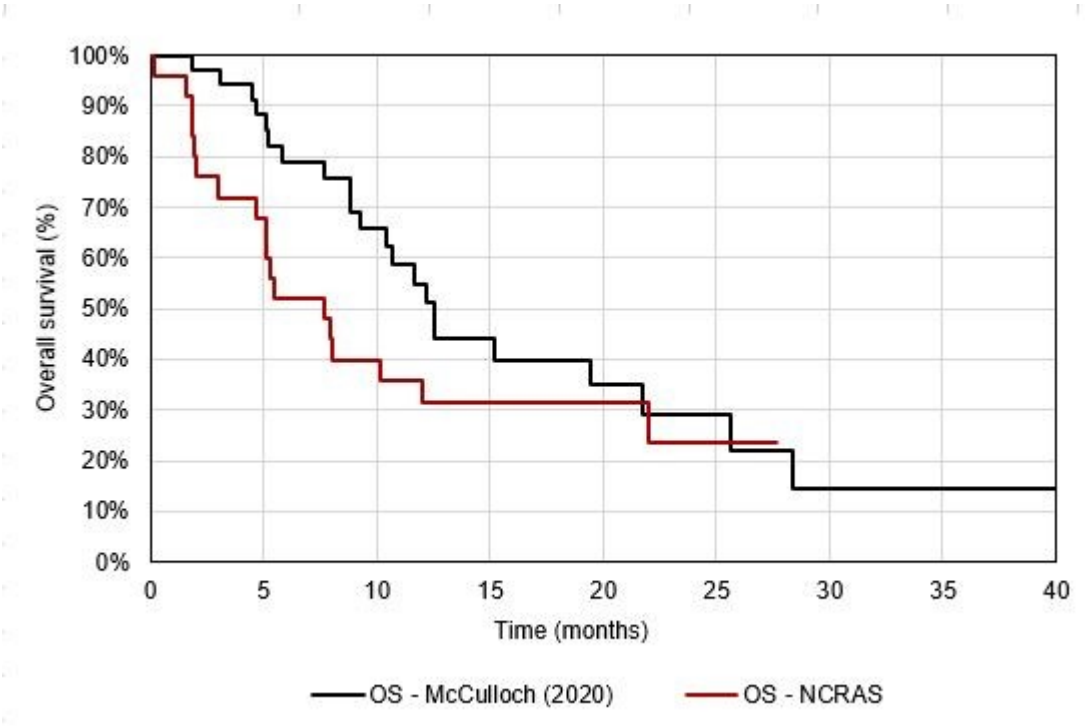
Figure 2: OS for patients who failed second-line BTKi: NCRAS data



Key: BTKi, Bruton tyrosine kinase inhibitor; NCRAS, National Cancer Registration and Analysis Service; OS, overall survival.

To put these survival estimates into context, a comparison of Kaplan-Meier curves for OS with the ERG's preferred literature source of McCulloch et al. 2020 is presented in Figure 3. This comparison suggests survival outcomes with third-line treatment are poorer in clinical practice than reported in McCulloch et al. This reflects that more intensive but more effective treatments such as R-BAC are likely to be offered only to fitter patients. However, it is noteworthy that by about month 20 both survival curves have converged reflecting the reality that although R-BAC may be the preferred current treatment option it only achieves relatively short-term survival benefits. All conventional therapies in this setting lack the potential for long-term survival offered by CAR T-cell therapy.

Figure 3: OS for patients who failed second-line BTKi: NCRAS data versus McCulloch 2020



Key: BTKi, Bruton tyrosine kinase inhibitor; NCRAS, National Cancer Registration and Analysis Service; OS, overall survival; PFS, progression-free survival.

Follow-up analyses (data cut-off 31 December 2019)

Follow-up analyses to the primary analyses for ZUMA-2 that have become available since the original CS support the initial conclusions that KTE-X19 provides an effective treatment option for patients with r/r MCL who have previously received a BTKi and the potential for long-term survivorship; particularly in patients with good depth of initial response.

In addition to the data described herein, we have also overlaid the two ZUMA-2 data cuts and have presented this in the model (Survival KM data sheet), as requested by the ERG in the technical engagement call on 27th August.

Inferential analysis set

At the time of follow-up analyses, the median follow-up among the patients in the IAS was [redacted] months, but the first 28 patients treated (47%) had at least [redacted] months follow-up with a median follow-up of [redacted] months.

Response and duration of response

No further responses were observed to those achieved by the time of primary analyses. One patient originally assessed to have a partial response was downgraded such that the total ORR reduced to [redacted]%; the proportion of patients with a CR was retained at [redacted]%. Across all responders (n=[redacted]), [redacted]% remain in response at the time of follow-up analyses.

The ORR using central assessment (IRRC) per Lugano classification in patients with ≥[redacted] months follow-up at the time of analysis (n=28) was [redacted]%, with a CR rate of [redacted]%. Of these patients, [redacted]% remain in response at the time of follow-up analyses, and the longest DOR to date is [redacted] months.

Progression-free survival

Figure 4 shows that the median PFS has still not been reached after a median follow-up of 17.5 months. [redacted] further patients had progressed since the primary analyses, meaning that [redacted] patients ([redacted]%) had progressed or died at the time of analysis. The estimated 24-month PFS rate slightly increased to [redacted]% and the estimated 33-month PFS rate was [redacted]%.

In patients with ≥ [redacted] months follow-up at the time of analysis (n=28), [redacted] patients ([redacted]%) had progressed or died and the estimated 33-month PFS rate was [redacted]%. Figure 5 provides the Kaplan-Meier (KM) plot for PFS in this group.

Figure 4: Progression-free survival using central assessment (IRRC) per IWG Lugano classification (inferential analysis set; follow-up analyses)

Key: CI, confidence interval; IRRC, independent radiology review committee; NE, not estimable; IWG, International Working Group.
Source: ZUMA-2 follow-up data files.

Figure 5: Progression-free survival using central assessment (IRRC) per IWG Lugano classification (patients with ≥ XX months follow-up)

Key: CI, confidence interval; IRRC, independent radiology review committee; NE, not estimable; IWG, International Working Group.
Source: ZUMA-2 follow-up data files.

Overall survival

Figure 6 shows that the median OS has still not been reached after a median follow-up of [redacted] months. [redacted] had died since the primary analyses, meaning that [redacted] patients ([redacted]%) had died in total at the time of analysis. The estimated 24-month OS rate therefore increased to [redacted]%; this was also the estimated 36-month OS rate ([redacted]%).

In patients with ≥ [redacted] months follow-up at the time of analysis (n=28), [redacted] were observed since the primary analyses and the estimated 36-month OS remained at the previously estimated 24-month OS rate of [redacted]%. The median OS was therefore still not reached and the longest observed survival to date is [redacted] months. Figure 7 provides the KM plot for OS in this group.

Figure 6: Overall survival (inferential analysis set; follow-up analyses)

Key: CI, confidence interval; NE, not estimable; OS, overall survival.
Source: ZUMA-2 follow-up data files.

Figure 7: Overall survival (patients with ≥ XX months follow-up)

Key: CI, confidence interval; NE, not estimable; OS, overall survival.
Source: ZUMA-2 follow-up data files.

Modified intent-to-treat group

At the time of follow-up analyses, the median follow-up among the patients in the mITT group was [redacted] months (range: [redacted] months).

Response and duration of response

No further responses were observed to those achieved by the time of primary analyses. One patient originally assessed to have a partial response was downgraded such that the total ORR reduced to [redacted]%; the proportion of patients with a CR was retained at [redacted]%. Across all responders (n=[redacted]), [redacted]% remain in response at the time of follow-up analyses.

Progression-free survival

Median PFS has still not been reached after a median follow-up of [redacted] months. [redacted] further patients had progressed since the primary analyses, meaning that [redacted] patients ([redacted]%) had progressed or died at the time of analysis. The estimated 24-month PFS rate slightly reduced to [redacted]% and the estimated 33-month PFS rate was [redacted]%.

Overall survival

Median OS has still not been reached after a median follow-up of [redacted] months. Two further patients had died since the primary analyses, meaning that [redacted] patients ([redacted]%) had died in total at the time of analysis. The estimated 24-month OS rate therefore increased to [redacted]%; this was also the estimated 36-month OS rate ([redacted]%).

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Table 1: Revised company base case, KTE-X19 for treating relapsed or refractory mantle cell lymphoma (adapted from ERG report, Table 22)

ERG-preferred amendments to CS base case (#in ERG report Table 22 | description in ERG report Table 22) included in revised company base case		**ICER**
0	Company submitted base case	[redacted]
1	0+ Correcting model errors	[redacted]
2	1+ Including the long-term health outcomes and costs of patients who did not receive KTE-X19	[redacted]
3	2+ Using McCulloch et al (2020) to inform the health outcomes of patients receiving SoC	[redacted]
4	3+ Excluding the costs of retreatment with KTE-X19	[redacted]
5	4+ Sourcing the number of doses of tocilizumab from ZUMA-2	[redacted]
6	5+ Calculating the costs of SoC based on McCulloch et al (2020)	[redacted]
7	6+ Assuming that long-term survivors have an annual haematology outpatient appointment	[redacted]
8	7+ Obtaining the number of days in ICU from ZUMA-2	[redacted]
9	8+ Including pancytopenia as an adverse event in the model	[redacted]
10	9+ Predicting PFS and OS with splines during the within-trial period and extrapolating beyond that based on adjusted general population mortality	[redacted]
Inclusion of confidential PAS discount in revised company base case (# change in this table | description)		
11	10+ Simple discount of [redacted]% to the list price of KTE-X19; **Revised company base case**	[redacted]
Key: CS, company submission; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; ICU, intensive care unit; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; SoC, standard of care.		

NICE National Institute for Health and Care Excellence

Technical engagement response form

KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Thursday 10 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
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- Do not use abbreviations.
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information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	**Dr Toby A. Eyre**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Oxford university Hospitals NHS Foundation Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Generalisibility of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice	
Question for clinical expert: Are the results of ZUMA-2 (conducted in people with a mean age of 63 years, median number of 3 prior therapies, 68% with an ECOG 0/1 and 43% having received a stem cell transplant) generalisable to people who would be eligible to receive KTE-X19 in NHS clinical practice? Please see Figure 1 in the technical report.	**In part yes. One issue with the KTE-X19 data is that it was performed in a selected patient population. Most patients outside of the clinical trial setting having a median of 3 prior lines of therapy are older and have a worse ECOG performance status. That said, these patients do absolutely exist. There is a surprisingly low number of pts having had a autoSCT in this population given the median age.**
Question for clinical expert: What is the natural history of this disease? is relapsed or refractory mantle cell lymphoma considered curable? • Is there evidence of long-term remission/cure for people with relapsed or refractory mantle cell lymphoma as there is for people with diffuse large b-cell lymphoma treated with non-CAR T-cell treatments? • How likely is it that patients that have received a stem cell transplant or a CAR T-cell therapy are cured of disease?	**Relapsed or refractory MCL is incurable in the vast majority of a patients. There are a small number of patients in this setting who might be bridged to allogenic stem cell transplantation with either a novel inhibitor such as a BTKi to alloSCT. These patients have approximately a 30-40% chance of cure with this approach but there is significant risk of transplant-related mortality with this. I think it is too early to know if MCL patients are cured with CAR-T therapy. Although responses are high and look durable the follow up at present is really quite short and so we can't be certain of this at present. It is very possible that some are cured but time will tell.**
If people are long term survivors following treatment with KTE-X19, are they expected to live as long as the general population, that is have a similar mortality risk as the general population? • If long term survivors have a lower life expectancy than the general population, what are the leading causes of mortality in this group?	**That is a difficult question to provide a certain answer for: they will have some morbidity associated with prior treatment which may lead to secondary effects that could effect their life expectancy. So I suspect they will have a moderately higher mortality risk. Causes: secondary solid tumours, cardiovascular mortality, infections, secondary blood cancers e.g. treatment related MDS for example.**

Issue 2: Blended standard of care comparator	
Question for clinical expert: What is the composition of standard of care used in clinical practice in the NHS? Is the company's composition of 65% R-BAC, 30% R-bendamustine, and 5% R-CHOP representative of current standard of care for the post-bruton's tyrosine kinase inhibitor mantle cell lymphoma population? **OR** is R-BAC representative of standard of care in most centres in the UK as favoured by the ERG?	**This is difficult to be 100% certain about as no-one has done a large national survey recently. I think the 65% - 30% - 5% estimate is probably reasonable. It is possible that RCHOP is slightly higher as many centres now use R-Bendamustine as front line therapy, and ibrutinib is funded at first relapse and therefore using RCHOP as 3rd line is very reasonable. In patients who have had an anthracycline (nearly all <65 years and many over) then yes, R-BAC (full or attenuated dosing) is probably the most well recognised standard of care**
Do stakeholders agree with the company's approach of pooling comparative evidence using a meta-analysis of comparator studies as a basket standard of care on the assumption that there is no 'true' standard of care for patients whose mantle cell lymphoma progresses following a BTK inhibitor to inform the comparison of KTE -X19 with established clinical management **OR** the ERG's preferred approach of using the results of the single retrospective cohort study McCulloch et al. 2020 to inform the comparison. McCulloch et al. 2020 was conducted in the UK and Italy, included people with median number of 2 prior therapies and 38% with prior stem call transplant. It provided comparator evidence for R-BAC which the ERG considered best representative of clinical practice in the UK. Both approaches have limitations. Are the results of the company's meta-analysis approach plausible? Please see Figures 2-5 of the technical report	**Pros and cons of both. McCulloch et al was a selected number of centres across the UK and Italy – so there is selection bias here at play. But patients fit for RBAC are probably those most likely mirroring the KTE clinical trial population. A widespread cohort post BTKi will include patients who are much less fit, and receiving less effective treatment.** **The meta-analysis approach is broadly reasonable and plausible.**

Issue 3: Indirect treatment comparison	
Do stakeholders consider that the company's approach of using an unadjusted indirect comparison of KTE-X19 (based on ZUMA-2 data) versus standard of care (based on the meta-analysed comparator studies) more appropriate? OR the ERG's preferred approach of using the results of the study McCulloch et al. 2020 to inform the comparison of KTE- X19 to a standard of care comparator? Both approaches have limitations. Are the results of the company's approach comparing KTE-X19 with standard of care plausible and in line with what is seen in clincal practice? Please see figures 6-7 in the technical report.	**Within all the limitations of indirect comparisons, the results are plausible and in line with standard clinical practice. I am sure the ERG is aware, but McCulloch 2019 and 2020 have a large overlap of the same patients i.e. they are no strictly separate data sets.**
Issue 4: Long term survival data from ZUMA-2	
Question for clinical expert: In clinical practice what is the average extension to life you would expect to see for a patient who experiences a complete response. Do results from ZUMA-2 below reflect what is seen in clinical practice? Please see figures 8-9 of the technical report	**In general in patients post BTKi, those who achieve a 'CR' I would expect to have a longer OS by perhaps 6-9 months compared to those with a PR or SD.**
Can the plateaus in the Kaplan-Meier survival curves be interpreted as providing robust evidence of a "cure" i.e people suriving long term? What is the anticipated "cure" point based on your experience in clinical practice and is	**I think this follow up is far too short to talk about cure. I'd want to see follow up for a minimum of 3 years before we can be more sure about using the word 'cure'.**

the length of follow- up of ZUMA-2 (median follow-up of [redacted] months) sufficient to provide an estimation? Please see figures 8-9 of the technical report	
Question for clinical expert: How do you interpret the high complete response rate in the ZUMA-2 trial? • Is a cure/long-term remission possible without a complete response for patients with relapsed or refractory mantle cell lymphoma? • How many people with a complete response do you think can considered to be long-term survivors/cured in clinical practice? Please see figure 10 of the technical report	- **The high CR rates demonstrate the strong proof of principle of efficacy of the KTE-19 product** - **PET-CT scans were used in the trial (and often aren't in clinical practice): PET-CT can lead to CMRs with PR on the CT component: this can lead to reports of higher CR rates reported compared to study where simply CTs are used.** - **Cure % is hard to estimate at the moment. Perhaps 30% of those in CR might end up being cured.**
Question for clinical expert: Can people who do not achieve a complete response go on to be considered long term survivors?	- **Very unlikely.**
Issue 5: Age at treatment of patient population	
Question for clinical expert: Is the median age of 65 years in the ZUMA-2 population reflective of the age of patients with relapsed or refractory mantle cell lymphoma that are likely to be treated with KTE-X19 in NHS clinical practice?	- **No it is probably approximately 8-10 years younger than the typical population having had 3 prior lines of treatment for MCL.**

Issue 6: Long-term PFS and OS of patients with relapsed or refractory mantle cell lymphoma after KTE-X19 treatment	
The estimated long-term survivor fractions in the company's base-case mixture cure models are PFS ([redacted])) and OS ([redacted])). The ERG's preferred spline models predict 5-year survival estimates at [redacted]%. This is lower than the long-term survivorship fraction estimated by the mixture cure models and similar to the long-term survivorship fraction estimated in previous NICE appraisal for a CAR T-cell therapy for axicabtagene ciloleucel in relapsed or refractory diffuse large B-cell lymphoma (TA559). Which model produces cure fractions that are clinically plausible?	**Probably the ERG model**
The estimated long-term survivor fractions differ between the company's base-case mixture cure, PFS (~[redacted]) and OS (~[redacted]) models. This implies that approximately 8.5% of ZUMA-2 patients relapsed and became long-term survivors following a subsequent treatment. 17/20 patients in ZUMA-2 who progressed received a subsequent anti-cancer therapy post-progression. Is it clinically plausible for subsequent anti-cancer therapy given to patients post-progression to lead to long-term survivorship in some patients?	**I think that it is highly unlikely (<5%) that patients relapsing post CAR-T therapy will be long term survivors.**
In TA559, the use of axicabtagene ciloleucel in diffuse large B-cell lymphoma was associated with a cure fraction of ~ 50% for OS and ~ 40-43% for PFS. There is uncertainty in the extent to which relapsed or refractory mantle cell lymphoma patients who relapsed	**It is possible but my expectation is that long term PFS will be of the 40-45% range**

at the third line or subsequent therapies can experience long-term remission and survivorship compared with patients with diffuse large B-cell lymphoma. Is it clinically plausible that the long-term survivorship fraction in relapsed or refractory mantle cell lymphoma is higher than in relapsed or refractory diffuse large B-cell lymphoma?	
Issue 7: Excess mortality risk experienced by long-term survivors	
The company's approach assumes that long-term KTE-X19 survivors experience a 9% higher probability of death compared to the general population. This moratality adjustment was sourced from Maurer et al. in a cohort of French newly diagnosed patients with DLBCL (n=820) who were event-free at 24 months: • Is the death rate of patients with relapsed or refractory diffuse large B-cell lymphoma comparable to patients with relapsed or refractory mantle cell lymphoma? • Would you expect the death rate observed in the general population to be higher in patients with relapsed or refractory mantle cell lymphoma than in relapsed or refractory diffuse large B-cell lymphoma?	**I would expect the probability of death to be slightly higher in a heavily pre-treated R/R MCL population than in a front line DLBCL population: for reasons highly previously. So 9% is probably reasonable.** **I don't know of any comparative studies of R/R DLBCL vs R/R MCL, but the death rate in the short term will be probably higher in DLBCL.**
The ERG considers that it is more appropriate to base the mortality adjustment on data from patients as in	**The Eskelund population were treated with an autoSCT not alloSCT.**

Eskelund et al. (newly diagnosed patients with mantle cell lymphoma mostly treated with allogeneic stem cell transplant and who achieved complete remission for 1 or 5 years (n=160)) rather than in data from patients with diffuse large B-cell lymphoma. Which data source is appropriate and likely to produce more clinically plausible results? Please see figures 11-12 of the technical report	**This data is suggesting that patients still have a higher overall mortality that the general population, but this is in the context where patients are known to not be cured. I think the reason why the DLBCL cohort has been used is that there is a consideration that pts are cured with KTE. Problem is the DLBCL cohort is front line patients, 1 line of therapy, younger patients. So neither are truly comparable.** **A better population would be to see if there is excess mortality in R/R DLBCL 'cured' with autoSCT. But I am uncertain if this data exists. I think the 9% additional mortality rate seems fair.**
Issue 8: Health related quality of life of long-term survivors	
Do stakeholders agree with the company's view that if a patient survives 5 years without progressing following treatment with KTE-X19, they will experience the same health related quality of life as the age-and sex-matched general population i.e they would be considered cured and to have the same mortality risk as the general population?	**I suspect they will have a slightly higher mortality and a worse QoL: As discussed earlier: Causes: secondary solid tumours, cardiovascular mortality, infections, secondary blood cancers e.g. treatment related MDS for example. They will have had 4 lines of treatment for MCL. Even if 'cured' this will have an effect. We know there are some issues with longer term immunosuppression/infection risk post CAR-T.**
Issue 9: Administration costs of KTE-X19	
The company costed KTE-X19 treatment at £[redacted] (included the same costs as the previous appraisals, except the cost of training that was accounted for in appraisal TA559) while the current NHS England tariff price for CAR T-cell therapies is considerably more at £[redacted]	

[redacted] The ERG was unable to assess which estimate most accurately reflect the costs to the NHS. The ERG uses the company estimate (updated with the preferred ERG assumptions) in its base-case, but presents a scenario using the NHS England tariff price. Can stakeholders comment on which costing is appropriate to be used in the cost-effectiveness analysis? Are the treatment costs used by the company and ERG in Figure 15 below reflective of costs to the NHS? Please see figure 13 of the technical report	

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Evidence Review Group's Critique of the Company's Response to the Technical Engagement Process

KTE-X19 for treating relapsed or refractory mantle cell lymphoma

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Date completed 18/09/2020

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are [redacted]

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1 CRITIQUE TO THE REVISED COMPANY'S BASE-CASE

The company submitted a revised company's base-case, which accepts all but one of the ERG's preferred assumptions and includes a patient access scheme (PAS) discount as part of a possible agreement if the Committee recommends KTE-X19 to the Cancer Drugs Fund (CDF). The only ERG preferred assumption that the company did not incorporate was the value of the mortality adjustment to the general population mortality, which represents the excess mortality risk of long-term survivors after KTE-X19 (ERG item 7). The PAS discount consists of [redacted] The ERG examined the company's revised model. The ERG confirmed that the company's revised model includes the ERG preferred assumptions, except the assumption regarding the mortality adjustment, that the PAS discount is correctly implemented. Table 1 shows the cost-effectiveness results of the company's revised base-case with and without the proposed PAS discount.

[redacted] 1 [redacted]

	Discounted costs		Discounted QALYs		ICER £/QALY
Scenario	KTE-X19	Standard of care	KTE-X19	Standard of care	
Without PAS discount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS discount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

2 CRITIQUE TO THE COMPANY'S RESPONSE TO THE ISSUES RAISED AT TECHNICAL ENGAGEMENT

2.1 Issue 1: Generalisibility of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice

The company responded that, although the mean age of 63 years of the ZUMA-2 population is younger than might be expected in the general relapsed or refractory mantle cell lymphoma UK population (r/r MCL), it is likely reflective of those who would be considered to be eligible for KTE-X19 in clinical practice. The company supported this quoting evidence from real-world data of 122 high-grade lymphoma patients approved for treatment with CD19 CAR-T in England up to July 2019

presented at a conference in 2019 (Kuhnl 2019) [1] and comparing age and fitness of these patients with that of those included in pivotal trials for axicatagene ciloleucel (ZUMA-1)[2] and tisagenlecleucel (Juliet).[3] In the 2019 conference abstract, the median age of patients with r/r high-grade lymphoma approved for CAR-T therapy through the CDF up to July 2019 was 57 years, (range 18-75) compared with 58 year (IQR 51-64) in the ZUMA-1 trial and 56 years (range 22-76) in the Juliet trial. Recorded ECOG status was 0-1 in all three cohorts.

2.1.1 **ERG critique**

The ERG agree with the company that the median age and fitness status of patients with high-grade r/r DLBCL approved for CAR-T therapy through the CDF up to July 2019 presented in Kuhnl (2019)[1] are broadly comparable to that of patients included in the ZUMA-1 and Juliet trials. However, the ERG identified a more recent abstract from the real-world NHS cohort, Kuhnl (2020),[4] that included an additional three patients (n=125) and reported a significantly higer median age of 62 (range 18-75) for patients approved for CAR-T therapy. The clinical advisor to the ERG who was involved in this study confirmed this was the most up to date data source, with further results expected in June 2021.

The characteristics of the NHS CAR-T cohort are presented in Table 2 along with the characteristics of ZUMA-1 and Juliet trials. The Kulhn (2020)[4] abstract reported that of 125 patients, 91 were infused, and 80 were evaluable. It is not clear to what extent the characteristics of the infused patients matched those of the Juliet and ZUMA-1 trials. Table 2 shows that response and survival results of the real-world CAR-T cohort are not as favourable as those reported in the CAR-T pivotal trials. Kuhnl (2020) report an overall response rate at 3 months of 35% (20% CR). This is significantly lower than the objective response rates reported in Zuma-1 (PR/CR: 74%, CR: 54%) and Juliet (PR/CR: 52%; CR: 40%). With a median follow-up of 4.8 months, the median event-free survival in the real-world cohort was 3.1 months, median OS was 9.1 months. In contrast, ZUMA-1 had a PFS of 5.9 months (3.3-15.0) and median OS was not reached at two years. Further details are reported in Table 2.

Table 2: Characteristics and results of real-world CAR-T data and pivotal trials in r/r large B-cell lymphoma

	ZUMA-1 (Phase 2, n=101) [2]	**Juliet (n=111)** [3]	**Kuhnl (2020)** [4] **(n=125) EHA conference**
Median age (range)	58 (51–64) Note, range is IQR	56 (22-76)	62 (18-75)
Male %	68 (67%)	Not reported	Not reported
Prior therapies 1	3 (3%)	5 (5%)	

2 3+	28 (28%) 70 (69%)	49 (44%) 57 (52%) Note, number not 100% due to rounding	53/125 (42%) Note, only data provided on number with 3+ prior therapies
Stage III/IV	85%	76% (Stage III, 20%; Stage IV 56%)	76%
ECOG 0/1	100% (42%, ECOG 0; 58%, ECOG 1)	100% (ECOG 0, 55%; ECOG 1, 45%)	100%
PR/CR	74% Note, IRC assessed	52%	35%
CR	54%	40%	20%
Median PFS	5.9 months (3.3-15.0)	Not reported	Not reported
Median OS	Not reached at 2 years	8.3 months (95% CI, 5.8 to 11.7)*	9.1 months*

*modified intent-to-treat analysis; EHA: European Hematology Association; ASH: American Society of Hematology

In the absence of real-world data for KTE-X19 it is unclear whether consistency between real-world and trial data would be observed for r/r MCL patients post-BTKi. A clinical advisor to the ERG stated that the UK and Italian cohort of MCL patients with BTKi failure reported in McCulloch 2020 was broadly comparable to that of patients who would be eligible to KTE-X19 in the NHS. However, as discussed in the ERG report, the comparability of ZUMA-2 population to McCulloch 2020 cohort is limited, as demonstrated notably by the significantly low effective sample size (ESS) yielded by the company's matched adjusted indirect comparison (MAIC) analyses that compared the two cohorts.

In the ERG report, concerns were also raised about the generalisability of the ZUMA-2 participants to the population of r/r MCL patients who may be eligible to CAR-T therapy in NHS clinical practice due to lack of clarity associated with the selection of trial participants (see section 3.2.1.1 of ERG report).

As discussed in section 6.2.2 of the ERG report, ERG scenario analyses have shown that even small variations in mean baseline age at treatment initiation can have a significant impact on ICER estimates. The ERG agree with the company that access to KTE-X19 for eligible r/r MCL patients via the CDF would significantly reduce the uncertainty associated with the generalisability of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice.

2.2 Issue 2: Blended standard of care comparator

The company responded that, although the original company's base-case assumed that standard of care consisted of a blend of Rituximab-Bendamustine Cytarabine (R-BAC), rituximab-bendamustine

(R-benda) and rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone (R-CHOP) for the purposes of costing, the revised company's base-case aligns with the ERG's preferred assumption of R-BAC.

2.2.1 **ERG critique**

The ERG welcomes the change in the company's base-case, and refers to the ERG report Section 4.2.9.2 for the rationale for costing standard of care with R-BAC.

2.3 Issue 3: Indirect treatment comparison

The company responded that the revised company's base-case now aligns with the ERG preference of using McCulloch et al. (2020) [5] as the single source of data to inform the progression-free and overall survival with SoC; and refers to the ERG report section 6.2 to note that this issue has a small impact on the cost-effectiveness of KTE-X19.

2.3.1 **ERG critique**

The ERG welcomes the change in the company's base-case, and refers to the ERG report Section 4.2.6.2 for the rationale for preferring McCulloch et al (2020) [5]. The ERG notes that the long-term outcomes of patients with r/r MCL who received standard of care, but who would be eligible to receive KTE-X19, remain uncertain. This uncertainty arises due to the limited evidence on the comparability of ZUMA-2 patients to patients in McCulloch et al (2020) or indeed the other studies identified by the company to inform the outcomes of standard care. As discussed in the ERG report (page 80), the reduction in ESS in the company's MAIC suggests that there is limited overlap among the baseline characteristics (i.e. limited comparability) between ZUMA-2 and the standard of care studies. This argument is equally pertinent to the unadjusted naïve comparisons. For these reasons, the ERG considers that the MAIC and the unadjusted naïve comparison are subject to significant risk of bias and uncertainty. Given the magnitude of comparative effectiveness, this is unlikely to have a major impact on the ICER.

2.4 Issue 4: Long term survival data from ZUMA-2

To the question about the expected extension to life in complete responders, the company responded that the ZUMA-2 trial is the single source of available evidence on the long-term survival of r/r MCL patients who received KTE-X19, hence it would be difficult for clinical experts to comment unless they were involved the the trial.

To the question about the robustness of the evidence supporting long-term survivorship, the company responded that it is plausible that KTE-X19 leads to long-term survivorship in a proportion of patients, as with other CAR T-cell therapies in the NHL setting. Additionally, the company referred to

the additional evidence, namely the 31/12/2019 cut-off of the ZUMA-2 study, which the company interpreted as evidence supporting long-term survivorship.

2.4.1 ERG critique

The ERG agrees that the ZUMA-2 trial is the single source of direct evidence on KTE-X19. As discussed in the ERG report section 4.2.6.1, the ZUMA-2 data (and any extrapolations based on these) are associated with considerable uncertainty given its small sample size, short follow-up and extent of censoring. The cost-effectiveness submission is based on the modified intention-to-treat (mITT) group of Cohort 1, using data from the 24/07/2019 cut-off of the ZUMA-2 trial. This data includes 68 patients who received KTE-X19, over a median follow-up= [redacted] months; maximum follow-up = [redacted] months. In this 31/12/2019 cut-off, the median follow-up of the mITT group was [redacted] months (range: [redacted] months).

Figure 1 shows the Kaplan-Meier curves based on the original (24/07/2019) cut-off and the new (31/12/2019) cut-off which were provided in the company's revised model. The new data cut-off of 31/12/2019 does not inform the company's revised model. The new PFS curve (in orange) is similar to the original PFS curve (in blue) up to approximately [redacted] when new events occurred. The new OS curve (in red) also follows the original OS curve (in blue) up to approximately [redacted]. There is less that [redacted]% of the original sample at risk at approximately [redacted] months for PFS and at approximately [redacted] months for OS (data not shown; based on the data submitted in the company's revised model).

[redacted]

The ERG concludes that, despite this additional data, the follow-up is still insufficient to robustly support an assumption of long-term survivorship. The ERG's original concerns remain valid and the illustrative analyses presented in the ERG report (Figure 8 page 68 and Figure 9 page 69) are still informative. These figures illustrate the uncertainty in the Kaplan-Meier curves in general, and the fragility in the plateau and the long-term survivor fraction in particular. Furthermore, the ERG notes the responses of Dr Toby Eyre to technical engagement "*I think it is too early to know if MCL patients are cured with CAR-T therapy. Although responses are high and look durable the follow up at present is really quite short and so we can't be certain of this at present. It is very possible that some are cured but time will tell*" (p3) and "*I think this follow up is far too short to talk about cure. I'd want to see follow up for a minimum of 3 years before we can be more sure about using the word 'cure'*" (p6). For these reasons, the ERG considers the data immature and the long-term extrapolations subject to high levels of uncertainty.

The ERG considers that precedent from previous technology appraisals in CAR T-cell therapies in other conditions is insufficient to support the assumption of long-term survivorship in r/r MCL. Furthermore, the ERG notes that the data on CAR T-cell therapy in r/r DLBCL (including DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma) is immature, given that the available follow-up is less than 3 years.[2, 3] Therefore, the extent of long-term remission with CAR T-cell therapies in r/r DLBCL is uncertain, as well as its generalisability to long-term remission in r/r MCL.

The ERG notes that there is indirect evidence on the life expectancy of complete responders in studies on the long-term outcomes of patients who achieved complete remission with other therapies. For example, Eskelund et al reports the 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial, in which patients received induction treatment and autologous stem cell therapy as first line therapy.[6] Although the treatment in Eskelund et al is different, and the patients in Eskelund are in first line therapy rather than r/r setting, this study provides evidence on the long-term prognosis of patients who have achieved completed response and continued in remission for some years. Whether the long-term prognosis after complete response with KTE-X19 is more favourable, given its different nature and mechanism of action, is uncertain.

2.5 Issue 5: Age at treatment of patient population

The company reiterated that patients receiving KTE-X19 would likely be younger and fitter than the broader r/r MCL populations, and responded that given the experience of the consistency between trial populations and real-world patient selection, a median age of 65 was reflective of patients who are determined to be eligible for KTE-X19.

2.5.1 **ERG critique**

The ERG agree with the company that the population who would be eligible for KTE-X19 is likely to be significantly younger and fitter than the broader r/r MCL population.

As discussed under Issue 1, the median age of patients with r/r high-grade lymphoma receiving CAR-T therapy through the CDF up to July 2019 is 57 years comapared to that of phase II CAR-T trials in large B-cell lymphoma (median 62 years versus 58 and 56 in Zuma-1 and Juliet trials respectively). In the absence of real-world data for KTE-X19 r/r MCL and based on comparisons with observational evidence of patients with r/r MCL receiving R-BAC, it is unclear whether the same difference in age between real-world and trial data would be observed for the r/r MCL population.

In his response to technical engagement, Dr Toby Eyre stated that the ZUMA-2 population was likely to be approximately 8-10 years younger than the typical population of patients having had 3 prior lines of treatment for MCL. As discussed above and in the ERG report, concerns about the selection of trial participants (see section 3.2.1.1 of ERG report) may further limit the generalisability of ZUMA-2 population to those eligible to KTE-X19 in the NHS.

As discussed in Section 6.1.2.5 of the ERG report, ERG scenario analyses have shown that even small variations in mean baseline age at treatment initiation have a significant impact on ICER estimates. The ERG agree with the company that collection of real-world data for r/r MCL patients under the CDF would significantly reduce the uncertainty associated with the generalisability of the ZUMA-2 population to the NHS.

Given the impact of age at treatment initiation in the scenario analyses reported in the ERG report (see Section 4.2.3, Section 6.1.2.5 and Scenario 5), the ERG conducted an additional scenario analysis but using the company's revised model. Table 3 shows the results.

[redacted] **3** [redacted]

Scenario	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs Standard of Care)
	KTE-X19	Standard of Care	KTE-X19	Standard of Care	
Company's revised base-case without patient access scheme discount and age = 63.2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's revised base-case without patient access scheme discount and age = 73.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.6 Issue 6: Long-term PFS and OS of patients with r/r MCL after KTE-X19 treatment

The company responded that their revised base-case follows the ERG base-case for the approach to extrapolation of PFS and OS, given that it provides a good fit to the trial data and plausible long-term extrapolations. The company reiterated that the ZUMA-2 trial provides the most robust data available on KTE-X19 given the absence of longer-term clinical evidence and noted the results of the 31/12/2019 data cut-off.

2.6.1 **ERG critique**

The ERG welcomes the change in the company's base-case assumptions to those preferred by the ERG. Nonetheless, the ERG notes that the long-term extrapolation is subject to considerable uncertainty, which is discussed extensively in the ERG report Section 4.2.6.1, as well as earlier in the current report in Section 2.4.1 and under Issue 7 below (see Section 2.7.1.).

2.7 Issue 7: Excess mortality risk experienced by long-term survivors

The company noted that the lack of evidence on the excess mortality risk also occurred in NICE TA559 on a CAR T-cell therapy for treating diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. In TA559, the NICE committee accepted the assumption that long-term survivors are at 9% greater risk of death than the age- and sex-matched general population, based on Maurer et al. [7, 8]. The company suggests that, similarly to TA559, a recommendation to the Cancer Drugs Fund would allow for further ZUMA-2 data collection to better inform this parameter while making KTE-X19 available to patients.

The company discussed the limitations of using Eskelund et al [6] to inform the excess mortality risk experienced by long-term survivors. Specifically, the company noted that the patients in Eskelund et al were treated with autologous stem cell transplantation, which would not be expected to achieve the same response rate and length of remission as KTE-X19. The company discussed the limitations of the ERG's method for deriving the estimates of the mortality adjustment using on the curves presented in Eskelund et al. Using Eskelund et al, the company re-estimated hazard ratios of 2.07 and 2.09 for patients in complete remission for 5 years (compared to the ERG estimation of 2.36) and of 4.34 and 4.45 for patients in complete remission for 1 year (compared to the ERG estimation of 4.37).

2.7.1 **ERG critique**

The ERG reiterates the concerns raised in the ERG report Section 4.2.6.1 regarding the generalisability of Maurer et al, [8] in newly diagnosed patients with DLBCL, to the r/r MCL population. Firstly, the ERG considers that the use of the mortality adjustment obtained from a study in DLBCL patients in previous NICE appraisals in DLBCL is not a valid justification to use the same mortality adjustment in r/r MCL. Secondly, the ERG's clinical advisors considered that the excess

mortality risk from DLBCL is not generalisable to r/r MCL and that the excess mortality risk compared to the general population is likely to be higher in r/r MCL than in DLBCL. Third, despite its limitations and uncertainty, the evidence from Eskelund et al[6] suggests that the excess mortality risk experienced by MCL patients who were in complete remission for some years is substantial and likely to be higher than in DLBCL.

As discussed in the ERG report (Section 6.1.1.11 and Appendix C), the ERG acknowledges the limitations of the method used to derive the mortality adjustment from Eskelund, which were unavoidable given the data limitations and timelines of the appraisal process, and notes the uncertainty in the estimated mortality adjustments. Nonetheless, the advantages of using Eskelund et al to inform the mortality adjustment outweigh the downsides because it refers to patients with MCL who achieved complete remission, whereas Maurer et al refers to newly diagnosed patients with another condition (specifically DLBCL).

In the ERG base-case (also in the company's revised base-case), the switch from ZUMA-2 survival to the adjusted general population mortality happens at the end of the original trial follow up, at [redacted] months. The ERG base-case uses its estimated lower and higher hazard ratio, based on Eskelund et al, as the lower and upper range of the mortality adjustment to the general population mortality risk. This assumes that the patients who are still alive in the model at [redacted] months are patients who have been in complete remission for 1 year or will be in complete remission for 5 years. The ERG considers that this assumption is plausible given the survival projections for standard of care, which indicate that non-responders are likely to have died by this point, and estimated 12-month and 24-month OS rate in complete responders in ZUMA-2 at [redacted]% and [redacted]%, respectively (see PfC A2). The company did not provide the OS rate in complete responders according to the new 31/12/2019 data cut-off. While it is possible that patients still alive at [redacted] months will remain in complete remission for 5 years (60 months), the limited number of patients at risk preclude robust predictions to support this. Conversely, the 1-year HR could be seen as more consistent with the original median follow-up of the ZUMA-2 trial at [redacted] months. Therefore, the ERG considers presenting results as a range, based on the two alternative HRs, to be a pragmatic approach.

To explore the impact in the differences in the estimated mortality adjustments, the ERG conducted a scenario analysis using the lower and upper bound of the company's hazard ratios, that is, 2.07 and 4.45, with the company's proposed discount and using the company's revised base-case model (see Table 4).

[redacted] 4 [redacted]

Scenario	Discounted costs	Discounted QALYs	ICER

	KTE-X19	SoC	KTE-X19	SoC	(KTE-X19 vs SoC)
Company's revised base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With patient access scheme discount					
Mortality adjustment = 2.07	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality adjustment = 4.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without patient access scheme discount					
Mortality adjustment = 2.07	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality adjustment = 4.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To illustrate the impact of the uncertainty on the long-term mortality risk of long-term survivors, the ERG conducted a univariate sensitivity analysis to the mortality adjustment in Figure 2, similar to the analysis the ERG report (see Section 7.2.3.1 Univariate sensitivity analysis to the mortality adjustment for long-term survivors), with the company's proposed discount and using the company's revised base-case model.

[redacted]

[redacted]

2.8 *Issue 8: Health related quality of life of long-term survivors*

The company considered the question to be unclear but did not provide their view on the question.

2.8.1 **ERG critique**

The ERG re-iterates its view that it is uncertain whether long-term survivors experience the health-related quality of life patients in ZUMA-2 or the health-related quality of life of the age- and sex-matched general population (see ERG report Section 4.2.8.1). As Dr Eyre commented in response to technical engagement: "*That is a difficult question to provide a certain answer for* [question on the expected life expectancy of long-term survivors following treatment with KTE-X19]*: they will have some morbidity associated with prior treatment which may lead to secondary effects that could effect their life expectancy. So I suspect they will have a moderately higher mortality risk. Causes: secondary solid tumours, cardiovascular mortality, infections, secondary blood cancers e.g. treatment related MDS for example*" (p3) and "*I suspect they will have a slightly higher mortality and a worse QoL: As discussed earlier: Causes: secondary solid tumours, cardiovascular mortality, infections, secondary blood cancers e.g. treatment related MDS for example. They will have had 4 lines of treatment for MCL. Even if 'cured' this will have an effect. We know there are some issues with*

longer term immunosuppression/infection risk post CAR-T" (p9-10). If long-term survivors are at an excess risk of mortality compared to the general population, their health-related quality of life may also be affected, and be lower than the the health-related quality of life of the age- and sex-matched general population. The ERG notes that the scenario analysis 9 to its base-case resulted in a ICER of [redacted] when the health-related quality of life of who remain in the pre-progression state for more than 5 years is 10% lower than the general population, and £[redacted]/QALY if 20% lower (compared to [redacted] in the ERG base-case).

2.9 Issue 9: Administration costs of KTE-X19

The company noted that, without a detailed breakdown of the resources included in the NHS England tariff, there is a risk of double counting some of the costs already included in the model (e.g. bed-days in the intensive care unit). Furthermore, the company considered that this tariff, having been prospectively derived when CAR T-cell therapy was first made available, should not be used in the cost-effectiveness assessment of KTE-X19.

2.9.1 **ERG critique**

As discussed in the ERG report Section 4.2.9.1, [redacted] the costs calculated by the company, which are broadly in line with other NICE appraisals, [redacted]. The impact on the cost-effectiveness results was explored in the ERG report Scenario 6.

3 CRITIQUE TO THE ADDITIONAL SUPPORTIVE EVIDENCE

The company submitted additional supportive evidence: the analysis of overall survival of patients diagnosed with MCL who failed a BTKi and who were initiated on a subsequent treatment, based on the National Cancer Registration and Analysis Service (NCRAS) dataset, and the analysis of the 31/12/2019 data cut-off of the ZUMA-2 trial, which has an additional 6 months' follow-up compared to the analysis reported in the original company's submission.

The results of neither analyses were incorporated in the cost-effectiveness calculations in the revised company's base-case and were provided only for validation purposes. The ERG did not incorporate these results in the cost-effectiveness calculations due to the limited resources and short timelines to respond to the company's response, and the lack of individual level data.

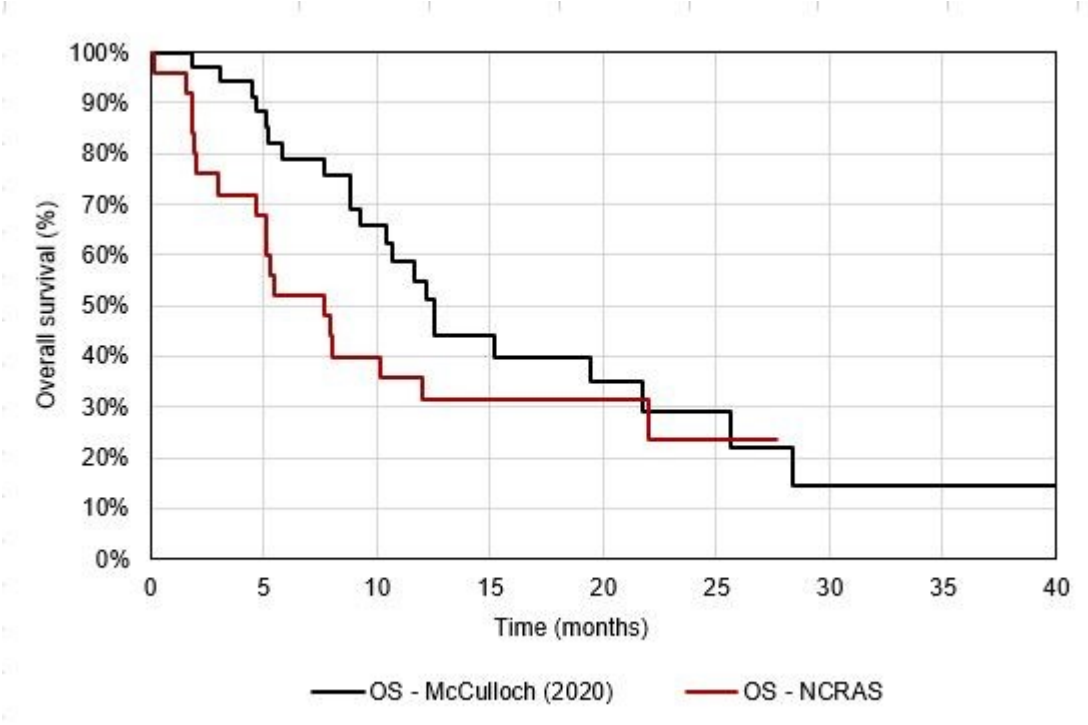
3.1 Critique to the overall survival data based on the National Cancer Registration and Analysis Service (NCRAS) dataset

To investigate post-BTKi treatment outcomes in UK clinical practice, the company commissioned a retrospective cohort review of 58 patients with MCL who failed BTKi and were initiated on a subsequent treatment from the National Cancer Registration and Analysis Service (NCRAS) dataset in England. Of these patients: 8 (13.8%) had been treated with BTKi at first-line; 25 (43.1%) at second-line and 25 (43.1%) at third- or later-line. The characteristics of the patients are reproduced in Table 5 below.

Survival analysis was conducted using Kaplan-Meier methods. No covariates were considered, and censoring was applied to patients alive at the end of the observation period. The starting point for tracking was at the start of treatment initiated following BTKi. The company did not report what treatments patients received post-BTKi. OS results for the McCulloch 2020 population (the ERG's preferred SoC population), which included post-BTKi high-grade MCL patients receiving R-BAC, were fitted in a naïve unadjusted comparison, and reproduced in Figure 3.

The K-M curves show poorer survival outcomes for the NCRAS BTKi failure cohort compared with McCulloch 2020, with curves converging at approximately 20 months. The median OS in the BTKi cohort was 8.1 months (7.8 months in the 25 patients who received BTKi at second line). In comparison, patients receiving R-BAC in McCulloch 2020 had a median OS of 12.5 months. The company concluded that "*should the NCRAS data have been incorporated they would have reduced the ICER estimates for KTE-X19*."

Figure 3 Overall survival for patients who failed second-line BTKi: NCRAS data versus McCulloch 2020 (from company response to Technical engagement, Figure 3).



Key: BTKi, Bruton tyrosine kinase inhibitor; NCRAS, National Cancer Registration and Analysis Service; OS, overall survival; PFS, progression-free survival.

Due to significant differences in patient characteristics, the ERG believe that the NCRAS BTKi failure cohort is not directly comparable with the cohort included in McCulloch 2020, nor with the ZUMA-2 population. Table 5 presents the characteristics of patients included in ZUMA-2 (mITT population), McCulloch 2020 and NCRAS (BTKi failure subset) and median OS. This shows significant differences between the three cohorts for a number of key prognostic characteristics. The NCRAS BTKi failure cohort was significantly older on average (mean/median age 67/70 years) compared with the ZUMA-2 mITT (63/65 years) and McCulloch 2020 populations (65/66 years). Nearly half of patients (approximately 47%) in the NCRAS population were 71 years old or above, and about 10% were 81 years old or above. Conversely, NCRAS patients had fewer prior therapies overall, and the proportion of stage III/IV patients was lower.

Given these differences in key prognostic characteristics and the absence of adjustments for covariates in the company's additional analyses (such as treatment post-BTKi), the ERG believe that the comparison between NCRAS and McCulloch 2020 cohorts is at high risk of confounding and unlikely to be reliable.

Table 5: Baseline characteristics of NCRAS (BTKi failure), ZUMA-2 and McCulloch 2020 cohorts

	ZUMA-2 (mITT) (n=68)	**McCulloch 2020 (n=36)**	**NCRAS (BTKi failure cohort, n=58)**
Mean age	63	65.2 (*at start of R-BAC*)	67
Median age	65	66 (*at start of R-BAC*)	70
Prior therapies 1 2 3+	 1 (1%) 12 (18%) 55 (81%)	 2 (5.6%) 30 (83.3%) 4 (11.1%) *Note, at initial diagnosis*	 8 (13.8%) 25 (43.1%) 25 (43.1%) *Note, line at which BTKi was used*
Stage III/IV	97% (Stage III, 12%; Stage IV, 85%)	100% (no break down by III and IV) *Note, at initial diagnosis*	77.5% (Stage III, 60.3%; Stage IV 17.2%)
ECOG 0/1	100% (ECOG 0: 65%, ECOG 1: 35%)	80% *Note, at start of R-BAC*	96% (data on 50 patients available only)
Median OS	Not reached (median follow up = [redacted])	12.5 months	8.1 months

The ERG do not believe that incorporating the NCRAS data would have significantly reduced the ICER estimates for KTE-X19. ERG scenario analyses presented in ERG report Section 6.2.2 showed that using different sources of SoC evidence for OS (including data with OS outcomes comparable to the NCRAS BTKi cohort) had no significant impact on the ICERs. Similarly, the ERG believe that incorporating a naïve comparison between ZUMA-2 and NCRAS into the model would likely have no

substantial impact on the ERG model ICERs, and would have limited validity due to clinically significant differences in patient characteristics between the ZUMA-2 and NCRAS BTKi cohorts.

3.2 Critique to the follow-up analyses (data cut-off 31/12/2019)

The company submitted data on (1) response and duration of response, (2) progression-free survival and (3) overall survival for the inferential analysis set and for the modified intention to treat group. The company reports the updated results for the inferential analysis set as Kaplan-Meier curves and narratively, and only narratively for the modified intention-to-treat group, without providing the updated Kaplan-Meier curves. The inferential analysis set (IAS; N=60) corresponds to the first 60 patients treated with KTE-X19 at the licensed dose. In this 31/12/2019 data cut-off, the median follow-up is [redacted] months. The modified intention-to-treat group (mITT; N=68) corresponds to the patients who received KTE-X19 at the licensed dose. In this 31/12/2019 data cut-off, the median follow-up is [redacted] months (range: [redacted] months).

3.2.1 Response and duration of response

The company reported that no further responses were observed since the primary analyses. One patient originally assessed to have a partial response (PR) was downgraded, reducing the total ORR reduced from 93% to [redacted]% in the IAS population, and from [redacted]% to [redacted]% in the mITT population; the proportion of patients with a CR was retained at [redacted]% in the IAS population (mITT: [redacted]%). Across all responders (n=[redacted] in IAS, n=[redacted] in mITT), [redacted]% of IAS participants ([redacted]% mITT) remained in response at the time of follow-up analyses.

The ERG welcome the additional response data from the company. The fact that the high CR rate was maintained since the last data cut-off is positive, but the lack of longer-term response and survival data mean that there is currently insufficient evidence to support the assumption of long-term cure following KTE-X19 treatment. Further follow-up data from ZUMA-2 would help to address this uncertainty.

3.2.2 Progression-free survival (PFS)

Table 6 summarises the new data submitted by the company.

[redacted] 6 [redacted]

Data set	Number of patients	Number of patients who progressed since original analysis	Total number of patients who progressed or died	24-month PFS rate	33-month PFS rate
Inferential analysis set all patients	60	[redacted]	[redacted]	[redacted]	[redacted]

Inferential analysis set patients with ≥ [redacted] months follow-up	28	[redacted]	[redacted]	[redacted]	[redacted]
Modified intention to treat all patients	68	[redacted]	[redacted]	[redacted]	[redacted]

The ERG welcomes additional data on PFS, but notes the extent of censoring and the small number of patients at risk. For example, Figure 4 of the company's response (page 22) suggests that, for the inferential analysis set, number at risk at 12 months is [redacted] patients, at 24 months there are [redacted] patients, and after [redacted] months [redacted].

3.2.3 Overall survival (OS)

Table 7 summarises the new data submitted by the company.

[redacted] 7 [redacted]

Data set	Number of patients	Number of patients who died since original analysis	Total number of patients who progressed or died	24-month OS rate	36-month OS rate
Inferential analysis set all patients	60	[redacted]	[redacted]	[redacted]	[redacted]
Inferential analysis set patients with ≥ [redacted] months follow-up	28	[redacted]	[redacted]	[redacted]	[redacted]
Modified intention to treat all patients	68	[redacted]	[redacted]	[redacted]	[redacted]

As with PFS, the ERG notes that the additional data on OS is still limited. For example, Figure 6 on OS for the inferential analysis set suggests that the number at risk at 12 months is [redacted] patients, at 24 months is [redacted] patients, and at 36 months is [redacted].

3.2.4 Comparison of additional data to survival curves predicted by the cost-effectiveness model

Figures 4-6 show the original Kaplan-Meier curves, the new Kaplan-Meier curves and the model predictions for OS and PFS for alternative mortality adjustments, namely 1.09, based on Maurer et al as preferred by the company (Figure 3), and 2.07 (Figure 4) and 4.45 (Figure 6) based on the company's analyses of Eskelund et al. Despite the additional data submitted by the company, the data on PFS and OS remains limited. From visual examination, the curves predicted by the model appear to fit the available data equally well for the period up to the end of the trial follow-up with stark differences appearing in the extrapolation period, due to the different mortality adjustments. Despite the additional data, the ERG concludes that substantial uncertainty remains.

[redacted] 4 [redacted]

[redacted]

[redacted] 5 [redacted]

[redacted]

[redacted]

[redacted] 6 [redacted]

[redacted]

[redacted]

4 CONCLUSION

The ERG conclusions hold from the original ERG report. Although the response and survival outcomes of KTE-X19 are promising, the key areas of uncertainty remain.

4.1 Key areas of uncertainty

The key areas of uncertainty in the clinical effectiveness are:

1. The precision and magnitude of efficacy and safety estimates from ZUMA-2 are highly uncertain. The limited evidence means survival results may not be robust to small chance variations in prognosis or survival outcomes.
2. ZUMA-2 survival data are immature and survival curves do not provide sufficient evidence of durable long-term survivorship. Median overall survival (OS) and progression-free survival (PFS) have not been reached.
3. The generalisability of ZUMA-2 patients is uncertain, and the risk that they may have a more favourable prognosis than patients who would be eligible for KTE-X19 under the anticipated license cannot be excluded.
4. The comparator evidence presented by the company is very limited, and most is not directly relevant to the NHS. The ERG considers the study by McCulloch et al (2020)[5] most relevant to the comparator population, as R-BAC is the most commonly used intervention in the post-BTKi MCL population.
5. Observed baseline imbalances between KTE-X19 and relevant SoC evidence, and results of MAIC analyses suggest unadjusted comparisons are subject to significant risk of bias and uncertainty.

The key areas of uncertainty in the cost-effectiveness evidence are:

1. Generalisability of the ZUMA-2 population to the UK patient population, and the effect of age at treatment in particular.
2. Long-term PFS and OS of r/r MCL patients after KTE-X19.
3. Excess mortality risk experienced by long-term survivors.
4. Naïve unadjusted comparison of KTE-X19 *versus* SoC.
5. The health-related quality of life of durable survivors who have not progressed in the long-term.
6. The administration costs of KTE-X19.

4.2 ERG base-case results

The ERG welcomes the company's revised base-case, which follows all the ERG preferred assumptions except the assumption regarding the mortality adjustment to represent the excess mortality risk of long-term survivors. The ERG maintains that, despite the limitations and uncertainties, the Eskelund et al is a more appropriate source of evidence to inform the mortality adjustment given that it refers to patients with MCL who were in complete remission, albeit newly diagnosed and who received a different treatment. The ERG highlights that without long-term data from r/r MCL patients sustaining complete remission after KTE-X19, it is difficult to accurately infer the excess mortality risk that long-term r/r MCL survivors after KTE-X19 are subject to, compared with the general population.

Table 8 shows the results for the ERG's base-case with and without the PAS discount. Due to the similarity of the deterministic and probabilistic results, and the time required to run the model probabilistically, the results with the PAS discount are deterministic. The ERG notes that the scenario and sensitivity analyses to the ERG base-case presented in the ERG report remain informative to illustrate the consequences of the uncertainty on the cost-effectiveness results.

The long-term follow-up of the patients in ZUMA-2 has the potential to address the uncertainties relating to the PFS and OS extrapolation and around the excess mortality risk, depending on the maturity of the data. These longer-term data could be supplemented with observational data on the long-term survival and HRQoL of r/r MCL patients in long term remission compared to the general population. Furthermore, data on the characteristics of patients eligible for KTE-X19 in the UK would help address the uncertainty specifically around the average age of patients at treatment and more generally around the generalisability of ZUMA-2 patient population to the UK patient population.

[redacted] 8

Treatment	Total discounted costs	Total discounted QALYs	ICER £/QALY
Without PAS discount (probabilistic)			

Treatment	Total discounted costs	Total discounted QALYs	ICER £/QALY
Standard of Care	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]
With PAS discount (deterministic)			
Standard of Care	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]

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Evidence Review Group's Addendum to the Critique of the Company's Response to the Technical Engagement Process

KTE-X19 for treating relapsed or refractory mantle cell lymphoma

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Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are [redacted].

Copyright statement

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1 ADDENDUM TO THE CRITIQUE TO THE REVISED COMPANY'S BASE-CASE

In September 2020, the company submitted a revised company's base-case, which accepted all but one of the ERG's preferred assumptions and included a patient access scheme (PAS) discount. The original PAS discount consisted of

In October 2020, NICE clarified that only the

henceforth referred to as the 'updated PAS'. Following this clarification, the company submitted revised cost-effectiveness results. The ERG was able to replicate these results.

Table 1 shows the cost-effectiveness results of the company's revised base-case, with and without the updated PAS. For reference, the only ERG preferred assumption that the company did not incorporate was the value of the mortality adjustment to the general population mortality, which represents the excess mortality risk of long-term survivors after KTE-X19 (ERG issue 7).

1

	Discounted costs		Discounted QALYs		ICER £/QALY
Scenario	KTE-X19	Standard of care	KTE-X19	Standard of care	
Without PAS					
With updated PAS					
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; 2					

2 ADDENDUM TO THE CRITIQUE TO THE COMPANY'S RESPONSE TO THE ISSUES RAISED AT TECHNICAL ENGAGEMENT – REVISED COST-EFFECTIVENESS RESULTS

2.1 Issue 5: Age at treatment of patient population

The ERG's Critique of the Company's Response to the Technical Engagement Process included a scenario analysis to the age at treatment initiation in Table 3 (p8). The ERG has now updated results

using the updated PAS. In doing so, the ERG noted a typo in the original Table 3. Table 2 shows the revised results.

[redacted]

Scenario	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs Standard of Care)
	KTE-X19	Standard of Care	KTE-X19	Standard of Care	
Company's base-case age = 63.2 years					
Company's revised base-case **without the PAS discount**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's revised base-case **using the updated PAS**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis with age = 73.2 years					
Company's revised base-case **without the PAS discount**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's revised base-case **using the updated PAS**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.2 ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year;

[redacted] ***Issue 7: Excess mortality risk experienced by long-term survivors***

The ERG's critique of the company's response to the technical engagement process showed the results of a scenario analysis on the mortality adjustment using the company's revised base-case, with and without the PAS discount in Table 4 (p10). Table 3 shows the revised results, with and without the updated PAS.

[redacted]

Scenario	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs SoC)
	KTE-X19	SoC	KTE-X19	SoC	
Company's revised base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With updated PAS					
Mortality adjustment = 2.07	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality adjustment = 4.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without PAS					
Mortality adjustment = 2.07	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality adjustment = 4.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year;

[redacted]

The ERG's critique of the company's response to the technical engagement process showed the results of a univariate sensitivity analysis to the mortality adjustment in Figure 2 (p11). Figure 1 shows the updated results using the updated PAS ([redacted]).

[redacted]

[redacted]

3 ADDEDUM TO CONCLUSION

The ERG's critique of the company's response to the technical engagement process showed the cost-effectiveness results for the ERG base-case, with and without the PAS discount in Table 8 (p20). Table 4 shows the updated results, with and without the updated PAS.

[redacted]

Treatment	Total discounted costs	Total discounted QALYs	ICER £/QALY
Without PAS (probabilistic)			
Standard of Care	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]
With updated PAS (deterministic)			
Standard of Care	[redacted]	[redacted]	[redacted]
KTE-X19	[redacted]	[redacted]	[redacted]

[redacted]