Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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Draft guidance comments form VERSION 1.0

Consultation on the draft guidance document – deadline for comments 5pm on 12 August 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Gilead Sciences

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Section 3.4 Generalisability of ZUMA-2	The draft guidance notes that the committee concluded results from ZUMA-2 were generalisable to patients in the NHS. However, the committee preferred to use the mean age of 66 from SACT as the starting age in the economic model. The company has conducted a scenario analysis using the committee preference for SACT evidence (see age scenario) and recognises the value of SACT data to inform patient characteristics. As such, the mean age in the company preferred base-case has been adjusted to reflect the SACT data. Even so, the company re-iterates that clinicians expect the age of patients over time to be lower compared to the mean age in the SACT data for several reasons. Firstly, in the first 12 months of brexucabtagene autoleucel (brexu-cel) availability there was a bolus of patients expecting treatment. Most of these patients had received additional lines of therapy at the time, while currently such patients receive brexu-cel earlier in their treatment pathway. Secondly, the recent BSH guidelines recommend early identification of relapse and treatment with brexu-cel to improve outcomes. As the guideline recommendation is being implemented, the age of patients is also subsequently expected to drop.

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	Thirdly, clinicians have become more familiar with the benefits of brexu-cel and subsequently more likely to select patients with the greatest potential for better outcomes. This has been reflected in the patient characteristics from Kite Konnect (the online ordering system), where an analysis of the average age of the first six months, versus the last six months demonstrated an age reduction (Feb-Jul 21, [redacted] years; Dec 24 – May 25, [redacted] years).
Section 3.6 Real world evidence for brexu-cel	The committee has recommended combining UK real-world evidence (SACT and O'Reilly datasets) with ZUMA-2 trial data to provide a pooled analysis for brexu-cel clinical outcomes in the economic model. In the revised model, overall survival (OS) is estimated using pooled ZUMA-2 and SACT data, while progression-free survival (PFS) is derived from ZUMA-2 and the O'Reilly dataset. In the base case the company has used the most recent SACT data cut (September 2022), which includes patients treated after the August 2022 update to the British Society for Haematology (BSH) guidelines. These guidelines, first introduced in the 2022 BSH Addendum and then reinforced in the 2023 full guideline update, advocate for earlier identification and referral of high-risk mantle cell lymphoma (MCL) patients for CAR-T therapy. Full implementation of the guideline recommendation is expected with time. This shift enables treatment at a more favourable disease stage, improving feasibility and outcomes. This is reflected in the latest O'Reilly 2024 UK real-world study, which shows a significant increase in infusion rates from 59.8% (2022) to 69.7% (2024), importantly this later 2024 dataset includes all patients from the earlier 2022 period including those that did not reach infusion, therefore still underestimating the number of patients that could currently be expected to reach infusion. The latest infusion rate from the Kite Konnect data has continued to improve and in the last 6 months is approximately 85%. These improvements are attributed to earlier referral, better disease control, and reduced manufacturing failure rates. Further support for the expectation of improved CAR-T outcomes over time comes from the Boyle et al. 2023 study in large B-cell lymphoma (LBCL), which demonstrated a clear learning curve in UK CAR-T delivery. Comparing patients treated in 2019 versus 2020–2022, the study found significant improvements in infusion rates (from 73% to 83%), 1-year progression-free survival (from 32% to 50%), and 1-year overall survival (from 40% to 60%), intensive care unit admission rates (from 32% to 20%). Importantly, the use of post-August 2022 SACT data also avoids confounding from earlier cohorts affected by manufacturing delays and the COVID-19 pandemic. During the pandemic, CAR-T recipients were among the most vulnerable patient groups, with early studies reporting COVID-19 related mortality rates of up to 50%. However, outcomes improved significantly over time. A large European multicentre study showed a reduction in COVID-19–related mortality from 43.6% in 2020 to 7.5% in 2022, driven by increased vaccination, improved supportive care, and the emergence of less virulent SARS-CoV-2 variants. These findings underscore the importance of using contemporary data to reflect current clinical practice. They also highlight how pandemic-era outcomes may underestimate the true potential of CAR-T therapy when used in optimal conditions. Together, the integration of updated real-world data, evolving clinical practice, and guideline-driven patient selection provides a more accurate and contemporary view of brexu-cel's performance in the UK. It supports the expectation that outcomes will

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	continue to improve over time as referral pathways, supportive care, and clinical experience mature.
Section 3.7 Subsequent alloSCT after R-BAC	The draft guidance notes that the committee preferred modelling to assume a 15% rate of subsequent alloSCT following R-BAC, rather than the 31% observed in McCulloch et al. (2020) data-set. The committee also welcomed further clinical input and data to inform the proportion of patients receiving alloSCT after R-BAC. In response, the revised company base case assumes 15% of patients in the R-BAC arm proceed to alloSCT. The analysis presented here provides useful insights into potential outcomes in an R-BAC-treated population with lower alloSCT rates than those reported in McCulloch. However, these findings should be considered exploratory rather than definitive as: • The updated SLR for the re-appraisal did not identify additional evidence of R-BAC effectiveness and subsequent allo-SCT rates. R-BAC is no longer recommended in guidelines as a treatment option for R/R MCL in patients who are eligible for CAR-T. Further, it is unlikely that additional evidence to inform the proportion of patients likely to receive subsequent alloSCT following R-BAC will emerge as CART has become the standard of care for treating eligible patients. It is worth noting that in the previous appraisal (TA677), the committee accepted McCulloch et al. as the most appropriate data source for R-BAC and considered the observed alloSCT rate (of 31%) to be representative of clinical practice at the time, prior to the widespread adoption of CAR-T therapy. Please note, the preference in this scenario to adjust outcomes based on rates of alloSCT means that outcomes need to be estimated separately for patients based on whether they did or did not receive subsequent alloSCT. Subsequently, a credible approach needed to be found to model outcomes for: • **Patients who did not receive allo-SCT subsequent to R-BAC**: Both the EAG and the company, removed alloSCT patients from their R-BAC cohort, in order to model outcomes, based on the sub-groups reported in McCulloch study. • **Patients who did receive allo-SCT subsequent to R-BAC**: While McCulloch et al. (2020) reported outcomes for 11 patients who received alloSCT following R-BAC, the small sample size, short follow-up, and limited number of events make robust extrapolation challenging. This was therefore not modelled by the EAG. The company's revised scenario therefore includes the Liebers et al (2025) study to inform allo-SCT outcomes. The rationale for using Liebers et al. (2025) to inform alloSCT outcomes is that: o It includes 64 patients who underwent alloSCT for R/R MCL, matched by propensity score to patients from the ZUMA-2 trial. o The median follow-up was 34.1 months. o Patients in the matched alloSCT cohort had similar ECOG performance status and BTKi exposure to those in McCulloch, supporting comparability.

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	○ The study was conducted using data from the European Bone Marrow Transplant (EBMT) registry, a well-established source of real-world transplant outcomes. ○ The generalisability of the EBMT data was confirmed by clinical expert opinion. ○ Using the Liebers study allows extrapolation of alloSCT outcomes from a larger, better-characterised cohort, improving the credibility of modelled estimates.
Section 3.9 Modelling of the pre-infusion period - approach	The treatment pathway for CAR-T therapy includes apheresis, a process in which a patient's blood cells are collected to manufacture the CAR-T product. However, a small number of patients approved for CAR-T will not proceed to apheresis and an even smaller number of patients (<10%) will not receive an infusion once apheresis has taken place, often due to disease progression or clinical deterioration. In the submission, the company has modelled a modified intention-to-treat (mITT) population, where outcomes are measured from the point of infusion. In order to account for the small proportion of patients who undergo apheresis but do not proceed to infusion, the costs of apheresis are included for all patients who reach that stage. The company maintains its agreement with the committee's conclusions from the previous TA677 appraisal, which determined that the mITT population is the most appropriate for the base case. This approach is consistent with prior CAR-T technology appraisals, where committees have consistently concluded that the mITT population provides the most appropriate basis for analysis. This includes appraisals: • TA559; Axicabtagene autoleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies • TA677; Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma • TA872; Axicabtagene autoleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies • TA893; Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over • TA895; Axicabtagene autoleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy • TA975; Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under • TA1048; Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable It is important to highlight that the comparator, R-BAC (rituximab, bendamustine, cytarabine), is an intensive and toxic chemotherapy regimen. The McCulloch et al. (2020) study, which is often cited in this context, reflects outcomes in patients who were able to initiate and complete R-BAC treatment. This does not capture the broader

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	real-world population, where a significant proportion of patients may not be eligible or may discontinue treatment early due to toxicity. Indeed, in the McCulloch study: • 56% of patients required chemotherapy dose reductions, including 71% of those who received at least four cycles. • 90% of patients aged ≥70 years required dose reductions, most commonly to cytarabine. • 50% of patients experienced unplanned hospital admissions, with neutropenic fever accounting for 94% of these events. • 68% required blood transfusion support, and although there were no treatment-related deaths, the regimen was deemed too intensive for many patients These findings underscore the regimen's toxicity and the clinical challenges associated with its administration. Clinical expert opinion further supports that 20–30% of patients considered for R-BAC would likely not proceed to treatment due to frailty or rapid disease progression. Therefore, using the intention-to-treat (ITT) population from ZUMA-2, which includes patients who never received CAR-T infusion, would not represent a like-for-like comparison with the McCulloch R-BAC cohort, which only includes patients who were treated. To ensure consistency with previous CAR-T appraisals and to avoid introducing bias into the comparative analysis, the company proposes that the mITT population should remain the base case for comparison.
Section 3.9 Modelling of the pre-infusion period – drop out rates	In line with the comments in the draft guidance, an analysis from the point of apheresis is reported as a scenario (see section 3.16 tabulation) and is not part of the updated company base case. This scenario models outcomes from the point of apheresis (as requested by the committee) using the ZUMA-2 drop-out rate (see company rationale below), however this should be considered exploratory. The draft guidance notes that the committee prefers: • to use SACT data to inform the proportion of patients who receive apheresis but do not proceed to infusion (estimated at about 25% [as reported by the NHSE representative at the first committee meeting] To support the committee's understanding, the company provides further detail on how drop-out data are collected and proposes a refinement of the CAR-T pathway to distinguish between: - those that drop out **prior** to apheresis - and to those that drop out **after** apheresis (but prior to infusion).

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	SACT collect data from two forms, a request for apheresis (PART 1) and request for infusion (PART 2). PART 1 is completed before apheresis but often there is some delay in apheresis taking place, meaning some patients do not proceed to apheresis despite having a request for apheresis form (PART 1) completed. Therefore, patients who have a request for apheresis form (PART 1) completed but include both those who drop out between approval and apheresis, and those who drop out between apheresis and infusion. This is an important distinction as the drop-out rate of 25% currently assumes that all patients underwent apheresis based on the collection of the "request for apheresis" (Part 1) forms. In reality, many drop-outs occur before apheresis is performed. According to the company's ordering system (Kite-Konnect) data from Jan-2024 to Jun-2025: • [redacted]% of approved patients did not go on to infusion (a similar figure to that cited in the committee meeting) • [redacted]% of patients did not proceed to apheresis (aligning with the figures from the O'Reilly study) • [redacted]% of approved patients dropped out after apheresis but before infusion (see figure below), closely matching the [redacted]% drop out figure in ZUMA-2 who dropped out between apheresis and infusion.  The company has limited insight into the individual reasons why approved patients do not receive apheresis - as this data is not collected in either ZUMA-2 or in SACT dataset. However, the clinical eligibility, patient preference and progressive disease may all play a role.

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	For this scenario analysis, the company has used the ZUMA-2 dropout rate noting it is consistent with the O'Reilly apheresis to infusion data and not meaningfully different from the rate of drop-out between apheresis and infusion seen in the Kite Konnect data ([redacted] % vs [redacted] %). This approach ensures alignment with clinical evidence and avoids overestimating the proportion of patients who reach apheresis.
Section 3.9 Modelling of the pre-infusion period – outcomes for non-infused patients	The draft guidance notes that the committee prefers: • that outcomes data for non-infused brexu-cel patients should be taken from the SACT data or, if unavailable, based on the DESCAR-T data presented by the EAG. The company notes that SACT do not report outcomes for patients who do not receive infusion and that the committee separately determined that the DESCAR-T study was not a suitable evidence base to inform brexu-cel outcomes. The main reason for unsuitability of the DESCAR-T study discussed during the committee meeting was that patients with an ECOG score ≥2 at enrolment were included in DESCAR-T (15% of the total population) whereas such patients are not eligible for CAR-T in the NHS. Of those patients who dropped-out from treatment in the DESCAR-T study, approximately 40% had an ECOG score ≥2. This means that the population that dropped-out in the DESCAR-T study is not comparable with the population dropping-out from treatment in the NHS. Therefore, the company have analysed data from ZUMA-2 patients who received apheresis but not infusion to estimate outcomes for these patients (see the technical addendum for a summary). Finally, in order to meet the standards of a fair assessment, the company notes that if the brexu-cel arm is adjusted, it is reasonable to also adjust the R-BAC arm: the McCulloch cohort only reports outcomes for patients who received R-BAC (equivalent to the brexu-cel mITT population and so suitable to inform the outcomes of the R-BAC arm in the company's mITT base case). Simple methods were applied (reported in the technical addendum).
3.10 Cure assumption: Timing of LTS assumption	The company position remains that brexu-cel represents a step change in management of r/r MCL and that based on the ZUMA-2 survival data, the appropriate model is the 48mo LTS. Long term survivorship (LTS) means that, after a period of time, the original disease is no longer expected to be the main driver of patient death. Company notes that few events were reported beyond 48 months in ZUMA-2 and no events after month 65, although follow up continues to month 88.

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	Further to this, it is important to note that the PFS and OS curves from Zuma-2 do not cross, indicating a consistent and sustained treatment benefit over time. At a median follow-up of 67.8months, the median PFS was 25.3 months and the median OS was 46.5months. Notably, 32% of patients remain progression-free at 60 months, highlighting the potential for long-term remission in a population with historically poor outcomes. In stark contrast, extrapolated data for the comparator arm suggest that only 0-5% of patients would be progression-free at 60 months. This marked difference underscores the transformative impact of brexu-cel which offers a level of durable disease control that has historically been unattainable in relapsed/refractory mantle cell lymphoma. The committee requested a standard parametric modelling scenario but this is not the recommended base case. The implausibility of MRAFs calculated from the later portions of the ZUMA-2 survival curves (see MRAF comments below) support the move to an alternate modelling approach for long-term survivors. The company has not re-explored the potential for a mixture cure model (MCM) approach. In the initial model development, a mixture-cure survival modelling approach was taken for the base case analysis. However, as the ZUMA-2 trial data matured, the mixture-cure survival modelling became more unstable, and the decision was taken to remove the MCM. Note that while the original submission was MCM, an LTS-based model was preferred by the committee in TA677.  For these patients who continue to have a progression free outcome, the possibility of a cure in treatment cannot be ruled out.
3.10 Cure assumption: Mortality weighting	The draft guidance notes that the committee would like additional data about the most appropriate standardised mortality ratio (SMR) to use.

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SMRs are multiplied by general population mortality to estimate risk of death. The company believes that by applying a SMR from a younger population to the SACT cohort NICE has overstated additional mortality in long term survivors.

The company's preferred source (Maurer et al, 2014) had a mean age of 63, similar to 63 in ZUMA-2. General population mortality over the 5 years after 63 averages 1.18% per year. The observed 1.09 SMR in LTS Maurer (2014) implies excess mortality of 0.11% per year (0.09 excess x 1.18%).

In appraisal TA893 (EAG preferred source) patients had a mean age of 46. General population mortality over the 5 years after age 46 averages 0.30% per year. This results is the observed SMR of 3.0 implies excess mortality of 0.59% per year (2.00 excess x 0.30%, allowing for rounding).
Eskelund 2016 offers another example, with mean age of 56, an SMR of 2.36 and excess mortality of 0.87% per year.

However, in the EAG model patients have a mean age of 72.5 when the SMR is applied. General population mortality over the 5 years after age 72.5 averages 2.95% per year. Applying the SMR of 3.0 gives excess mortality of 5.91% per year, around 10 times the excess mortality observed in TA893. The company believes that this level of excess mortality is not plausible and is an unreasonable extrapolation of the 0.59% annual excess mortality from TA893.

Company notes that the EAG report presented a MRAF of [redacted] in support of choosing a higher SMR. When asked, EAG declined to elaborate on how this number was derived and, in addition, reported it as 'bordering on the implausible' in the committee meeting. Company believes the MRAF of [redacted] is incorrect and should be disregarded by the committee. An MRAF of [redacted] would give an excess mortality of ~15% (which the company agrees is implausible.

Table: excess mortality in LTS, different sources

	Maurer 2014	TA893	Eskelund 2016	Company model	EAG model
Age[a]	63	46	56	67	72.5
SMR	1.09	3	2.36	1.09	3
General population mortality, deaths per year[b]	1.18%	0.30%	0.64%	1.70%	2.95%
Annual mortality in LTS, deaths per year[c]	1.29%	0.89%	1.50%	1.85%	8.86%
Excess mortality in LTS, deaths per year[d]	0.11%	0.59%	0.87%	0.15%	5.91%

LTS – long term survivors
a - age at which SMR applied
b - general population mortality, weighted average of male and female, average of following 5 years
c - SMR multiplied by general population mortality

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	d - Annual mortality in LTS less general population mortality Observed excess mortality from the three sources (Maurer [2014, age 63], TA893 (age 46) and Eskelund [2016, age 56]) was 0.11%-0.87% per year. Excess mortality in the company model is within this range. Excess mortality in the EAG model is 5.91% per year, much higher than in the sources used. In TA559, TA895, TA1048 and the committee for the original appraisal of brexu-cel for r/r MCL (TA677) found that the Maurer estimate of 1.09 to be appropriate to quantify the expected mortality (SMR) for patients who are considered long-term survivors. This adjustment on background mortality represents a cohort of patients who are fit enough to receive CART treatment and have had a successful outcome. The adjustment reflects the impact of successive lines of therapy prior to CART, however it should be noted that the SMR of 3.0 sourced from TA893 for acute lymphoblastic leukeamia, included a significant number of patients (38% from Zuma-3) who had prior allo-SCT. Allo-SCT is an invasive treatment with poor outcomes, a high incidence of graft-versus-host disease, and intense chemotherapy pre-conditioning; the effects of all being likely to impact the survival of patients when undergoing subsequent lines of therapy. The committee for TA893 noted the risk of dying (SMR of 3) was linked to the proportion of prior allo-SCT in the ALL cohort, which is not an expected treatment for patients with MCL. When considering the relevance of different SMR sources, the company believe that the committee would find data generated in populations of similar age to the R/R MCL population more relevant to the decision problem in question. As such, the company asserts that the SMR of 1.09 for LTS remains unchanged in its base case.
Section 3.11 CAR-T tariff and ICU costs The committee recommends use of a £60,462 (if costs can be updated to 2025/26 cost year) or a £58,964 tariff (stated as relevant for cost year 2024-2025) with added ICU costs.	We respectfully submit that the Committee recommendation to adopt a CAR-T tariff of £58,964 or £60,462 does not meet the standards of procedural fairness, transparency, and methodological rigour required for a robust cost-effectiveness assessment of brexu-cel. We believe this approach is potentially flawed, lacks evidentiary transparency, and risks unjustly restricting patient access to a clinically valuable therapy. **<u>Company base case tariff</u>** The company base case uses a tariff of £41,101 and separately adds IVIg, bridging and conditioning therapy costs (following previous appraisals where this tariff was agreed and used by NICE). This figure has its origins in TA872: during this appraisal Gilead held various discussions with NICE and NHS England on what was the most appropriate CAR T-cell therapy delivery cost to be used by NICE in its assessment of cost effectiveness. The compromise figure of £41,101, based on transparent communication and shared cost inputs, was agreed following extensive discussions with NICE and NHS England, resulting in this compromise, aligned with real world considerations. The company notes that the EAG in this TA made its own estimate of the cost of CAR-T administration (EAG addendum Table 8). This bottom-up costing included the costs of ICU stay. If the company revert to the CS AE rates (see company fact check) and the cost of IVIg is excluded (as per tariff explainer), the EAG estimated cost is close to the agreed tariff figure of £41,101 (table below).

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Table 8: Clarification of the scenario used to estimate CAR-T infusion and monitoring costs (EAG addendum, [company comments added])

CAR-T Tariff components	Value	Formula/source
Leukapheresis	£1,927.09	CS, Company's model
Administration	£6,605.79	CS, Company's model
Hospitalization: ICU	£13,032.85	Proportion of ICU (27%) coms from RWE: O'Reilly et al. (2024) Other data are sourced from the CS, Company's model
Hospitalization: non-ICU	£7,561.10	CS, Company's model Other data are sourced from the CS, Company's model
Emergent AEs	£17,695.07 [Company estimates £12,690 combining EAG costs and submission-reported AE rates]	Incidences of AE: CSR cohort 1 derived from Table 14.3.2.1.1a CSR and clarification responses T14.3.3.1.1a Table Costs of AEs: Event cost (NHS England. 2022/23 National Cost Collection Data Publication)
IVIG	£14,023 [NHSE states IVIg is not included in CAR-T tariff]	IVIG proportion comes from Wang et al. (2023) (38% for one year), Other data are sourced from the CS, Company's model
All other costs occurring within the first 100 days post infusion (including monitoring and training)	£0.00	Not available
CAR-T infusion and monitoring total cost	£60,845* [With adjustments above, total comes to £41,816]	-

CS: Company Submission; ICU: Intensive Care Unit; RWE: Real-World Evidence; AE: Adverse Event; CSR: Clinical Study Report; IVIG: Intravenous Immunoglobulin; NHS: National Health Service (UK)
***The EAG can confirm that there is a slight difference between this value and the value of £61,585 in Table 36 of the main report, due to the exclusion of some overlap between AEs, as the company mentioned in the FAC stage.**

The £41,101 figure is not arbitrary: it reflects a negotiated consensus between the company, NICE, and NHS England, grounded in real-world delivery costs and consistent with prior CART appraisals:

- TA872; axicabtagene autoleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies

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	- TA893; brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over - TA895; axicabtagene autoleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy - TA975; Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under Departing from this precedent without a transparent and evidence-based rationale undermines consistency in NICE's decision-making. **<u>Origins of increased NHS tariff cost</u>** In the recent committee meeting the Cancer Drugs Fund (CDF) lead told the committee that this value was outdated. The CDF lead stated a figure of £58,964 for the 2024 to 2025 financial year and stated that this had been revised in line with inflationary pressures for 2025 to 2026, giving a CAR-T cost of £60,462 (verbal communication). The committee agreed that this was the current cost of delivering CAR T-cell treatments, despite the fact there has not been a transparent, clearly reported update of the previously agreed tariff. The company notes that in TA1048 an updated cost was referenced by NHS England (NHSE) - £57,080. This cost was inflated by NHSE to £58,694 to reflect 2024/25 financial year and, we understand, subsequently used in the TA1048 analyses. We understand from NHSE that this increased figure was based on a bottom-up costing exercise undertaken by a '*CAR-T Tariff Review Working Group*' established by NHSE in 2023 and was shared with CAR-T centres in the '*Future approach to CAR-T Tariff design – Final Options Appraisa*l' document. We have not had visibility of this document, nor of details of the costs associated with each component of the tariff, despite repeated requests to NHSE for the same. We understand from NICE that the committee also only has a high-level summary of the tariff components as set out in slide 50 of the committee meeting slides. The reliance on verbal communication from the CDF lead, without supporting documentation or a published methodology, is inconsistent with NICE's commitment to evidence-based appraisal. NICE decisions such as the one in this appraisal, with the potential for significant patient impact must be based on transparent evidence of the highest standard possible (NICE Methods Guide 3.1.1), and the company submits that informal and unpublished sources do not meet this requirement. The company submitted a response to the ACD in TA1048 which covers the concerns around the increasing tariff in more detail, including: • An increase in CAR-T tariff seems inconsistent with the fact that the infrastructure for CAR T cell therapy delivery within the NHS is now well-established. Additionally, healthcare professionals now have significant experience delivering this treatment, and the expected increase in patient numbers will only further enhance efficiency in NHS delivery • A 2023 study of 726 UK patients treated with CAR T for relapsing and remitting large B-cell lymphoma also demonstrated that the costs of delivering CAR T should be decreasing with scale and experience. This is

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	due to a significant reduction in incidence of cytokine release syndrome and need for ICU admissions over time • The clinical treatment most similar to CAR-T treatment in terms of complexity and NHS activity is autologous stem cell transplant (ASCT) which has a tariff rate of £17,181 (inflated from 2019/2020 HRG tariff elective SA26A £16,668). The discrepancy between the tariff rates for CAR T-cell therapy delivery and ASCT suggests that the proposed cost increase may not accurately reflect the actual resources required for CAR T-cell therapy delivery. (The company's full response in relation to the tariff can be found on pages 51-53 of the Committee Papers for TA1048 dated 20 February 2025) **Lack of transparency** It is clearly in the public interest for the '*Future approach to CAR-T Tariff design – Final Options Appraisa*l' document to be made available to NICE and the company, to ensure a fair and transparent decision-making process. As such we submitted a Freedom of Information (FOI) request to NHSE in December 2024. NHSE has refused to provide any further details of the methodology used to reach the new tariff figure, and so in March 2025 we filed a formal complaint with the Information Commissioners Office (ICO) which has been accepted for investigation. Unfortunately, we do not anticipate the outcomes of the complaint to be received ahead of the planned second committee meeting for brexu-cel. The refusal by NHSE to disclose the methodology, despite a formal FOI request and an ongoing ICO investigation, raises serious concerns about accountability. In the absence of transparency, stakeholders—including NICE—cannot meaningfully scrutinise or validate the cost inputs. If the tariff has been calculated unfairly, if the figures used are unreasonable, or if the tariff includes elements which are not directly attributable to use of a specific product (and therefore are not the company's responsibility to pay for), this is likely to mean that brexu-cel is found not to be cost- effective, with the result that patients are denied access to treatment. There is accordingly a high public interest in ensuring that the basis for this calculation is transparent and available to be scrutinised and tested, so that stakeholders can understand the basis for reimbursement decisions on CAR-T therapies that affect them. **Resolution** The information provided by NHS England to NICE does not: • provide sufficient transparency on the methods used to calculate the updated NHS tariff • indicate the evidence on which the calculation was based In light of the above, we respectfully request that NICE revert to the previously agreed tariff of £41,101—augmented by separately accounted IVIG costs—until such time as a fully transparent and evidence-based update to the CAR-T delivery cost is made available. This approach ensures consistency with prior appraisals, maintains procedural fairness, and upholds NICE's commitment to transparency and evidence-based decision-making.

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	As requested, the 58k tariff has been provided as a scenario but the company notes an updated cost year (to 2024-25) could not be implemented as the NHS Reference costs have not yet been updated.
3.12 Utility values	In the draft guidance, it is noted that the committee reached a preference for use of utility values that were capped to the population norm for patients in pre progression and that the post progression health state utility should be taken directly from TA502. We are concerned that the removal of the pre-progression patient-generated utilities does not comply with the NICE reference case which states a clear preference for patient-generated utilities. Previous discussion on this topic has emphasised the clinician-approved expectation that these patients (who are fit enough for brexu-cel infusion ie ECOG performance score 0 or 1) may reasonably report a higher quality of life than an age-matched population who do not fit the criteria for brexu-cel infusion (i.e. are less fit and able including a significant proportion of ECOG performance score >2). The company applies utility values from Zuma-2 in the base case; consistent with the NICE reference case. In addition the EAG recommended that utility values from TA502 i.e. 0.78 pre progression and 0.68 post progression are used to estimate the relative difference between these two health states (ie post progression utility is 13% lower than pre progression utility). The company agrees that post progression utility should be estimated based on pre progression utility as the EAG recommend, and uses this approach in the base case.
3.13 Intravenous immunoglobulin therapy costs	In the draft guidance it is noted that at the committee meeting, both clinical experts stated that IVIg use of between 10 and 20% for a duration of 1 year aligned with their own experiences of post CAR-T management. The committee however, concluded that the figure from Wang et al (rates reported in the ZUMA-2 trial) was more representative (38%). However, in the ZUMA-2 study patients received IVIg based on the presence of severe hypogammaglobulinemia alone. This is not consistent with practice in the UK, where typically the presence of infection <u>in addition</u> to severe hypogammaglobulinemia is required for treatment with IVIG. Therefore, company suggests that UK clinical experience is the most appropriate source for this figure (versus trial-based values from different country settings) and propose to include a rate of 15% IVIg use for brexu-cel patients as the mid-point of the clinician-reported rates of real-world use of IVIg. This rate has been included in the updated model base case; the duration of treatment was kept at 12 months (as in the company submission). The company suggests that this more than captures likely use of IVIg; SACT data from axi-cel 3L for treatment of R/R DLBCL conclude rates of use of 16.5% with a mean duration of treatment of 6.5 months, suggesting that by including a treatment duration of 12 months a conservative approach is adopted.
Section 3.14 The committee agrees that use of a severity modifier of 1.2 is appropriate	Brexu-cel was originally assessed under the end-of-life criteria and was considered to have met these criteria, as outlined in TA677. However, NICE have determined it will be reassessed in this TA using the severity modifier due to a change in NICE Methods in 2022. **<u>Appropriate severity weighting</u>**

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	The committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate in the current analysis. But the company appreciates the committee's agreement to consider the QALY shortfall in the new analysis and the appropriate severity weighting to be used at the second committee meeting. We also appreciate that is has been confirmed that NICE can potentially offer flexibility in its application of the severity modifier, and we would ask the committee to exercise its discretion in this regard and apply severity weighting of 1.7 to reflect additional uncaptured benefits: • **McCulloch**: Whilst McCulloch is recognised as the most appropriate source of evidence in the absence of brexu-cel, it would be remiss to not mention the limitations with the evidence and its application to NHS E practice. McCulloch selected 36 patients via 23 centres over a 42-month period. Over a similar time frame of 52 months, brexu-cel has treated 222 patients, demonstrating the highly selective evidence base of McCulloch, and the scope to benefit additional patients through treatment with brexu-cel. In addition, 64% of patients within McCulloch had prior high-dose cytosine-based therapy versus 21% observed via the CDF. This implies that McCulloch had a fitter evidence base than patients eligible for treatment with brexu-cel, suggesting that the true outcomes observed in the NHS for 3L R-BAC would be less favourable than those reported in McCulloch. • **Covid**: During the pandemic, CAR-T recipients were among the most vulnerable patient groups, with early studies reporting COVID-19 related mortality rates of up to 50%. However, outcomes improved significantly over time. A large European multicentre study showed a reduction in COVID-19–related mortality from 43.6% in 2020 to 7.5% in 2022, driven by increased vaccination, improved supportive care, and the emergence of less virulent SARS-CoV-2 variants. These findings underscore the importance of using contemporary data to reflect current clinical practice. They also highlight how pandemic-era outcomes may underestimate the true potential of CAR-T therapy when used in optimal conditions. • **Practice changes (BSH guidelines)**: Following the introduction of brexu-cel for R/R MCL patients in 2021 – new guidelines were introduced to improve patient selection and care. These guidelines, first introduced in the 2022 BSH Addendum and then reinforced in the 2023 full guideline update, advocate for earlier identification and referral of high-risk mantle cell lymphoma (MCL) patients for CAR-T therapy. This shift enables treatment at a more favourable disease stage, improving feasibility and outcomes. This is reflected in the latest O'Reilly 2024 UK real-world study, which shows a significant increase in infusion rates from 59.8% (2022) to 69.7% (2024), importantly this later 2024 dataset includes all patients from the earlier 2022 period including those that did not reach infusion, therefore still underestimating the number of patients that could currently be expected to reach infusion. These improvements are attributed to earlier referral, better disease control, and reduced manufacturing failure rates. Further support for the expectation of improved CAR-T outcomes over time comes from the Boyle et al. 2023 study in large B-cell lymphoma (LBCL), which demonstrated a clear learning curve in UK CAR-T delivery.

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	Comparing patients treated in 2019 versus 2020–2022, the study found significant improvements in infusion rates (from 73% to 83%), 1-year progression-free survival (from 32% to 50%), and 1-year overall survival (from 40% to 60%), intensive care unit admission rates (from 32% to 20%). There are examples of NICE applying flexibility in its application of the standard criteria, including in order to allow continued access to a highly effective treatment option after 4 years of managed access within the CDF (TA509). In TA509, the committee agreed to apply the then end-of-life criteria, "*in the context of ensuring continued access to a highly effective treatment option*" on the basis of the exceptional benefit seen, and the fact that the treatment had become, in the minds of patients and clinicians, the standard of care. In this current appraisal of brexu-cel, we see a similar situation where the committee has noted that "*The patient expert highlighted that people who had accessed brexucabtagene autoleucel through the Cancer Drugs Fund had found it to be a life-changing treatment*" and that "*there is an unmet need in this population and that patients and healthcare professionals would welcome new treatments*." **Appropriate willingness to pay threshold** The company believes that brexu-cel should have followed the Highly Specialised Technology (HST) appraisal route, under which the willingness to pay threshold is £100,000 per QALY. The company was informed by NICE at the time of the decision problem that the HST route could not be used because brexu-cel was appraised using the Single Technology Appraisal (STA) route in TA677. The company believes that if brexu-cel was appraised as a new product the HST route would be appropriate. Restarting the appraisal process at this stage through the HST route would not be an effective use of NICE or company resources and would delay patient access. Therefore, the company invites NICE to review brexu-cel against the HST criteria set out below and apply discretion to implement the higher £100,000 threshold at the second committee meeting. **Cross-check against HST criteria** Brexu-cel is a highly innovative therapy which meets all 4 criteria for evaluation through the HST route, noting that[i]: 1. The disease is very rare. 'Very rare' is defined as a disease that has a prevalence in England lower than 1 in 50,000 people, or about 1,100 people The number of patients with relapsed or refractory MCL after 2 or more systemic treatments including a BTK is around 90 per year[ii]. 2. The number eligible for treatment with this therapy is low. Normally, no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications Brexu-cel is curently available through the Cancer Drugs Fund (CDF) and is standard of care for eligible patients in the UK. Company data shows that 54 treatments were

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	delivered to sites in the 12 months to September 2024[iii]. This may slightly overstate the number of treatments delivered, but the company believes 54 is an upper limit for the number of eligible patients per year. In addition, around 90 people per year, with relapsed or refractory B-cell acute lymphoblastic leukaemia who are 26 years and over are also eligible for treatment with brexu-cel[iv]. 3. The disease significantly shortens life expectancy (no specific threshold is stated). A United Kingdom real-world study of patients with progressive disease after second line ibrutinib, conducted before brexu-cel became available, found median life expectancy of only 1.4 months. Life expectancy was longer but still very limited for patients well enough to received further therapies (median of 0.4 months for patients who did not receive third line treatment; 11.6 months for those who received some form of third line therapy)[v]. 4. There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options Brexu-cel is the recommended standard of care for eligible patients in the UK. Management options for patients who have failed a covalent BTK inhibitor and are unfit for, or have already received, CAR-T are poorly defined and no standard of care is currently recognised. [i] NICE-wide topic prioritisation: the manual: 29 May 2024; Appendix 1: highly specialised technologies. Available from https://www.nice.org.uk/process/pmg46/chapter/appendix-1-highly-specialised-technologies#routing-criteria, accessed October 2024 [ii] Company BIM, 2021. [iii] Gilead data on file [iv] NICE: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over Technology appraisal guidance; 07 June 2023; Resource impact statement, available from https://www.nice.org.uk/guidance/ta893/resources/resource-impact-statement-13069430317, accessed October 2024. **NICE discretion** In a recent appeal, NICE acknowledged that "*fairness required NICE to recognise that they could depart from their usual processes and to consider whether this was the right approach in this particular case"* (review of TA658 [ID4067] appeal outcome letter; page 25). In light of the change from end-of-life criteria to the severity modifier since brexu-cel entered the CDF, to ensure a fair process the company urges NICE to consider either: • Applying a 1.7 severity modifier to reflect uncaptured benefits; or • Implementing the £100,000 willingness to pay threshold which would have been in place had the HST route been followed as requested. It is incumbent on NICE to adopt a procedurally fair and flexible approach, in order to avoid the situation where a highly effective technology which has been available through the CDF for 3 years is no longer available to patients with a high unmet need, simply because NICE's methods have changed in a way which disadvantages the brexu-cel patient population (predominantly older patients).

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Section 3.16 Committee's preferred assumptions

The company has updated the economic model in response to the committee's preferred assumptions, reported in the table below. The company proposes a preferred base case reflecting the comments made above and presents selected scenarios to reflect committee discussions.

#	Preferred assumption	Inc costs	Inc QALYs	ICER	Impact on ICER
Company base case		[redacted]	[redacted]	£50,270	-
1	Patient age - 66 years	[redacted]	[redacted]	[redacted]	[redacted]
2	RWE plus ZUMA-2 for brexu-cel outcomes[1]	[redacted]	[redacted]	[redacted]	[redacted]
3	15% alloSCT for R-BAC patients[1]	[redacted]	[redacted]	[redacted]	[redacted]
4	2024-25 NHSE £58,964 tariff	[redacted]	[redacted]	[redacted]	[redacted]
5	Updated cost base (2024-25 cost year)[2]	[redacted]	[redacted]	[redacted]	[redacted]
6	Pre-prog utility capped (post prog weighted)[3]	[redacted]	[redacted]	[redacted]	[redacted]
7	Pre-prog utility ZUMA-2 (post prog weighted)	[redacted]	[redacted]	[redacted]	[redacted]
8	38% IVIg post brexu-cel (based on ZUMA-2)	[redacted]	[redacted]	[redacted]	[redacted]
9	15% IVIg post brexu-cel (clinician advice)	[redacted]	[redacted]	[redacted]	[redacted]
10	60mo cure assumption	[redacted]	[redacted]	[redacted]	[redacted]

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	for LTS (vs 48 mo)[4]					
11	SMR of 3.0 (not an age-matched SMR)[4]	[redacted]	[redacted]	[redacted]	[redacted]	
12	Adjusting for pre-infused patient outcomes[5]	[redacted]	[redacted]	[redacted]	[redacted]	
Revised company base case (1,2,3,7,9)		[redacted]	[redacted]	[redacted]	[redacted]	
As above, with severity modifier 1.7		[redacted]	[redacted]	[redacted]	[redacted]	
As above with severity modifier 1.2		[redacted]	[redacted]	[redacted]	[redacted]	

[1] See technical addendum pasted below for a summary of company approach; [2] The majority of cost inputs are from NHS Reference Costs and the 2024-25 tariffs are unavailable, 2023-24 remains latest available data; [3] The committee suggested an un-anchored 0.68 but see explainer above for why a weighted value is needed; [4] 48month vs 60month LTS; [5] all other settings as for the revised company base case listed in the row below

Insert extra rows as needed

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Technical addendum

Contents

Introduction

Following the first committee meeting for brexu-cel (brexu-cel), Draft Guidance has been produced. NICE have requested additional analyses requiring adjustment of the previously submitted clinical evidence, for both brexu-cel and R-BAC.

This technical addendum describes how the survival curves in the economic model used to support the economic analysis have been adapted to accommodate this request and provides a short description of minor model adaptations made to incorporate these data.

Survival curves

Key sources of evidence

For brexu-cel a pooled dataset was created based on ZUMA-2 plus SACT (NDRS, 2024) for OS and ZUMA-2 plus UK RWE (O'Reilly 2024) for PFS; Updated R-BAC outcomes were estimated separately for patients not receiving subsequent alloSCT (estimated from McCulloch 2020) and patients receiving subsequent alloSCT (data from Liebers 2025).

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Note. Brexu-cel OS was analysed using SACT data consisting of individuals infused from September 2022 onwards (reflecting changes to the BSH guidelines and a time-to-infusion better in-line with what is expected of contemporary clinical practice).

An additional request was to estimate outcomes for non-infused patients (UK RWE only estimates outcomes from the point of infusion). These data were taken from ZUMA-2. These outcomes were applied to any individual who did not reach active treatment.

Data retrieval

In the absence of access to the individual patient data (IPD) from the respective studies and target populations, data on survival were obtained via the digitisation of Kaplan-Meier (KM) curves from available publications. Digitization of the KM curves was performed by using the WebPlotDigitizer tool (WebPlotDigitizer, 2025).

By extracting the survival rates at specific timepoints, in combination with the corresponding number at risk, a pseudo-IPD dataset was generated using the IPDfromKM tool (IPDfromKM, 2025).

Where data needed to be pooled from different sources – ZUMA-2 plus SACT for OS and ZUMA-2 plus O'Reilly (2024) for PFS – the pseudo-IPD datasets were combined to generate a composite pseudo KM-curve before extrapolating survival curves.

Brexu-cel OS

OS data for patients infused with brexu-cel were obtained from two sources: patients in the ZUMA-2 trial, and SACT data. The KM data from ZUMA-2 is shown in Figure 1. For SACT, the dataset containing patients infused after August 2022 (n=43, blue line) is shown in Figure 2 (data as provided by NICE during the submission). Data from ZUMA-2 and SACT were pooled to create composite KM curves for all relevant brexu-cel infused patients. The combined KM curves and the extrapolations from these are shown in Figure 3. For the base case, lognormal distribution was selected based on assessment of goodness of fit. Estimated coefficients and statistical fit for each distribution are shown in the appendix.

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Figure 1: Overall survival from ZUMA-2 (mITT analysis; Cohort 1)

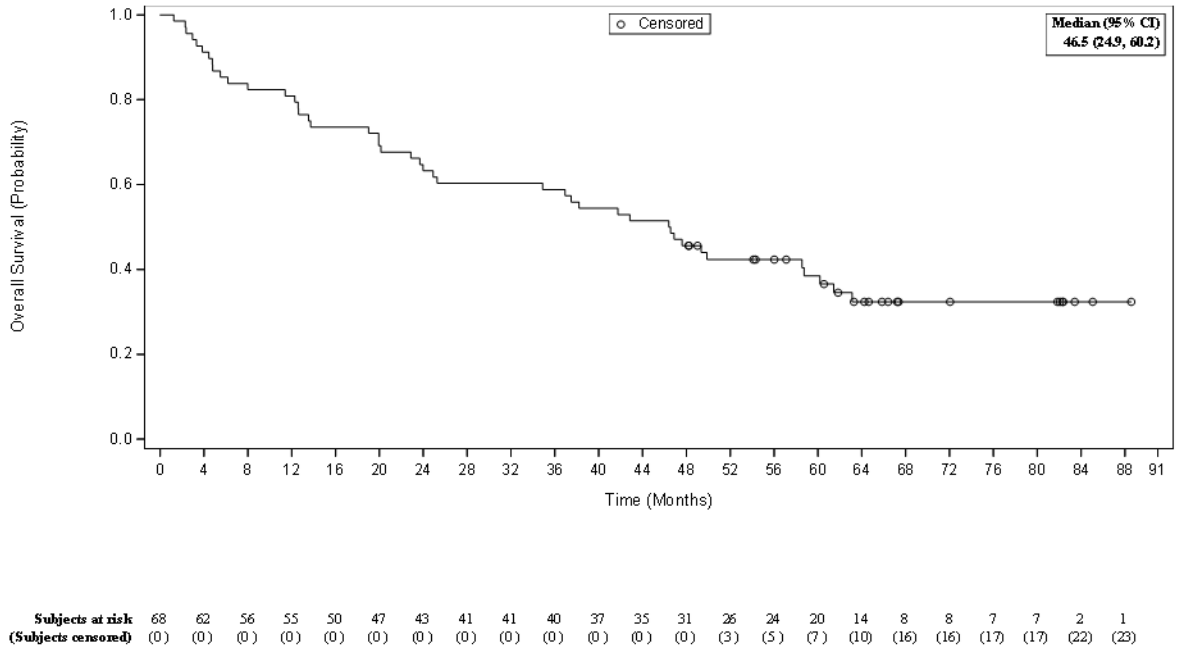

Figure 2: OS data from SACT, partial data provided from NHSE

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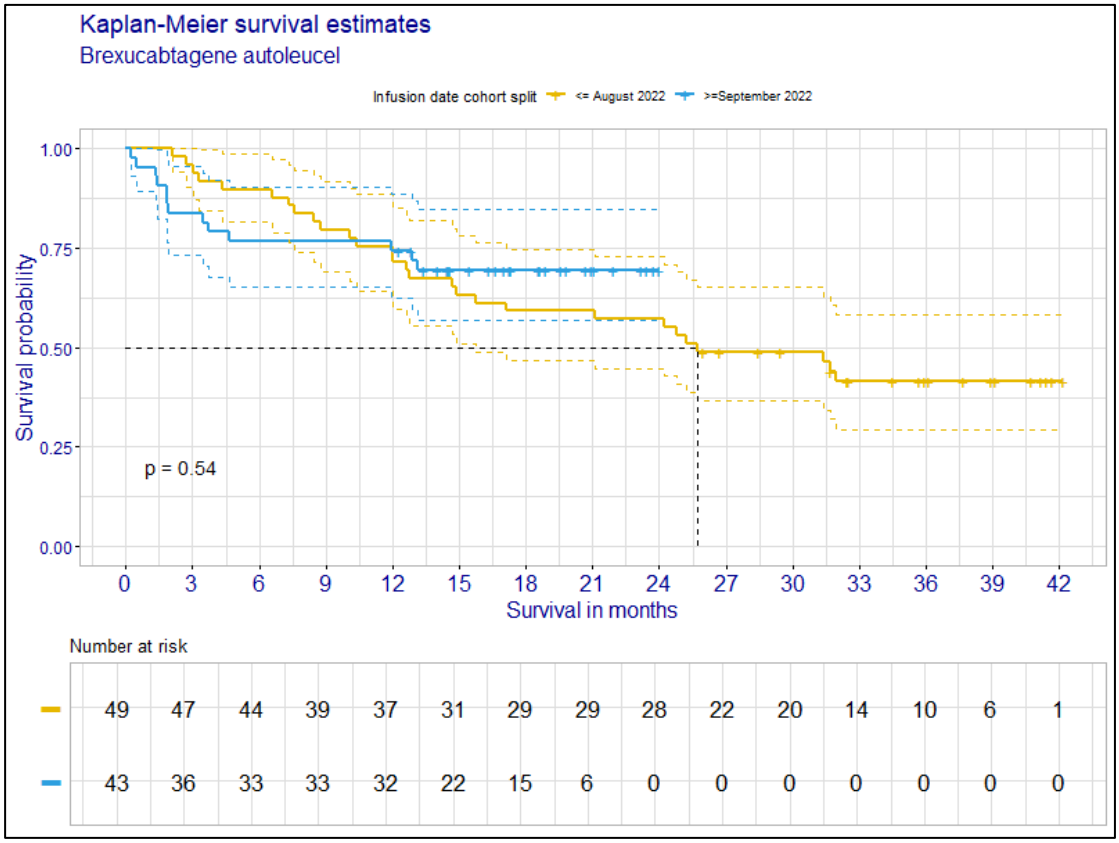

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Figure 3: Pooled OS using pseudo-IPD from ZUMA-2 (n=68) and SACT dataset enrolled from September 2022 onwards (n=43), including extrapolations

It is not certain that all patients intended for treatment with brexu-cel will receive the treatment (patients defined as early progressors). A survival curve was fitted for the 6 non-infused patients in ZUMA-2 to represent this pathway. For the base case, a lognormal distribution was chosen. The estimated survival by each month is shown in Figure 4. Estimated coefficients and statistical fit for each distribution are shown in the appendix.

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Figure 4: Estimated monthly OS and PFS for non-infused patients from ZUMA-2 (n=6), lognormal distribution

The non-infused OS curves were extrapolated; these are shown in Figure 5. For the base case, a lognormal distribution was used. Estimated coefficients and statistical fit for each distribution are shown in the appendix.

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Figure 5: Overall survival extrapolations for non-infused patients based upon ZUMA-2

Brexu-cel PFS

Since no PFS data was recorded in SACT, PFS data for patients who were infused with brexu-cel were obtained by combining data from ZUMA-2 with those reported by O'Reilly (2024). The KM curves for the respective studies are shown in Figure 6 and Figure 7. The KM curve from the pooled pseudo-IPD dataset and the extrapolations based upon this are shown in Figure 8. For the base case, lognormal distribution was selected. Estimated coefficients and statistical fit for each distribution are shown in the appendix.

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Figure 6: Progression-free survival from ZUMA-2 (mITT analysis; Cohort 1)

Figure 7: Progression-free survival from O'Reilly et al. (2024)

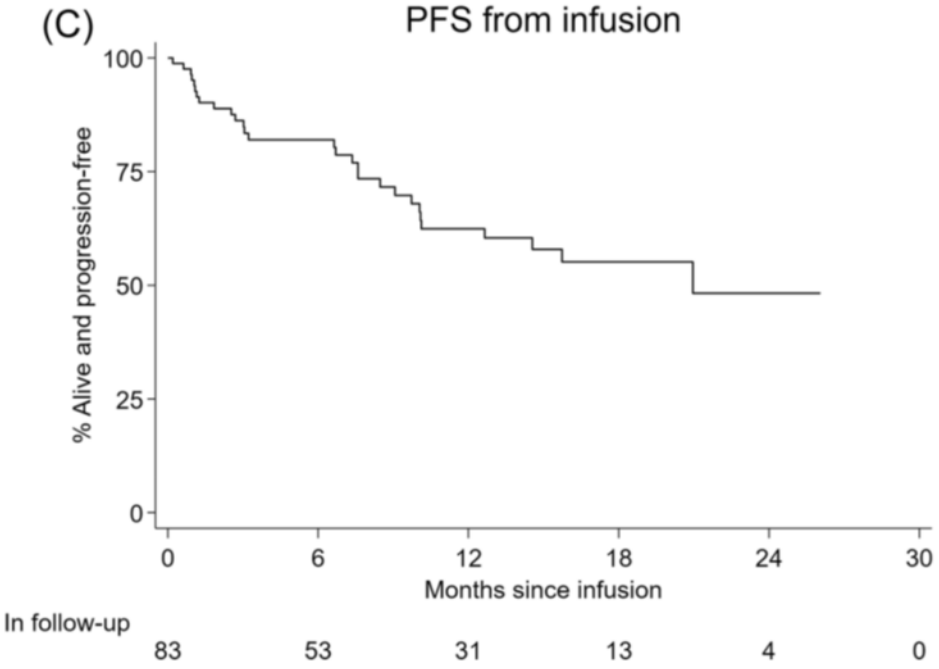

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Figure 8: Pooled PFS using pseudo-IPD from ZUMA-2 (n=68) and O'Reilly (n=83), including extrapolations

For non-infused patients, PFS was estimated based upon the 6 patients in ZUMA-2 who did not receive brexu-cel. The estimated PFS curve for these is shown above in Figure 4.

R-BAC OS

In the original submission, R-BAC survival was obtained from McCulloch et al. (2020). However, to accommodate NICE's request for the R-BAC survival to reflect a target population with a lower share of patients receiving alloSCT, the survival curves for OS and PFS had to be decomposed into separate dataset for patients who received alloSCT and patients who did not receive alloSCT. The EAG provided such a decomposition, with separate survival estimates for each sub-group. The OS for the full McCulloch (2020) dataset (n=36) and for OS decomposed by allo-SCT status as estimated by NICE's EAG are shown in Figure 9 and Figure 10. The number of patients receiving alloSCT in the McCulloch study was small (n=11) with short follow up and very few events observed. An alternate source was used to estimate outcomes for these patients (Liebers et al 2025).

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Figure 9: Overall survival for R-BAC patients in McCulloch (2020), full dataset

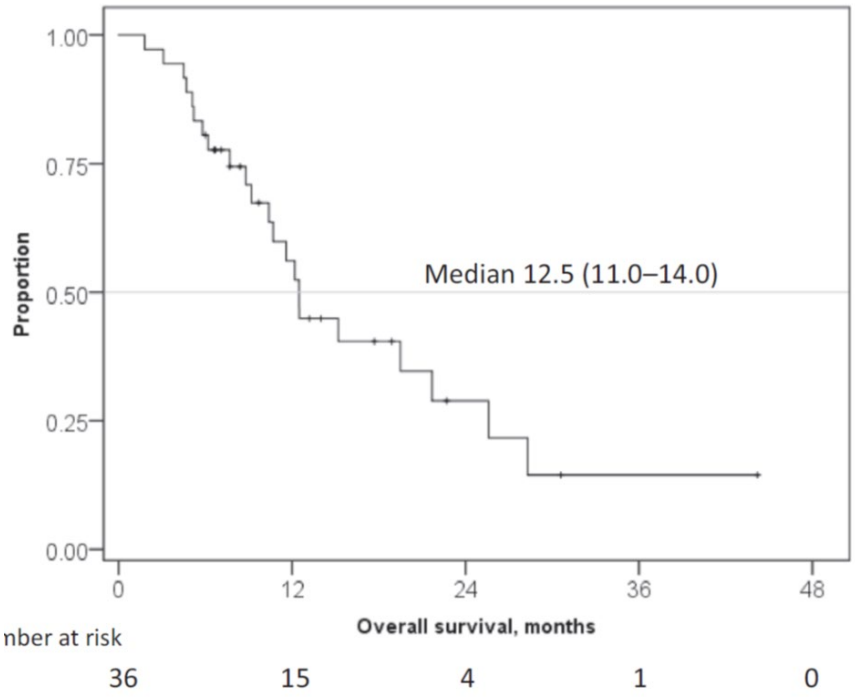
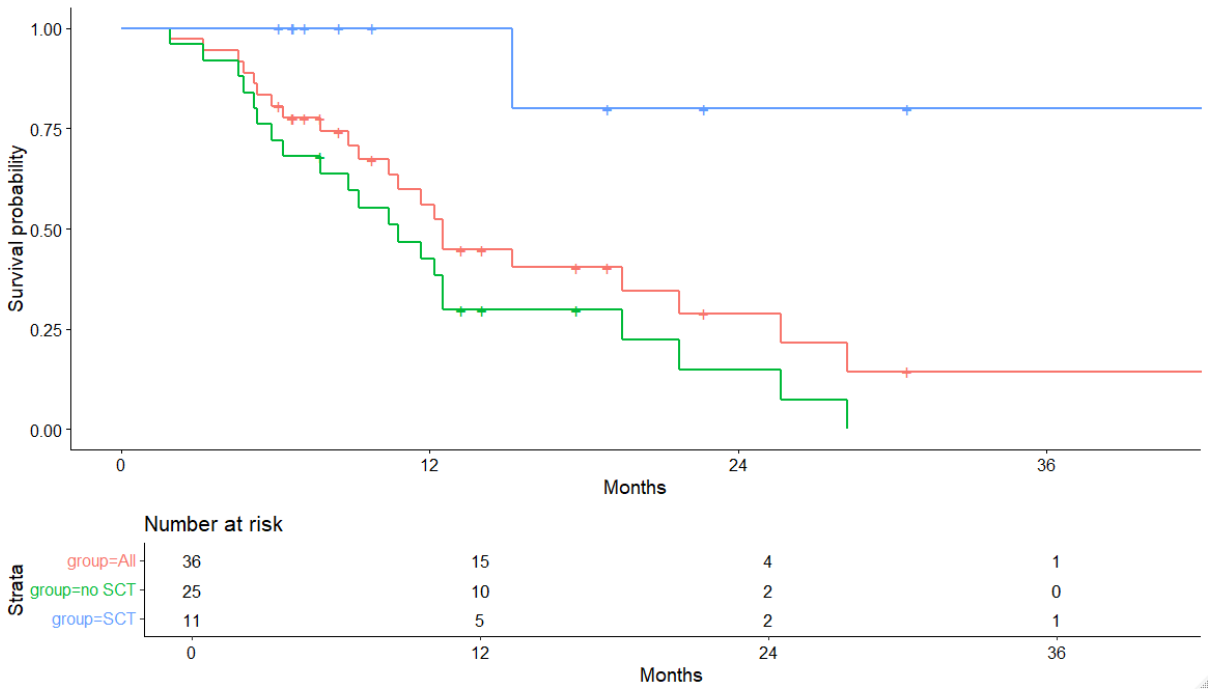


Figure 10: Decomposition of overall survival by alloSCT status provided by NICE's EAG



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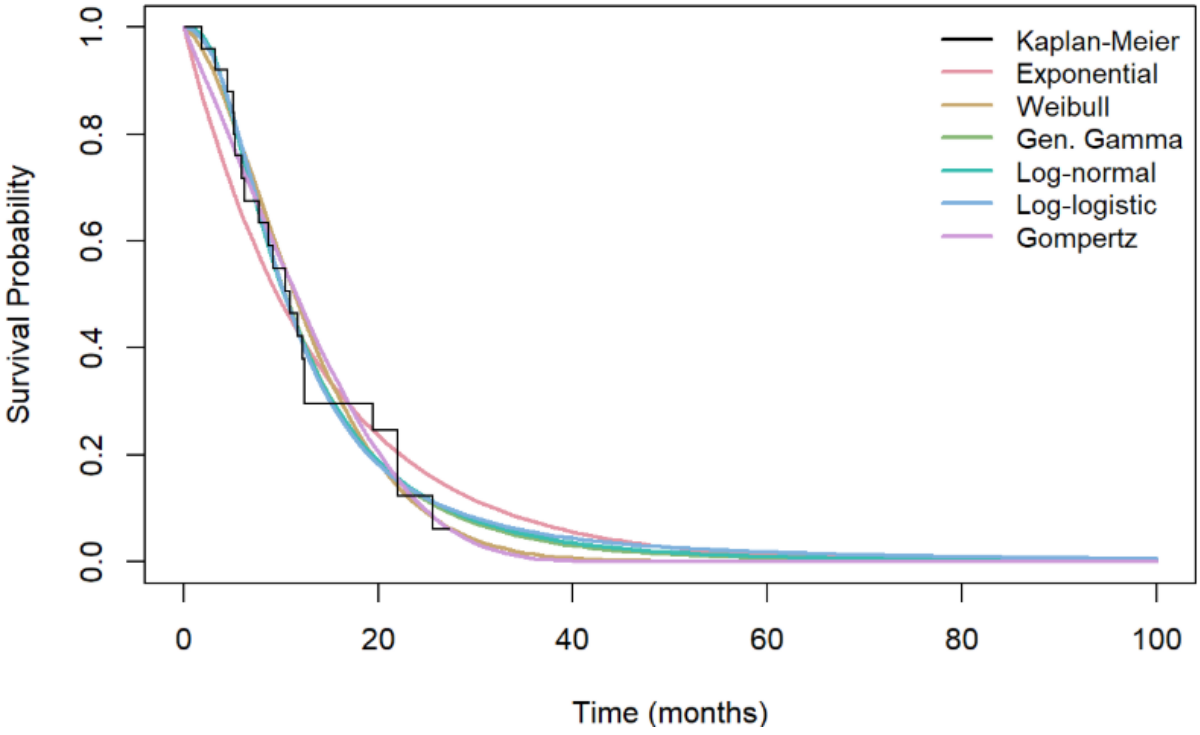
The decomposed KM curves provided by the EAG were digitised using the WebPlotDigitizer[1] tool, and pseudo-IPD were generated using the IPDfromKM[2] tool. Once the pseudo-IPD had been extracted, survival curves for non-alloSCT patients were extrapolated based on these digitisations. The estimated OS curves for non-alloSCT patients are shown in Figure 11. For the base case, lognormal distributions were used. The estimated coefficients and the statistical fit are presented in the appendix.

Figure 11: Overall survival for non-allo-SCT patients in McCulloch (2020), including extrapolated survival curves



The number of patients receiving alloSCT in the McCulloch study was small (n=11) with short follow up and very few events observed (note the blue line in Figure 10). Outcomes for these patients were taken from a cohort study (Liebers et al 2025) that matched alloSCT patients from the European Bone Marrow Treatment registry (n=64, follow up 34.1 months) with patients from ZUMA-2 and was considered generalisable to a UK setting. The KM curve for OS among these subsequent alloSCT patients is presented in Figure 12 (dark blue). Following digitisation and generation of pseudo-IPD, survival extrapolations were fitted to this dataset. These OS extrapolations are presented in

Figure *13*. The estimated coefficients and the statistical fit are presented in the appendix.

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Figure 12: Overall survival for alloSCT R-BAC patients, as reported by Liebers et al. (2025)

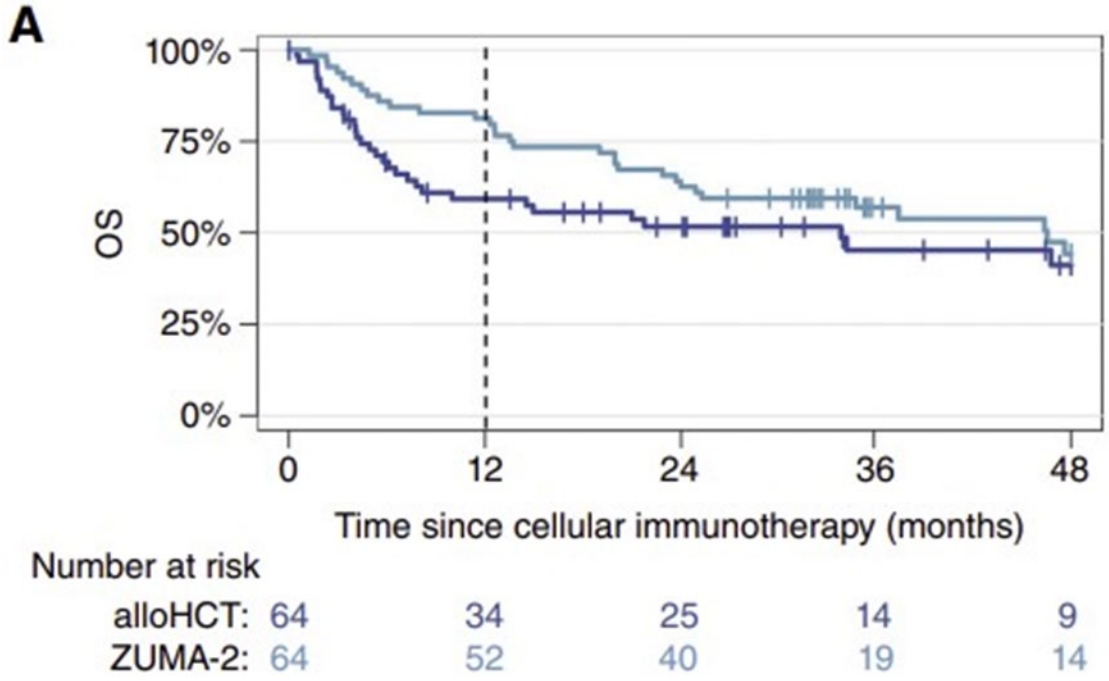
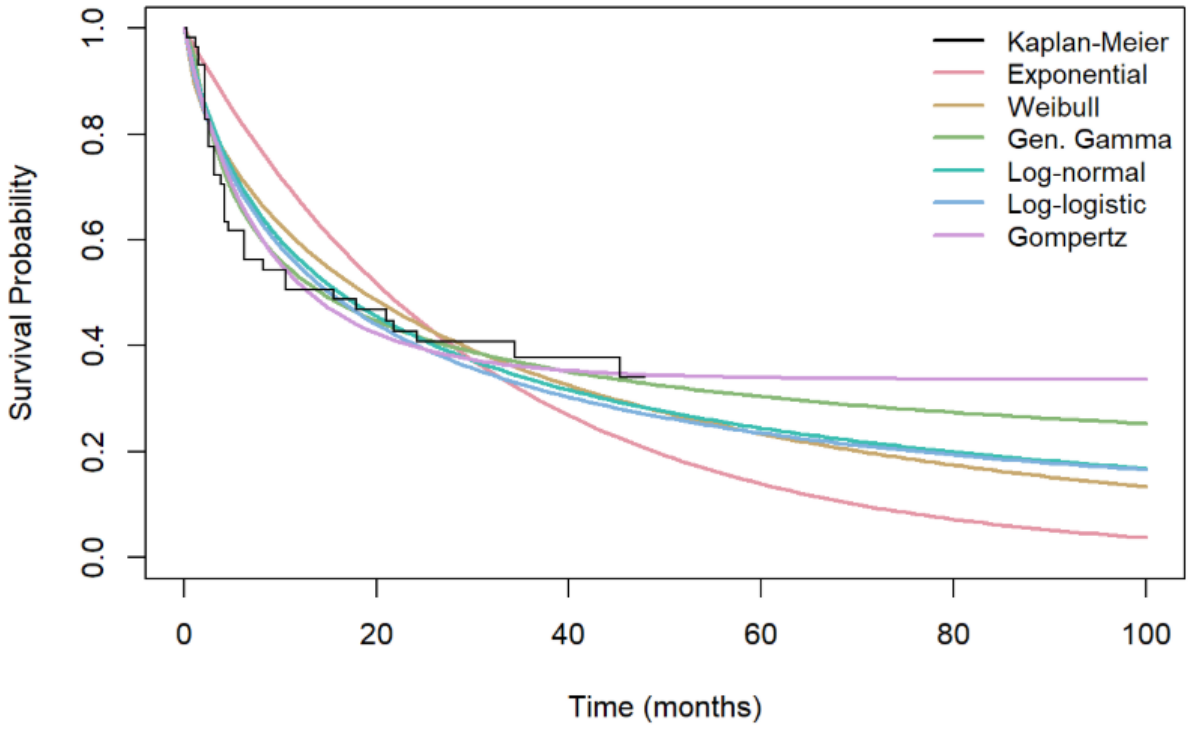


Figure 13: Overall survival extrapolations for alloSCT R-BAC patients, based upon Liebers (2025)



R-BAC survival obtained from McCulloch et al. (2020) and Liebers et al. (2025) only reflected patients who received R-BAC as intended (the mITT group), i.e. excluding patients who would progress too early to receive treatment. To accurately reflect the OS of an intended target population, the survival data from these sources were therefore weighted together with the survival of non-infused patients. The estimated OS curve for non-infused patients is described earlier and is shown above in Figure 4.

R-BAC PFS

The approach for R-BAC PFS was highly similar to that one of R-BAC OS (see above). The PFS for the alloSCT subgroup of McCulloch et al. (2020) is shown in Figure 14. The PFS from Liebers et al. is shown in Figure 15. The final PFS extrapolations (after digitisation and generation of pseudo-IPD) for the alloSCT and non-alloSCT subgroups are shown in

Figure *16* and Figure 17. Lognormal distributions were used for the base case. Estimated coefficients and statistical fit are presented in the appendix.

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Figure 14: Progression-free survival among R-BAC patients receiving alloSCT in McCulloch et al. (2020)

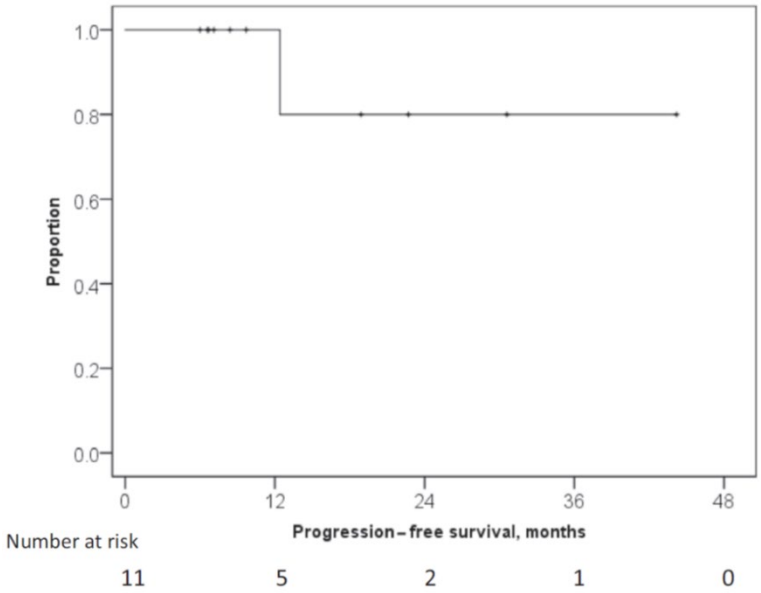

Figure 15: Overall survival for non-alloSCT R-BAC patients, as reported by Liebers et al. (2025)

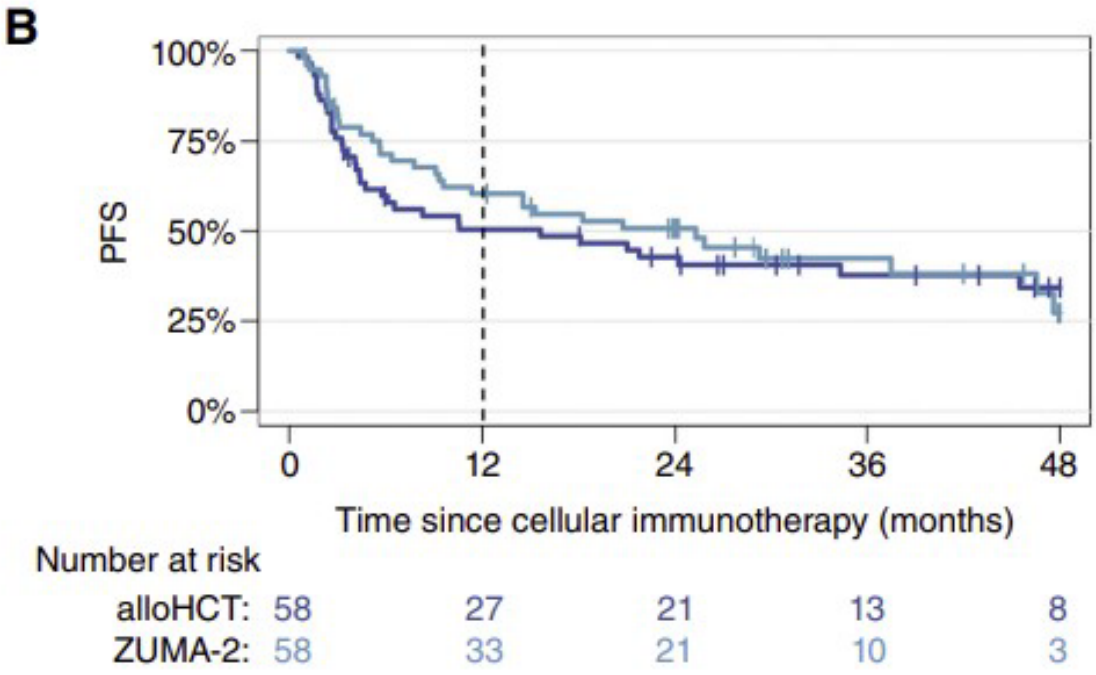

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Figure 16: Progression-free survival extrapolations for R-BAC patients receiving alloSCT

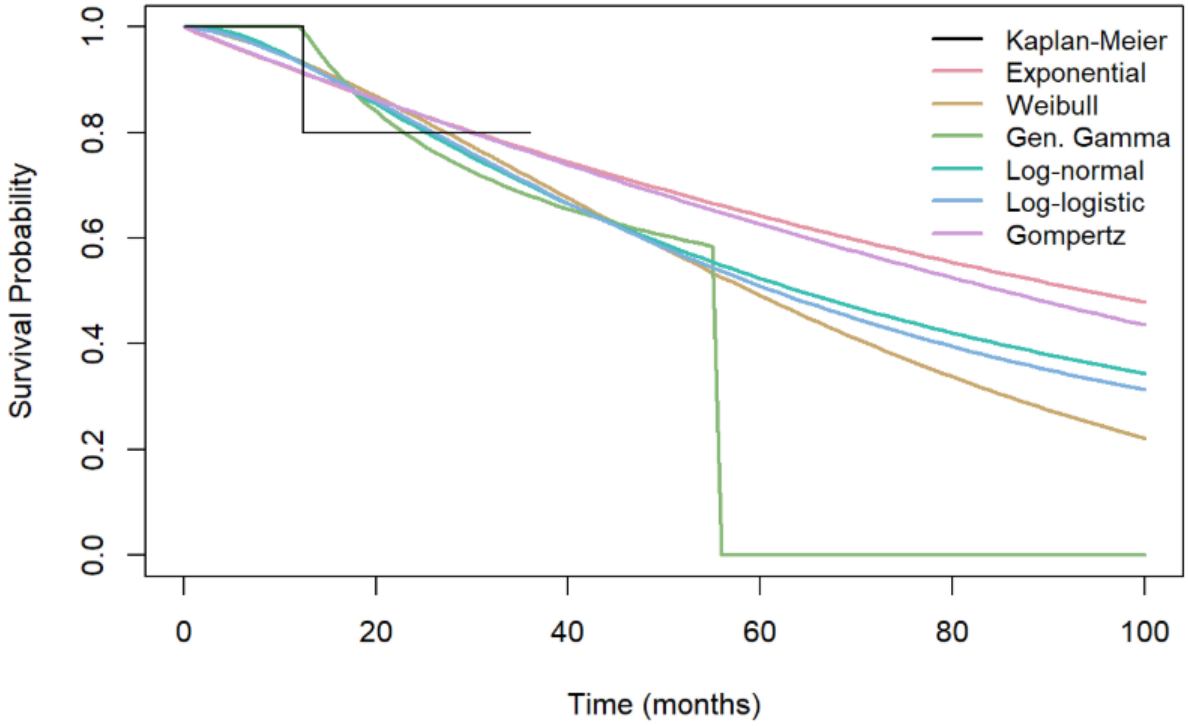

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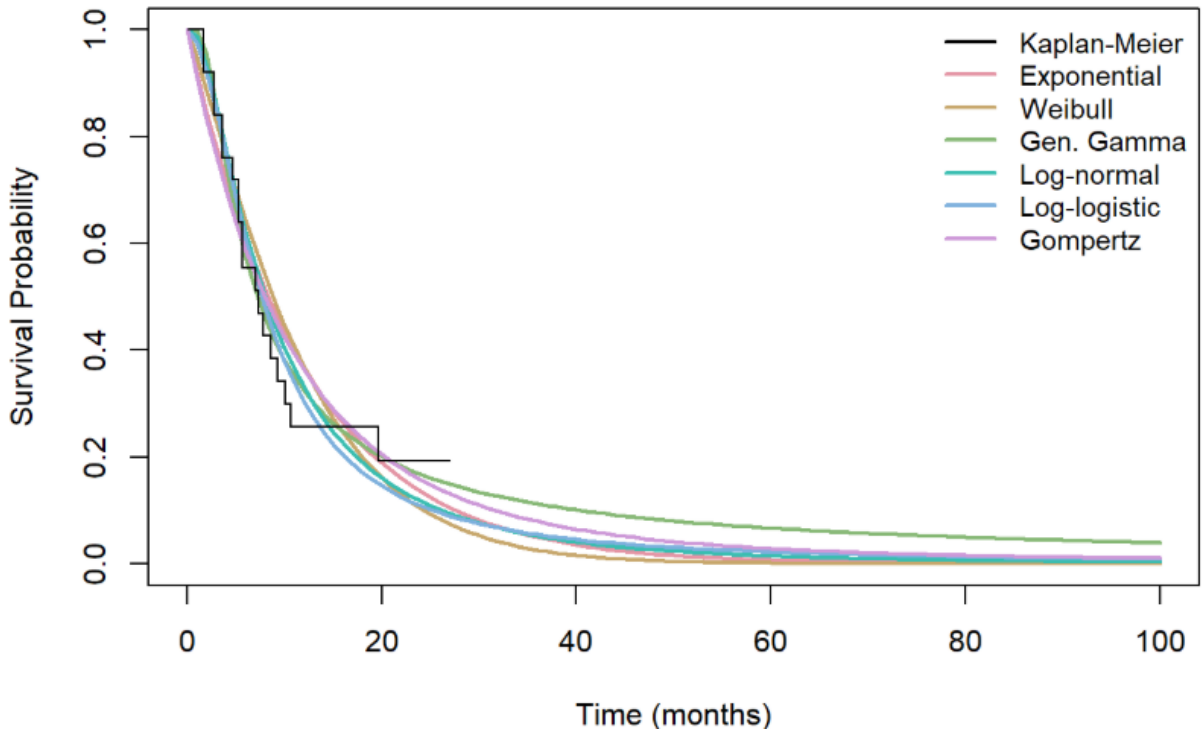
Figure 17: Progression-free survival extrapolations for R-BAC patients not receiving alloSCT



R-BAC survival obtained from McCulloch et al. (2020) and Liebers et al. (2025) only reflected patients who received R-BAC as intended (the mITT group), i.e. excluding patients who would progress too early to receive treatment. To accurately reflect the PFS of an intended target population, the survival data from these sources were therefore weighted together with the survival of non-infused patients. The estimated PFS curve for non-infused patients is described earlier and is shown above in Figure 4.

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Model adaptations

Weighting of survival curves

For scenario analyses, NICE had requested a set of modified survival curves to incorporate patients who underwent apheresis but did not receive infusion. Note . The primary reason for drop-off between apheresis and infusion is disease progression. To replicate an expected ITT curve for brexu-cel, the mITT survival data was combined with survival data for patients who underwent apheresis but who did not receive the infusion.

A similar approach was used for R-BAC, where survival data for patients who received the treatment were combined with that of those patients who were intended for treatment but never received it (conservatively, the same weighting was applied as for brexu-cel).

For R-BAC, a further distinction was made between patients who received alloSCT and those who did not. Real world evidence (RWE) data for patients treated with R-BAC was originally obtained from McCulloch et al. (2020). However, 31% of these patients had received alloSCT which NICE committee deemed too high for usual NHS practice, Separate survival data were therefore obtained for alloSCT and non-alloSCT patients, the OS and PFS for these were combined, using a 15% weight for the alloSCT curve (note that this can be user defined) applied in each cycle of the economic model.

Timing of survival curves

Time to treatment is important when considering an ITT cohort or patients who go on to receive subsequent treatment (alloSCT post R-BAC). The model was extended to allow a delay of mortality/progression by a user-defined number of monthly model-cycles.

For infused patients, OS and PFS were defined as the time from the brexu-cel infusion date to the date of disease progression or death from any cause. The time between apheresis and brexu-cel infusion was therefore added to the OS and PFS infused patient traces (n=2 delay cycles). For the R-BAC cohorts, a similar adjustment was made to account for time to subsequent alloSCT in the alloSCT patient traces (n=5 delay cycles).

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<Accessed on 2025-07-21>

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McCulloch, R., Visco, C., Eyre, T.A., et al. (2020), Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. Br J Haematol, 189: 684-688. https://doi.org/10.1111/bjh.16416

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O'Reilly MA, Wilson W, Burns D, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in the United Kingdom: A real-world intention-to-treat analysis. Hemasphere. 2024 Jun 13;8(6):e87. doi: 10.1002/hem3.87. PMID: 38873532;

WebPlotDigitizer (2025)
https://web.eecs.utk.edu/~dcostine/personal/PowerDeviceLib/DigiTest/index.html
<Accessed on 2025-07-21>

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Appendix

Estimated coefficients

Overall survival

Table S 1: Estimated coefficients for brexu-cel OS, Pooled OS from ZUMA-2 (n=68) and SACT from 2022 dataset (n=43)

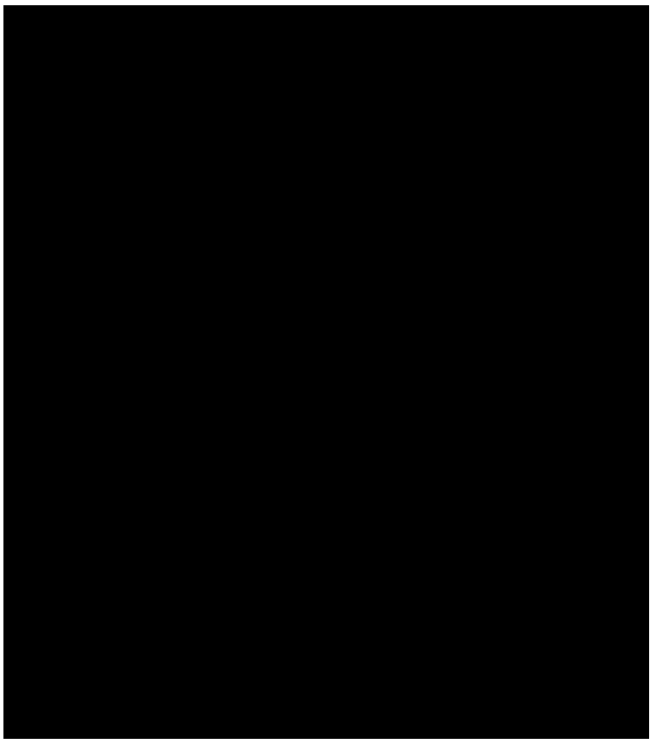

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Table S 2: Estimated coefficients for R-BAC OS, non-alloSCT patients, McCulloch (2020)

```
$Exponential
            est       L95%       U95%          se
rate 0.02736482 0.02178926 0.03436709 0.003181096

$Weibull
             est       L95%       U95%         se
shape  0.7805596  0.6502618  0.9369661 0.07273516
scale 39.6410025 29.2499557 53.7234688 6.14822905

$GenGamma
             est      L95%      U95%        se
mu     2.9152296  2.197419 3.6330401 0.3662366
sigma  1.8199463  1.472696 2.2490747 0.1965874
Q     -0.3006929 -1.231363 0.6299774 0.4748405

$Lognormal
            est     L95%     U95%        se
meanlog 3.11111 2.765818 3.456402 0.1761727
sdlog   1.73030 1.461458 2.048596 0.1490734

$Loglogistic
             est       L95%      U95%        se
shape  0.9871099  0.8196885  1.188727 0.0936044
scale 22.2611485 15.9608773 31.048339 3.7788128

$Gompertz
              est        L95%         U95%          se
shape -0.02434928 -0.04074784 -0.007950724 0.008366764
rate   0.04079728  0.02968200  0.056074981 0.006620821
```

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Table S 3: Estimated coefficients for R-BAC OS, alloSCT patients, Liebers (2025)

```
$Exponential
            est       L95%       U95%          se
rate 0.02495529 0.01764778 0.03528867 0.004411515

$Weibull
             est       L95%       U95%         se
shape  0.6792438  0.5033081  0.9166792  0.1038907
scale 48.4582268 27.9317805 84.0691034 13.6213880

$GenGamma
            est       L95%       U95%        se
mu     1.759335  0.6676673  2.8510033 0.5569837
sigma  1.774058  1.2714292  2.4753890 0.3015302
Q     -1.968313 -3.4546994 -0.4819267 0.7583743

$Lognormal
             est     L95%     U95%        se
meanlog 3.254262 2.674497 3.834028 0.2958043
sdlog   1.924048 1.467376 2.522846 0.2659909

$Loglogistic
             est       L95%      U95%        se
shape  0.8513625  0.6374442  1.137069 0.1256961
scale 24.9550773 14.0135024 44.439703 7.3473170

$Gompertz
              est        L95%        U95%         se
shape -0.06334641 -0.10151299 -0.02517983 0.01947310
rate   0.05627573  0.03417881  0.09265851 0.01431777
```

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Progression-free survival

Table S 4: Estimated coefficients for brexu-cel PFS, Pooled OS from ZUMA-2 (n=68) and O'Reilly (2024)

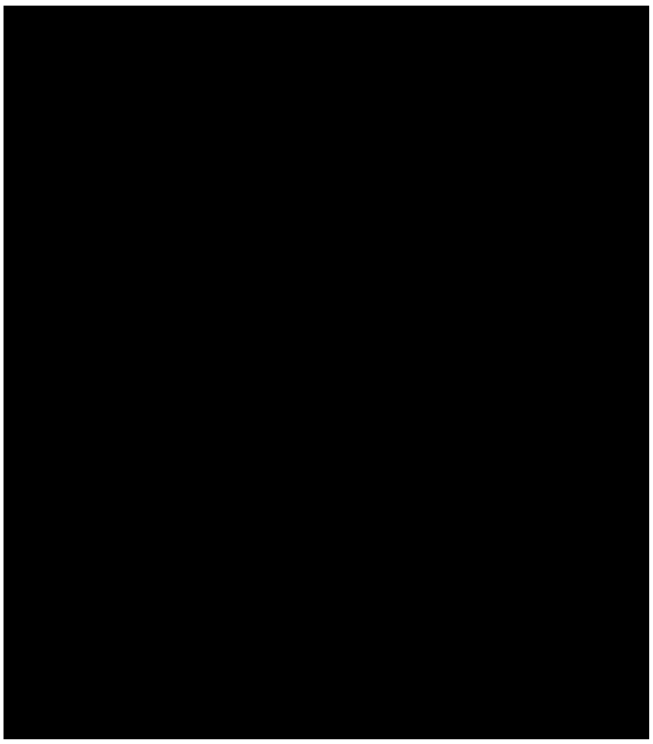

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Table S 5: Estimated coefficients for R-BAC PFS, non-alloSCT patients, McCulloch (2020)

```
$Exponential
           est      L95%      U95%         se
rate 0.0832293 0.0530881 0.1304834 0.01909411

$Weibull
            est      L95%      U95%        se
shape  1.180815 0.8241952  1.691741 0.2166192
scale 12.035351 8.2209041 17.619676 2.3405995

$GenGamma
             est       L95%      U95%        se
mu     1.6146654  0.9259094 2.3034214 0.3514126
sigma  0.8489784  0.5696319 1.2653160 0.1728497
Q     -1.1343466 -2.6375344 0.3688412 0.7669466

$Lognormal
              est      L95%     U95%        se
meanlog 2.0794664 1.7008003 2.458132 0.1932005
sdlog   0.9255178 0.6613964 1.295113 0.1586631

$Loglogistic
           est     L95%      U95%        se
shape 1.833939 1.259521  2.670326 0.3515749
scale 7.634729 5.232511 11.139793 1.4717231

$Gompertz
              est        L95%       U95%         se
shape -0.01628628 -0.09540170 0.06282913 0.04036575
rate   0.09292576  0.04695532 0.18390243 0.03236362
```

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Table S 6: Estimated coefficients for R-BAC PFS, alloSCT patients, Liebers (2025)

```
$Exponential
            est       L95%       U95%         se
rate 0.03287453 0.02360371 0.04578665 0.00555681

$Weibull
              est       L95%       U95%         se
shape   0.6370789  0.4808708  0.8440303 0.09143384
scale  33.3715546 19.5995011 56.8208677 9.06156121

$GenGamma
            est       L95%       U95%        se
mu     1.552873  0.7009199  2.4048259 0.4346779
sigma  1.712496  1.3015641  2.2531687 0.2397411
Q     -1.591308 -2.6206453 -0.5619714 0.5251816

$Lognormal
             est     L95%     U95%        se
meanlog 2.786068 2.238271 3.333865 0.2794935
sdlog   1.893188 1.465494 2.445700 0.2473451

$Loglogistic
             est      L95%      U95%        se
shape  0.8559475 0.6512331  1.125014 0.1193726
scale 15.1346350 8.5996569 26.635618 4.3649053

$Gompertz
               est        L95%        U95%         se
shape -0.07780553 -0.11723719 -0.03837387 0.02011857
rate   0.08473418  0.05331111  0.13467891 0.02003284
```

Statistical fit

Overall survival

Table S 7: Goodness-of-fit for brexu-cel OS, Pooled OS from ZUMA-2 (n=68) and SACT from 2022 dataset (n=43)

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Table S 8: Goodness-of-fit for R-BAC OS, non-alloSCT patients, McCulloch (2020)

	AIC	BIC
Exponential	154.449	155.668
Weibull	150.888	153.325
GenGamma	151.399	155.056
Lognormal	149.427	151.864
Loglogistic	149.941	152.379
Gompertz	153.262	155.699

Table S 9: Goodness-of-fit for R-BAC OS, alloSCT patients, Liebers (2025)

	AIC	BIC
Exponential	302.203	304.362
Weibull	296.640	300.958
GenGamma	286.234	292.711
Lognormal	290.162	294.480
Loglogistic	293.058	297.376
Gompertz	290.254	294.572

Progression-free survival

Table S 10: Goodness-of-fit for brexu-cel PFS, pooled from ZUMA-2 (n=68) and O'Reilly (2024)

Table S 11: Goodness-of-fit for R-BAC PFS, non-alloSCT patients, McCulloch (2020)

	AIC	BIC
Exponential	134.474	135.693
Weibull	135.718	138.156
GenGamma	130.660	134.316
Lognormal	130.806	133.244
Loglogistic	131.172	133.610
Gompertz	136.305	138.743

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Table S 12: Goodness-of-fit for R-BAC PFS, alloSCT patients, Liebers (2025)

	AIC	BIC
Exponential	311.054	313.114
Weibull	300.999	305.120
GenGamma	287.742	293.924
Lognormal	292.593	296.714
Loglogistic	295.381	299.501
Gompertz	291.525	295.646

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action Anthony Nolan Blood Cancer UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Lymphoma Action** • **Gilead Sciences Ltd** £15,000 contribution towards our Peer Support Services. • **BeiGene UK** £20,561.34 contribution towards our Lymphoma Essentials and Preparing for Treatment provision and sponsorship of Lymphoma Management course for HCPs. Payment for patient volunteer expenses to attend BeiGene event. • **Roche** £20,000 contribution towards our Helpline, Information Provision, and Preparing for Treatment project. **Anthony Nolan** • **Autolus Therapeutics:** o £50,000 commercial income for the provision of cord blood for cell and gene therapy research and development in immunotherapy/oncology o £10,000 donation towards Anthony Nolan's CAR-T CNS • **Kite, Gilead:** £18,200 research grant towards the Anthony Nolan CAR-T Patient Experience Study • **Sanofi:** £20,000 grant to support the development of a report highlighting the psychological impact of stem cell transplant and CAR-T on patients and families **Blood Cancer UK** • **Gilead** - £9,865 for translated health information, £91,290 for the BCAP, £20,000 for the direct referral, £15,000 for CTSS • **BeiGene** - £30,000 for the CTSS • **Pfizer** - £7,000 for the Patient Charter, £64.59 for travel expenses to a meeting, £30,000 for CTSS, £2,550 for CEO consultancy • **Roche** - £15,000 for CNS programme of support, £25,000 for the direct referral
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 12 August 2025. Please submit via NICE Docs.

Name of commentator person completing form:	[redacted], Lymphoma Action [redacted], Anthony Nolan [redacted], Blood Cancer UK

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We do not feel that the recommendation has given due consideration to the patient perspective. The patient's voice offers a unique and invaluable perspective that quantitative data alone cannot fully capture – the voices and experiences of our community should serve as a crucial factor in the decision to make this treatment available to a wider population. This is the experience of a male patient aged 74: *"I was diagnosed with Mantle Cell Lymphoma in September 2021 and underwent several treatments, including chemotherapy. Before treatment the lymphoma made my life very difficult. I lost my hearing completely in one ear, had no appetite, and lacked energy, transitioning from a very active person to someone who couldn't do anything. Various treatments were tried without success until I was offered Brexucabtagene Autoleucel CAR-T therapy as a last resort in January 2023. Since receiving treatment, my life has returned. Initially, I had to be very cautious about socialising. Currently, I am taking a precautionary antibiotic three times a week and receiving regular infusions to boost my immunity. I am now able to socialise more normally and am gradually returning to a near-normal life. While the treatment does have potential side effects, which were thoroughly explained, I was fortunate to experience only a mild episode of neurotoxicity three weeks post-treatment, requiring only an overnight hospital stay. I am very thankful that the treatment was effective. I consider it the perfect solution, and I would undergo it again given the marvellous outcome. I feel more or less cured."* And that of a male patient aged 66: *"It was a huge shock when I was diagnosed with mantle cell lymphoma 4 years ago, as I keep a very active life. I have tended to take/accept each bout of treatment as I have had to undergo it - chemotherapy, stem cell replacement, radiotherapy and CAR T cell replacement. The NHS care and treatment has been exceptional and can't be faulted. The worst thing is the unknown - will it/when will it come back? I try and do push this to the back of my mind and get on with life.*

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	Brexucabtagene autoleucel arrested and cleared my cancer growth in my upper gastric area. I was very fortunate to undergo CAR-T cell replacement and can see no disadvantages to the treatment. *This treatment is truly remarkable and carried out by truly remarkable health professionals. I owe my continued healthy existence to everyone who has treated and cared for me during my Brexucabtagene autoleucel journey."*
2	We are concerned that the recommendation has not sufficiently taken into account the psychological burden and mental strain that comes with the fear both of relapse and that there will be no suitable treatments available. The 2024 Lymphoma Coalition UK survey (total respondents 1204; 3% MCL) reported that fear of progression/relapse of lymphoma was the most prevalent concern amongst the over 80% of lymphoma patients who reported some type of emotional impact attributable to their diagnosis. For our patient community, the fear of relapse is ever-present and can manifest through symptoms such as insomnia and anxiety.
3	The draft guidance acknowledges there is an unmet need in this population and that patients and healthcare professionals would welcome new treatments. The committee concluded that "brexucabtagene autoleucel is clinically effective, with a high overall response rate". We are concerned that this may not have been given due consideration in the decision-making process. Brexucabtagene autoleucel is the only CAR-T option currently available for patients and would provide hope to patients with a diagnosis of MCL and an important option for patients who have relapsed after an auto transplant and who may not be able to find a donor match on the stem cell transplant register. Without a CAR-T option at this stage, the only option left is likely to be palliative care.
4	We note that the committee requested updated analysis from the company. However, we are concerned that a draft negative recommendation was issued despite this request. We urge NICE and the company to engage in further discussion regarding the areas of uncertainty and the proposed commercial arrangements to ensure this important treatment remains available on the NHS.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential

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information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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TO WHOM IT MAY CONCERN

As a group of consultant haematologists and oncologists who specialise in treating lymphoma, we would like to express our grave concern at the possibility of CAR T-cell therapy (specifically Brexucabtagene autoleucel) not being available for patients with relapsed / refractory mantle cell lymphoma (MCL) in England and Wales.

MCL remains an incurable and aggressive disease, limiting the survival of affected individuals. Anti CD19 chimeric antigen receptor (CAR) T cell therapy represents a national[1] and internationally recognised standard of care approach for suitable patients in the third line and beyond setting and this has been routinely used in the England and Wales via the cancer drugs fund since 2021.

Without this treatment, 3rd line treatment options are very limited and durable response rates observed with anti-CD19 CAR T cell therapy remain unprecedented.

Removal of this therapeutic option would see England and Wales fall behind Scotland and the many countries in mainland Europe who have routine access in this specific setting.

Were this treatment to be removed, many patients would then be considered and exposed to either relatively ineffective and toxic chemoimmunotherapy in this setting or would be considered for an allogeneic stem cell transplantation, with the well documented risks and health care utilisation costs associated with this (BSBMTCT adult HSCT indications[2]). Furthermore, it is well described that patients from ethnic minorities have fewer donor options and are less likely to receive an allogeneic stem cell transplant.

We would urge NICE to consider all of these important points before final decisions are made regarding ongoing access and funding for Brexucabtagene Autoleucel.

References

1 – Management and management of mantle cell lymphoma: A British Society for Haematology Guideline. Eyre et al BJHaem 2023.

2 - https://bsbmtct.org/wp-content/uploads/2023/02/HSCT-adult-indications_final.pdf

Sincerely,

[redacted]

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

Data request – numbers of people who are not infused with brexucabtagene after leukapheresis

Data was taken from the NHS England prior approval system (Blueteq) on 4th August 2025 to identify patients with an approved Blueteq Form A (apheresis) but no Form B (infusion). 65 patients were identified with an A form but no B form. Data was shared with CAR T centres to confirm whether these patients were apheresed and infused, and if not the reason for not progressing with treatment. Of the 65 patients with no B form centres confirmed that 5 have been infused.

Of the 60 patients identified as not being infused, 20 did not proceed to apheresis. The reasons for not proceeding to apheresis are provided in Table 1.

Table 1 – Reason for not proceeding to apheresis

Reason for not proceeding to apheresis	Total
Progressive disease	15
High white cell count	2
Deterioration in performance status	2
Alternative therapy pursued	1
	20

40 patients were confirmed as being apheresed but not infused. The reasons for not proceeding to infusion are provided in Table 2.

Table 2 – Reason for not proceeding to infusion

Reason for not proceeding to infusion	Total
Progressive disease	26
Patient fitness/deterioration in performance status	7
Manufacturing failure	6
Second malignancy diagnosed	1
	40

Overall survival

Of the 40 patients with an approved Blueteq Form A (apheresis) but no Form B (infusion), as presented in Table 2, two patients had a missing NHS Number so were excluded from the OS analysis as they could not be traced for their vital status. Thirty-eight patients were included in these analysis.

The median OS was 2.3 months [95% CI: 1.8, 2.9] (70 days).

Figure 1: Kaplan-Meier survival plot (N=38)

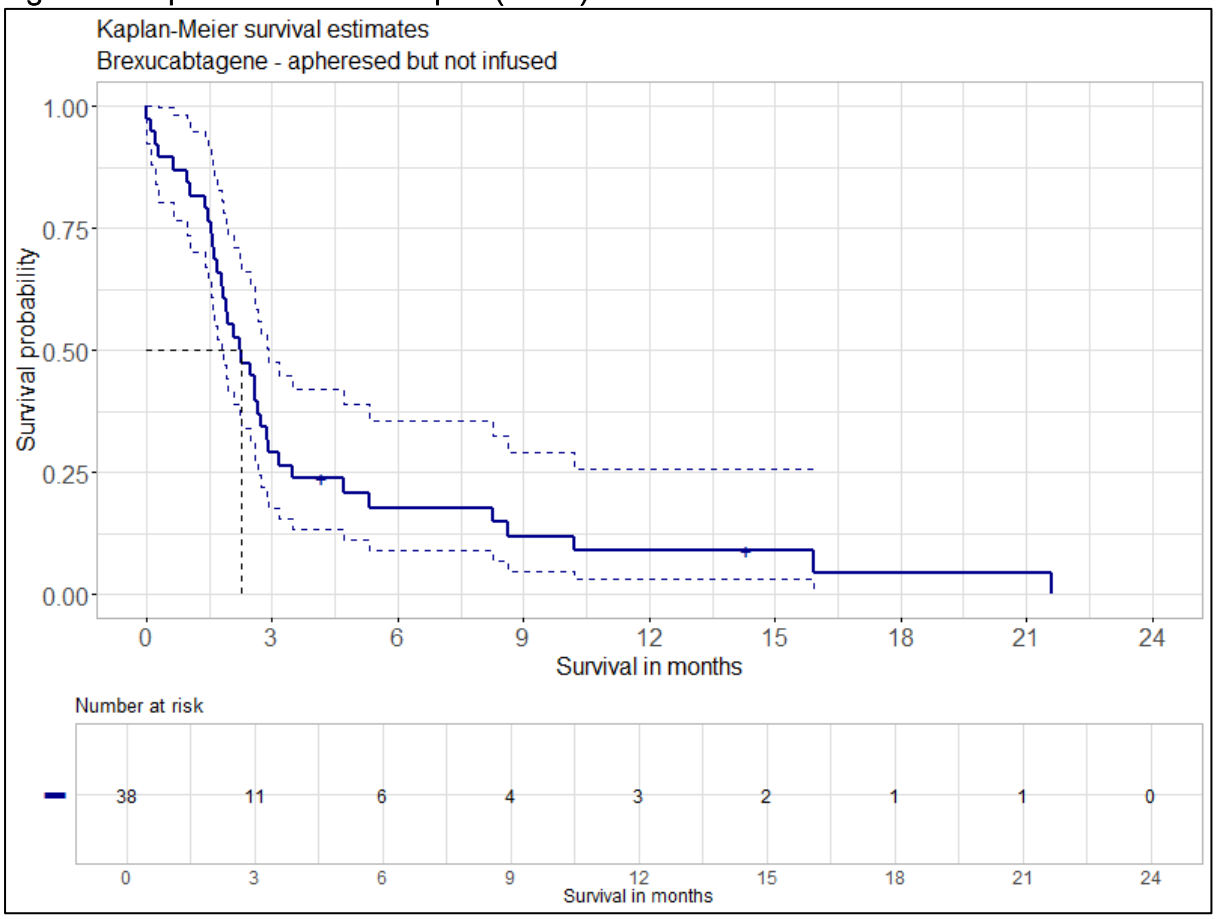

Table 3: OS at 6, 12 and 18-month intervals

Time period	Overall survival		
	(%)	LCI	UCI
6 months	18%	9%	36%
12 months	9%	3%	26%
18 months	4%	1%	25%

I can confirm the following form Blueteq data which has been submitted, and this includes dates up to the end of July 2025

- Since Brexu-cel became available in the Cancer Drugs Fund (CDF) (March 2021)
    - 250 “A” forms submitted
    - 175 “B” forms submitted
    - Therefore, **30%** of patients who had an “A” form submitted did not have a “B” form submitted
- In the last 24 full calendar months
    - 112 “A” forms submitted
    - 83 “B” forms submitted
    - Therefore, **26%** of patients who had an “A” form submitted did not have a “B” form submitted
- In the last 12 full calendar months
    - 49 “A” forms submitted
    - 39 “B” forms submitted
    - Therefore, **20%** of patients who had an “A” form submitted did not have a “B” form submitted

BW,

James.

James Richardson

National Specialty Advisor (Cancer Drugs)

Medicines Negotiation and Managed Access Team

Medicines Value and Access

NHS England

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments (review of TA677): EAG response to DG comments after AC1 [ID6325]

Produced by	*Centre for Evidence and Implementation Science*
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Declared competing interests of the authors
The authors of this report have no conflicts to declare.
The EAG's clinical advisor has participated in advisory boards and received honoraria from Kite Gilead.

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

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

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External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

Following the initial appraisal committee (AC) meeting to review the evidence for brexucabtagene autoleucel (brexu-cel) in treating relapsed or refractory mantle cell lymphoma [ID6325], the committee concluded that it could not recommend the technology at that stage. In response, the company submitted a document containing comments on the draft guidance (DG), including a technical addendum addressing specific concerns raised by the committee. The EAG has reviewed this submission and provides a summary and critique of each of the points raised.

2 EAG response to Company Comments

2.1 *Comment 1: Section 3.4 Generalisability of ZUMA-2*

Following AC1, the company noted that the mean age of 63.2 years in ZUMA-2 was younger than expected for UK patients with relapsed or refractory mantle cell lymphoma. NHS England highlighted that, based on the SACT dataset for the three years up to May 2025, the mean age of patients treated with brexu-cel was 66. The committee therefore considered the SACT mean age of 66 more representative than the ZUMA-2 figure.

In its generalisability comments, the company explained that during the first year of brexu-cel availability, a backlog of patients, many with additional prior treatments, were treated contributing to the older age seen in the SACT dataset. The company attributes this to treatment timing, whereas NHS England stated that "*people in the NHS with relapsed or refractory mantle cell lymphoma will have had fewer treatments before treatment with brexu-cel than people in ZUMA-2*".

The company claims that the implementation of BSH guidelines will lead to the selection of younger patients, as clinicians are more likely to choose those with greater potential for better outcomes. To support this, it presented six months of Kite Konnect ordering data showing a slight decrease ([redacted] years) in mean age (Feb-Jul 2021: [redacted] years; Dec 2024-May 2025: [redacted] years). However, the EAG noted that these assumptions were not properly sourced or referenced, and no further

supporting information was provided. It is unclear whether this population is restricted to the UK or even to MCL.

While the BSH guideline includes updates to address the aggressive and fast-progressing nature of relapsed/refractory MCL, the EAG does not consider that earlier relapse risk assessments to reduce delays to less than 8 weeks affect patient age significantly. As noted in the addendum, "*With the requisite time delays built into CAR T-cell delivery (referral to a CAR centre, T-cell harvest and manufacture), CAR T-cell return can take up to eight weeks*." Although an 8-week delay is unlikely to influence patient age, it underscores the disease's rapid progression.

2.2 *Comment 2: Section 3.6 Real world evidence for brexu-cel*

Given the uncertainties surrounding brexu-cel in TA677, NHS SACT data was collected to address limitations such as generalisability to UK practice, informing assumptions around age and clinical outcomes. In AC1, the company used the more optimistic survival estimates from ZUMA-2, which were used in its cost-effectiveness model. "*The company agreed with the EAG that UK data from SACT and O'Reilly et al. (2024) was representative of people who would have brexucabtagene autoleucel in the NHS, but did not agree that the data from France and the US was generalisable*"(DG doc, page 11). The committee concluded that utilising SACT and O'Reilly data with ZUMA-2 would improve generalisability, particularly given ZUMA-2's longer follow-up.

However, slightly contrary to its position in AC1, the company later chose to restrict SACT overall survival data to follow-ups from August 2022 onward, arguing this would reduce the proportion of non-infusions following BSH guideline updates aimed at minimising treatment delays (to under eight weeks). The EAG notes that failure rates in both O'Reilly and SACT NHS datasets remain around 30%. As was highlighted by the committee, "*in the context of a strictly controlled clinical trial, and a higher attrition rate would be expected in real-world clinical practice*".

The company notes that COVID-19 significantly impacted CAR T-cell therapy outcomes, with early pandemic-era data showing high mortality rates among recipients, but later improvements, driven by vaccination, better care, and milder variants, have reduced the mortality rates from mortality from 43.6% in 2020 to 7.5%

in 2022. While the company cites this study to justify excluding pre-2022 data due to elevated COVID-related mortality, this rationale is undermined by several limitations of the study itself.[1] The sample size is small and likely unrepresentative (only 39 patients in 2020, 35 in 2021, and 106 in 2022 across all European countries), the definition of COVID-related mortality is unclear, and the patient population is heterogeneous (including acute leukaemia, B-NHL, and multiple myeloma). No additional analyses or supporting evidence were provided in the company's submission or clinical study report to validate and support claims regarding COVID-19 impacts or associated deaths. Given the low numbers of people in the study, it would seem CAR T recipients took adequate shielding measures.

In Section B.2.13.6 of the CS, the company states: "*Subsequent to this change, the manufacturing failure rate has fallen below* [redacted]*%*" and elsewhere claims: "*The latest infusion rate from the Kite Konnect data has continued to improve and in the last 6 months is approximately* [redacted]*%*", but it is unclear for what population these figures are relevant. They do not plausibly support the claimed magnitude of impact of BSH guideline changes on r/r MCL patients or NHS care.

Overall, the company's claims are not adequately supported by references. The submission and the clinical study report contain no information regarding the impact of COVID-19, and none of the cited sources appear to be related to the BSH addendum. Consequently, the EAG cannot confirm the plausibility or credibility of the company's assertions. Furthermore, as part of the final report, the EAG examined the influence of BSH guidelines on the SACT data and found no significant difference in survival outcomes between the two groups (Figure 1).

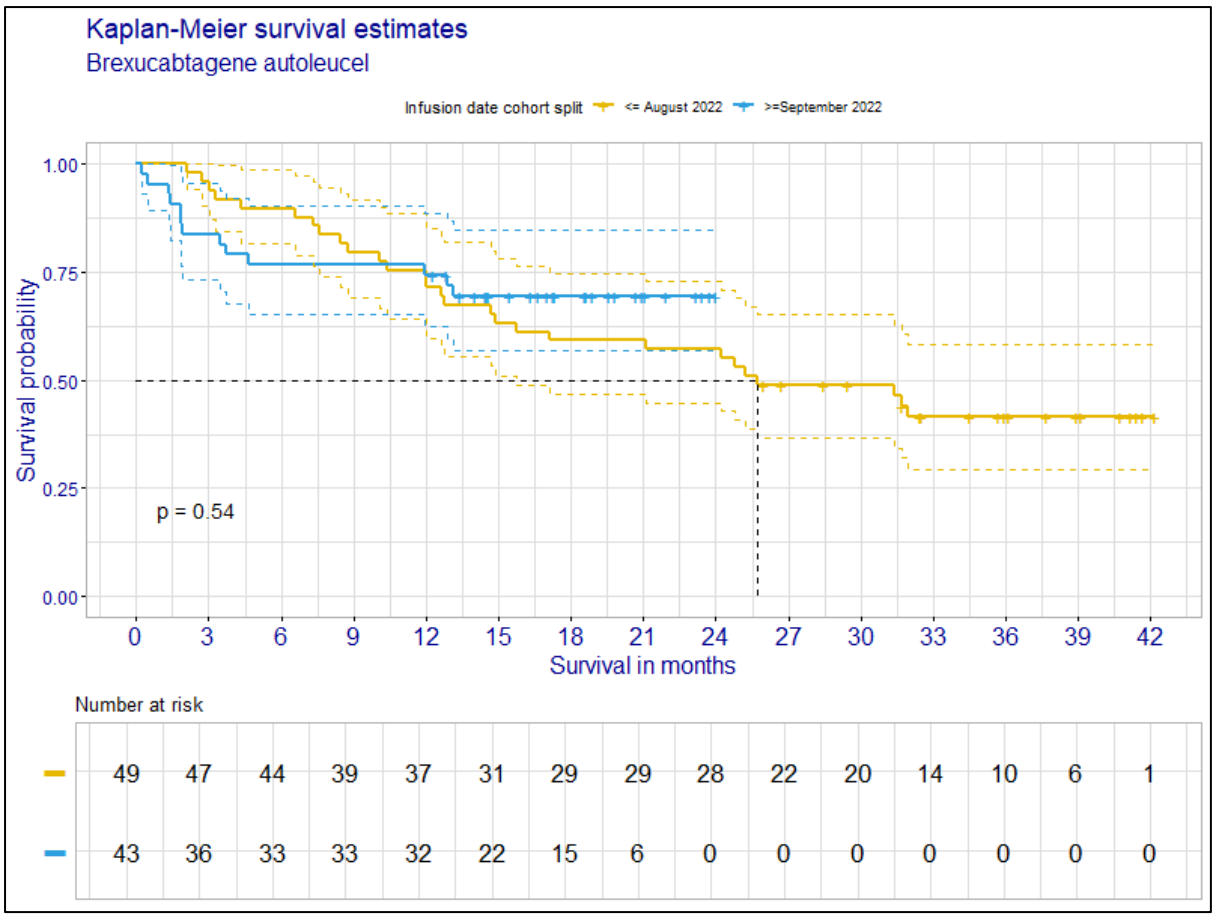

Figure 1: SACT brexu-cel overall survival, by BSH guideline cut-off

2.3 *Comment 3: Section 3.7 Subsequent alloSCT after R-BAC*

The company note that the committee's preference was to model a rate of 15% of subsequent alloSCT following R-BAC treatment, whilst welcoming additional data to inform this uncertain parameter.

A search undertaken by the company did not identify any additional sources of data, and so the company apply the 15% rate in their base case for the modelling of both the costs and effects of alloSCT.

For patients who do not receive alloSCT, the company uses the same approach as the EAG did previously, to adapt the reported PFS and OS times from McCulloch et al.[2] by removing survival times for people who did receive alloSCT.

For patients who did receive alloSCT, the company identified an alternative source, a published paper by Liebers et al.[3] This paper applied propensity score matching to

compare outcomes for 64 people aged ≥ 50 with relapsed/refractory MCL from the European Bone Marrow Transplant registry to 64 people in the ZUMA-2 trial. The EAG agrees that this source is preferred over the subgroup of the McCulloch study population due to the longer follow-up and larger sample size, however ideally outcomes for the broader alloSCT population without matching (n=272) would be available. The detail of the extrapolation of this dataset is included in the comments on the technical addendum.

When using this dataset to inform to a comparison of brexu-cel, the EAG is concerned that if using the ZUMA-2 data to extrapolate for brexu-cel, even if pooled with SACT data, then there is a high risk of bias from comparing trial data for brexu-cel, to real-world data for R-BAC. However, this concern goes away if focusing extrapolations on the SACT data for brexu-cel.

2.4 *Comment 4: Section 3.9 Modelling of the pre-infusion period – approach*

Following AC1, the committee's preference aligned with the EAG, which was to capture the costs and effects associated with all people undergoing leukapheresis, which is part of the CAR T manufacturing process.

The company however maintains its preference to focus on the infused population but includes the costs of leukapheresis for people who go through this stage of the CAR T process but do not receive an infusion, citing consistency with other NICE appraisals of CAR T technologies.

The company also describe how expert opinion stated that 20-30% people considered for R-BAC would not actually receive it due to frailty or rapid disease progression. The company's view is that outcomes for these people should also be accounted for if the model is to start from the point of leukapheresis. The company has not provided any supporting evidence in terms of timelines from previous therapy or disease progression to either R-BAC or CAR T leukapheresis or infusion, hence the EAG does not consider this adjustment appropriate. However, if people who would not receive R-BAC would undergo leukapheresis, and potentially infusion, then it raises the question of whether an alternative comparator is needed (e.g. palliative care) for CAR T therapy in this population. Additionally, there is the consideration of whether the screening stage for CAR T should also be included.

The company also list toxicities associated with R-BAC that were reported by McCulloch et al.,[2] but states that this paper "reflects outcomes in patients who were able to initiate and complete R-BAC treatment". However, the EAG understands that the impacts of these are likely to already be either directly or indirectly captured in the data and therefore represented in the economic modelling. Furthermore, 28% of the McCulloch et al. population stopped early due to progressive disease or toxicity, suggesting the company's interpretation of this evidence to be incorrect.

The company concludes that using the efficacy estimates for the infused population from ZUMA-2 to compare to R-BAC efficacy estimates from McCulloch et al.[2] is the best comparison. However, their preference for modelling from the point of enrolment is to weight the outcomes to factor in outcomes for people not receiving R-BAC, setting this to be equivalent to the non-infused people from the CAR T population.

As no clear new evidence is provided to support the company's preference, the EAG maintains its preference to base cost and efficacy estimates on the enrolled population for brexu-cel, starting at the point of leukapheresis, and does not consider it appropriate to apply an adjustment to the R-BAC extrapolations.

2.5 *Comment 5: Section 3.9 Modelling of the pre-infusion period – drop out rates*

Despite the company's preference to model efficacy using the infused population, they do present a scenario analysis where the model starts at the point of leukapheresis.

The company introduces data from their ordering system, Kite-Konnect, spanning the period from January 2024 to June 2025. The EAG is not able to verify this data, and is unclear why this date range is chosen, or which countries and patients it is representing. As brexu-cel is approved for other indications, this information could be being skewed by patients with less severe disease and so are more likely to receive an infusion.

The company state that the data from Kite-Konnect is consistent with pre-leukapheresis drop out from O'Reilly et al.,[4] and is also consistent with the post-

leukapheresis drop-out from ZUMA-2 (Table 1). Hence the company use the estimate from ZUMA-2 ([redacted]).

The company's comparison is slightly biased as the denominator appears to vary between ZUMA-2 and Kite-Konnect, but the EAG accepts that the dropout post-leukapheresis would remain similar between ZUMA-2 and Kite-Konnect.

However, the EAG notes that the Kite-Konnect combined dropout is below what is reported by both SACT and O'Reilly et al.[4] Unfortunately, the desired post-leukapheresis dropout information is not available from SACT, and it only reports the combined dropout from approval to leukapheresis, which is 30%. This is consistent with the combined total of the O'Reilly paper, which does provide the desired breakdown (20% dropout between leukapheresis and infusion), and is maintained as the preferred source of information by the EAG. This choice is consistent with the EAG's preferred sources of efficacy, due to the overlapping populations of O'Reilly and SACT, and avoids the uncertainty associated with the Kite-Konnect source. At AC1, the CDF lead stated 25% of applications did not reach infusion, based on data excluding the first 12 months of data which were affected by manufacturing problems.

Table 1: Comparison of drop out rates between key CAR T process steps

	ZUMA-2	**O'Reilly Paper[4]**	**Kite-Konnect**	**Company Preference**	**EAG preference**
Drop out pre leuka-pheresis	NR	13% (of approved patients)	[redacted] (of approved patients)	Not modelled	Not modelled
Drop out between leuka-pheresis and infusion	[redacted] (of leuka-pheresed patients)	18% (of approved patients) 20% (of leuka-pheresed patients)	[redacted] (of approved patients)	[redacted] (scenario analysis)	20% (base case)

2.6 *Comment 6: Section 3.9 Modelling of the pre-infusion period – outcomes for non-infused patients*

To estimate the outcomes for people who are leukapheresed but not infused, the EAG previously used information from DESCAR-T, as this was the only available source identified at the time.[5] The company highlight how the committee considered the DESCAR-T population less relevant to the UK than the SACT and O'Reilly data. The company emphasises how 39% of the DESCAR-T non-infused population had ECOG ≥ 2, stating this as a limitation. The EAG considers that this proportion could be plausible given that a failure to proceed to infusion is associated with disease worsening.

As an alternative approach the company have sourced this equivalent information from ZUMA-2, however this is presented in the technical addendum, which the EAG critiques in section 3.1. The EAG notes that the outcomes for non-infused people from ZUMA-2 are more pessimistic than those from the DESCAR-T study, which appears inconsistent with the company's concerns of using DESCAR-T. However, the EAG is happy to utilise the company's preference in the EAG base case.

The company also state that if outcomes for non-infused people are included in the model, then so should outcomes for people considered for, but not treated with, R-BAC. Justification for this remains unclear and does not account for clear differences in the timings, and management of patients prior to treatment (e.g. use of bridging therapies prior to CAR T infusion). The company apply an adjustment to account for the outcomes of those not treated with R-BAC in their scenario which combines the extrapolations for R-BAC with the non-infused extrapolations brexu-cel, to obtain an estimate for the combined population. Given the lack of information around timelines and equivalency mentioned in section 2.4, the EAG does not support applying any adjustment to the R-BAC population.

2.7 *Comment 7: Section 3.10 Cure assumption: Timing of LTS assumption*

Following AC1, the committee remained uncertain about the timing of the implementation of a cure assumption within the economic model. Previously, the EAG preferred to model this from 60 months, whilst the company preferred from 48

months. These preferences are maintained respectively following AC1. The company provided a breakdown of OS events, by time and cause. The EAG does not consider this supports implementing a cure assumption from 48 months and may support implementing one from later than 60 months, given that [redacted]

The company has not implemented mixture cure models, stating these models were unstable with longer follow-up from ZUMA-2. The committee also requested survival models to be fitted without any cure assumption applied, which the company has not explored in any scenario analyses. Instead, the company commented on the proportion of people remaining progression-free as evidence that modelling a cure is plausible. The EAG accepts that it is plausible that a proportion of patients could be cured, however it is unclear whether that proportion is reliably estimated from the implemented methods due to the limited follow-up, and ultimately long-term outcomes (10+ years) remain unknown. The EAG explores models without a cure assumption, to support the committee's decision-making.

2.8 *Comment 8: Section 3.10 Cure assumption: Mortality weighting*

Following the implementation of the cure timepoint, the economic model applies a standardised mortality ratio to the mortality rate of age and sex matched general population mortality rate, to represent an inflated mortality rate for people after receiving CAR T treatment. The company's preference was to implement a SMR of 1.09.

To support this, the company presents a comparison of different sources of SMR and combines them with estimates of their population age and to calculate their absolute difference in excess mortality. where they have been applied. The company justify their preferred SMR, stating its excess mortality falls within the range of sources identified. However, the only value beneath the company's is the source where the company obtained their preferred SMR. Furthermore, the company has not described how these sources were identified, raising questions about whether these are truly representative of relevant modelling assumptions.

On the company's unusual choice of comparison, it is unclear why the company is averaging across 5 year periods, or why the starting age is directly relevant to this

decision, and the EAG considers these factors are likely exaggerating the extent of the difference between the EAG's approach and the other sources identified by the company. It is logical that applying a SMR to an older population with a higher reference mortality rate will result in a larger absolute difference in mortality and unclear why this is part of the company's rationale. The differences stated by the company should also be scaled down to the proportion assumed cured at 3 years, which further reduces the absolute difference.

There is also no clear evidence to say that the SMR as applied by the EAG is at all inaccurate, and it may very well represent long-term outcomes for this population.

Finally, the company incorrectly recall events where they state that the EAG did not decline to elaborate on their analysis comparing mortality rates from long-term follow-up of ZUMA-2 to general population mortality but clearly described when asked by committee.

The EAG has already described its concerns with relying on the study by Maurer et al. where no participants received CAR T therapy, and the estimate is instead relevant to a population who had newly diagnosed diffuse large B-cell lymphoma and were treated with immunochemotherapy. The generalisability of this to the desired population of people with r/r MCL after 2 or more systemic treatments, and then subsequent CAR T is questionable.

Another study identified by the company is by Eskelund et al.[6] The company describe an SMR of 2.36 from this source, however the EAG could not identify this in the paper or supporting information. Instead, this value appears to relate to a hazard ratio derived by the EAG of TA677 (the original appraisal of brexu-cel for this indication), reported alongside another hazard ratio of 4.37, with the EAG expecting the true value to lie between 2.36 and 4.37. The current EAG considers this is supportive of applying a SMR of 3 in this appraisal, though it notes that SMR and hazard ratios are not identical.

The final source introduced by the company is TA893, which used a SMR of 3 but with this parameter described as "highly uncertain" in the final draft guidance. TA893 was the appraisal of brexu-cel for relapsed or refractory B-cell acute lymphoblastic leukaemia, with a model starting age of 46 matching the ZUMA-3 trial. As already stated, the EAG do not consider the difference in starting age to be a contributing

factor to the choice of SMR, and so conclude this source supports the use of a SMR of 3 in the current appraisal of brexu-cel.

The EAG has repeated its comparison of post-60-month mortality rate from ZUMA-2, and background mortality for people aged 71 (= 66 starting age + 5-year cure start). An exponential model fitted to the post-60-month ZUMA-2 follow-up produced a per-cycle probability of death of [redacted]. Using background mortality as modelled by the company in the economic model, the desired age group has a per-cycle probability of death of [redacted], producing a ratio of [redacted].

The EAG concludes that this parameter remains uncertain based on the information provided by the company and considers a SMR of 3 to be reasonable.

2.9 *Comment 9: Section 3.11 CAR T tariff and ICU costs*

The company raised concerns that the Committee's recommendation to apply a CAR T tariff of £58,964 (2024/25 cost year) or £60,462 (2025/26 cost year) does not meet the required standards of transparency, methodological rigour, and procedural fairness for a robust assessment of brexu-cel. Instead, the company prefers to retain a tariff of £41,101 in its base case, supplemented by IVIG, bridging, and conditioning therapy costs.

The EAG considers this approach inconsistent. On the one hand, the company criticises the updated tariff values as being non-transparent and methodologically weak, but on the other, it continues to apply a lower historic tariff (£41,101) without providing robust evidence that this figure remains valid or accurately reflects current NHS delivery costs. If the principle is transparency and methodological robustness, this rationale should apply equally to the company's preferred tariff figure.

The company also argues that its approach is aligned with previous STAs in which the £41,101 tariff was agreed. However, these earlier appraisals also recognised the need to add costs (for example IVIG, bridging, and conditioning). By this same logic, ICU costs should also be added, since NHS England has confirmed that ICU admissions are not covered within the CAR T tariff itself but represent a separate resource use. The company's position appears selective in how precedent is applied.

With respect to the EAG's bottom-up scenario (including leukapheresis, administration, ICU and non-ICU hospitalisation, emergent AEs, and IVIG), the

company highlights a total of £60,845 and then subtracts IVIG costs to approximate £41,816—close to its preferred tariff. The EAG notes several issues here:

- Excluding IVIG (£14,023) reduces the total to £46,822, which remains materially higher (around 14%) than £41,101.
- The costing assigns **£0** to "all other costs in the first 100 days post-infusion" (such as monitoring and training). This omission clearly underestimates true delivery costs.
- Several measurements of cost items estimates are taken directly from company inputs rather than independent or validated NHS data, introducing additional uncertainty.

Regarding transparency of NHS England's updated tariff, the EAG acknowledges the company's concern that details of the methodology have not been published and agrees that greater transparency in tariff construction would be beneficial for stakeholders. However, this does not justify continued reliance on an outdated and likely underestimated figure. The most recent NHS England tariff (£58,964, inflated to £60,462 for 2025/26) reflects the best available evidence, and should be considered the most appropriate value for base-case analysis.

Therefore, while the company's critique of transparency is valid in principle, its chosen alternative tariff does not have stronger evidentiary support. The EAG maintains that the Committee's base-case approach (using the updated CAR T tariff (£58,964 or £60,462) supplemented with explicit ICU costs) is the most reasonable and methodologically robust option.

2.10 *Comment 10: Section 3.12 Utility values*

The company raised concern that capping pre-progression utilities to the general population norm is inconsistent with the NICE reference case, which specifies a preference for patient-reported outcomes. They argue that patients eligible for brexu-cel are typically fitter than the age-matched general population and may therefore reasonably report higher quality of life. The company therefore prefers to apply ZUMA-2 patient-reported utilities in its base case.

The EAG recognises the importance of patient-reported outcomes in line with the NICE reference case. However, based on clinical expert advice, the EAG does not

consider it reasonable for pre-progression utility values to exceed those of the general population at the same age. On post-progression utilities, the company, in most updated model, applies a relative difference approach using TA502 values. The EAG's position is that this method lacks robustness, as it depends on extrapolating relative changes from a different appraisal without direct trial data. Given the limited availability of robust post-progression data for brexu-cel, the EAG considers that directly applying the TA502 post-progression utility value of 0.68 is a more appropriate approach.

2.11 *Comment 11: Section 3.13 Intravenous immunoglobulin therapy costs*

The company argues that IVIg use in the UK is lower than the rate observed in ZUMA-2 and that clinician-reported estimates of 10–20% more accurately reflect current practice. They therefore propose using a midpoint value of 15% for one year of IVIg treatment in their base case, noting that this aligns with SACT data for axi-cel in third-line R/R DLBCL (16.5% use, mean duration 6.5 months).

The EAG acknowledges that there is some uncertainty in estimating the proportion of patients requiring IVIg after CAR T therapy. However, the company's preferred value of 15% may underestimate true need. Evidence from Wang et al. (2020, 2023) and previous NICE appraisals (TA677, TA567) indicates that rates are consistently higher (between 30% and 40%). In this context, the ZUMA-2 estimate of 38% is considered a more appropriate basis for analysis than the company's lower assumption.

With respect to treatment duration, the company assumes 12 months, citing a conservative approach. The EAG notes, however, that some previous appraisals have considered longer durations (up to three years, as in TA567) and that uncertainty remains about the long-term need for IVIg. For this reason, the EAG includes alternative scenarios that extend the duration of treatment beyond one year.

In summary, while the company's proposal reflects clinician input, the broader evidence base, and previous NICE decisions suggest higher rates of IVIg use are plausible. The EAG therefore prefers a base-case assumption of 38% of patients receiving IVIg for one year, with scenario analyses exploring both lower incidence (1.5% and 10%) and extended duration (two years).

2.12 *Comment 12: Section 3.14 Severity Modifier*

The company has requested that the Committee apply either a higher severity weight of 1.7 or adopt the £100,000 willingness-to-pay threshold usually associated with the Highly Specialised Technology (HST) process. They argue that brexu-cel was originally assessed under end-of-life (EOL) criteria in TA677, that NICE's subsequent move to a severity modifier represents a change in process which disadvantages this population, and that a higher weight would better capture the broader value of treatment.

The EAG notes that the company was invited to submit a case for an alternative severity weighting during clarification but chose not to do so. The EAG therefore has not explored or critiqued alternative weighting strategies on the company's behalf.

The EAG maintains that the Committee's conclusion to apply a severity weight of 1.2 is appropriate and consistent with NICE's 2022 updated methods. Based on the preferred assumptions set out in the main report (Table 2), both the company's and EAG's own base-case calculations support a 1.2 weight:

Table 2: QALY weight based on company and EAG's preferred assumptions for the base case

Factor	EAG's preferred assumptions (new base case-post ACM1)	Company's preferred assumptions (new base case-post ACM1)
Sex distribution (proportion of female)	23.00%	16.00%
Starting age	66 years	66 years
Expected years of life	[redacted]	[redacted]
Quality of life by age	[redacted]	[redacted]
Discount rate	3.5%	3.5%
Expected total QALYs for the general population (QALYs)	10.52	10.49
absolute shortfall	[redacted]	[redacted]
proportional shortfall	[redacted]	[redacted]
QALY weight	x 1.2	x 1.2
EAG: External Assessment Group; QALY: Quality-Adjusted Life Year;		

2.13 *Comment 13: Section 3.16 Committee's preferred assumptions*

The company has updated its economic model to reflect certain revised preference assumptions, consistent with the committee's preferred approach, as shown in the table below. A new preferred base case has been proposed, informed by the points outlined in the comments on DG, alongside selected scenarios designed to capture key aspects of the committee's discussions.

Table 3: Company's analysis based on preferred assumption

#	Preferred assumption	Inc costs	Inc QALYs	ICER	Impact on ICER
Company base case		[redacted]	[redacted]	£50,270	-
1	Patient age - 66 years	[redacted]	[redacted]	[redacted]	[redacted]
2	RWE plus ZUMA-2 for brexu-cel outcomes[1]	[redacted]	[redacted]	[redacted]	[redacted]
3	15% alloSCT for R-BAC patients[1]	[redacted]	[redacted]	[redacted]	[redacted]
4	2024-25 NHSE £58,964 tariff	[redacted]	[redacted]	[redacted]	[redacted]
5	Updated cost base (2024-25 cost year)[2]	[redacted]	[redacted]	[redacted]	[redacted]
6	Pre-prog utility capped (post prog weighted)[3]	[redacted]	[redacted]	[redacted]	[redacted]
7	Pre-prog utility ZUMA-2 (post prog weighted)	[redacted]	[redacted]	[redacted]	[redacted]
8	38% IVIg post brexu-cel (based on ZUMA-2)	[redacted]	[redacted]	[redacted]	[redacted]
9	15% IVIg post brexu-cel (clinician advice)	[redacted]	[redacted]	[redacted]	[redacted]
10	60mo cure assumption for LTS (vs 48mo)[4]	[redacted]	[redacted]	[redacted]	[redacted]
11	SMR of 3.0 (not an age-matched SMR)[4]	[redacted]	[redacted]	[redacted]	[redacted]
12	Adjusting for pre-infused patient outcomes[5]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case (1,2,3,7,9)		[redacted]	[redacted]	[redacted]	[redacted]
As above, with severity modifier 1.7		[redacted]	[redacted]	[redacted]	-
As above with severity modifier 1.2		[redacted]	[redacted]	[redacted]	-

1 See section 3 for more details; 2 The majority of cost inputs are from NHS Reference Costs and the 2024-25 tariffs are unavailable, 2023-24 remains latest available data; 3 The committee suggested an un-anchored 0.68 but see explainer above for why a weighted value is needed; 4 48month vs 60month LTS; 5 all other settings as for the revised company base case listed in the row below

As shown in Table 2, the company incorporated several preferred assumptions into its revised base case analysis (assumptions 1, 2, 3, 7 and 9):

- Patient age fixed at 66 years
- RWE plus ZUMA-2 for brexu-cel outcomes

- 15% alloSCT for R-BAC patients
- Pre-progression utility from ZUMA-2 (post-progression weighted)
- 15% IVIg use post brexu-cel (based on clinician advice)

Based on these, the revised company base case produced an ICER of £[redacted] per QALY, which represents a [redacted]% increase compared with the original base case (£50,270 per QALY).

In the two last columns, the company presented additional scenarios applying severity modifiers of 1.7 and 1.2. However, it is unclear how the company has implemented the severity modifier within the ICER calculation. According to the NICE reference case, the appropriate method is to calculate ICER as:

ICER=Incremental cost / (Incremental QALYs × Severity modifier)

For example, using the revised base case inputs, this would be £[redacted] ÷ ([redacted] × severity modifier). The company's reported figures do not align with this approach, suggesting their application of the severity modifier may not be methodologically correct. The EAG will therefore provide corrected results using a 1.2 severity modifier in the following section.

In addition, the company's revised base case does not include key supporting outputs normally expected for decision-making, including:

- total costs,
- total life years gained,
- probabilistic base case results, and
- sensitivity analyses.

These omissions limit the ability to fully validate and interpret the robustness of the company's updated model.

The EAG identified several errors in the company's submitted economic model. Upon opening, the file displays a warning that "this worksheet contains links to one or more external sources that could be unsafe." The EAG replicated the company's preferred assumptions (as used in the last verified version of the model). However, in the SoC arm, the company used data from the worksheet *Results vs SoC (REVISED)*, while in the PSA there is no option to select this revised dataset. If the selection is amended and the PSA re-run, the CEAC continues to rely on the original SoC option. To address this, the EAG applied a new macro for running the CEAC in its assessment. Another issue concerns the possibility of the PFS value exceeding the OS value. According to the company's approach, for some cycles PFS is greater

than OS, which results in a negative value for total undiscounted post-progression years. The correct approach is that PFS should always be less than or equal to OS. Additionally, for the scenario *'Adjusting for pre-infused patient outcomes'*, the company did not provide sufficient detail to allow replication of the analysis.

3 EAG response to Company Technical Addendum

This section details the preferences of survival extrapolation. Table 4 gives an overview of the estimated survival under the company and EAG base cases. Note, there is minor disagreement for R-BAC attributable to the differences in half-cycle correction implementation and rounding.

Table 4: Overview of landmark survival for outcomes

Population Outcome	24 months	48 months	60 months
Brexu-cel PFS: Company	[redacted]	[redacted]	[redacted]
Brexu-cel PFS: EAG	[redacted]	[redacted]	[redacted]
Brexu-cel OS: Company	[redacted]	[redacted]	[redacted]
Brexu-cel OS: EAG	[redacted]	[redacted]	[redacted]
R-BAC PFS: Company	[redacted]	[redacted]	[redacted]
R-BAC PFS: EAG	[redacted]	[redacted]	[redacted]
R-BAC OS: Company	[redacted]	[redacted]	[redacted]
R-BAC OS: EAG	[redacted]	[redacted]	[redacted]

3.1 *OS modelling for brexu-cel*

The draft guidance mentioned describes the committee preference to combine the SACT and ZUMA-2 sources, but EAG considers that the draft guidance is unclear on how the data from these two sources should be combined. It is possible that the company's interpretation of pooling the sources into a single dataset is consistent, where each person's data is considered equally representative of the desired modelling population, or that the ZUMA-2 data should only inform long-term shape of

the extrapolation by distinguishing by the source of each set of data using a covariate in the survival model, similar to the EAG's approach prior to AC1. However, the EAG notes that the company has only used data from SACT for people who received brexu-cel after August 2022 (n=43), rather than the whole SACT dataset (n=92), also discarding the longer follow-up of the earlier recipients of brexu-cel. This reduction means the SACT dataset carries lower weighting when combined with the ZUMA-2 data (n=68).

From the pooled datasets, the company's preferred extrapolation was the log-normal, which had the best statistical fit according to AIC and BIC. The EAG considers this extrapolation reasonable but explores the impact of modelling using the whole SACT dataset and combining with the ZUMA-2 data in either a pooled approach, or where the ZUMA-2 data only informs the shape of the extrapolations fitted to the SACT data. The EAG prefers the latter approach, as it considers that the SACT data are the most representative of NHS patients, and should not be given roughly equal weighting with the ZUMA-2 data. It also is a fairer comparison of two sources of RWE across the arms. The EAG maintains using the log-normal extrapolation but explores the impact of using the exponential model in a scenario analysis, with these two models having the best statistical fit according to AIC and BIC.

3.1.1 Outcomes for non-infused people

The company provided output for PFS and OS for people who were not infused with brexu-cel in the ZUMA-2 trial. The company's first plot (Figure 4 of Company comments) suggests that PFS and OS outcomes are almost identical for the 6 people not infused.

However, Figure 5 of the Company DG comments reportedly also represents OS for this same population but appears to begin with ~20 people at risk, with the outcomes clearly differing from the previous figure.

The EAG is unable to explain this discrepancy, however the economic model appears to use outcomes as they appear in Figure 4 for PFS and OS. The EAG is unclear whether Figure 5 has any relevance to the rest of the company submission.

The Kaplan-Meier estimator for PFS and OS for these people from ZUMA-2 is not provided, but according to the log-normal extrapolation the outcomes for this

population are [redacted]. The EAG has not been provided with sufficient information to comment on whether the log-normal model is a sensible choice, however, notes the extrapolation is highly consistent with several other parametric models that can be implemented within the economic model.

3.2 *PFS modelling for brexu-cel*

For PFS, data from the O'Reilly paper were pooled with ZUMA-2, as SACT did not report PFS. The full infused population was used from O'Reilly, as no breakdown by date of infusion was available. The company's preferred extrapolation from this pooled data was the log-normal, which was the model with the best statistical fit according to AIC and BIC. The EAG considers this extrapolation reasonable, but for the EAG base case, it implements survival models where the ZUMA-2 data only informs the shape of the extrapolations fitted to the O'Reilly data, using the log-normal model which had the best statistical fit.

3.3 *R-BAC OS*

For R-BAC, the company fitted separate models to re-created datasets, distinguishing whether subsequent alloSCT was received or not, and then combined the extrapolations assuming that 15% of the population would receive alloSCT.
For people not receiving alloSCT, these outcomes were taken from McCulloch et al.,[2] whilst outcomes for people who did receive alloSCT came from Liebers et al.[3]

Note that in Figure 11 of the company DG comments, the extrapolations are not a direct extrapolation of the pooled data informing the plotted Kaplan-Meier estimator but are instead weighted averages of the respective extrapolations of the alloSCT and non-alloSCT groups.
Previously, the EAG modelled the proportion receiving alloSCT to be [redacted]%, meaning the any assumptions relating to cure for R-BAC were less impactful on the cost-effectiveness analysis. Increasing this proportion to 15% means that the potential for cure from alloSCT should not be ignored, however the company has not enabled this

functionality in the economic model to make equivalent cure assumptions for R-BAC. This is despite the data in Liebers et al. suggesting a similar plateau to alloSCT and brexu-cel,[3] and alloSCT having curative potential despite high early mortality.[7, 8] The EAG notes that at 48 and 60 months, there are ~[redacted]% and ~[redacted]% alive in the R-BAC population respectively, the majority of which are from the alloSCT subgroup (~[redacted]%). The EAG has been able to apply the brexu-cel cure assumption for the R-BAC population in its base case analysis (i.e. from 60 months, SMR =3, increased utility value) which is applied to the alloSCT subgroup only.

In the company's ITT scenario analysis, they also included the non-infused brexu-cel population to inform outcomes for people who don't receive R-BAC.

The EAG notes an error in this section. Careful inspection of Figure 13 shows that it is actually the extrapolation of PFS data from Liebers et al., not OS. Also, the figure numbering jumps from 13 to 18 in the next section, and the EAG is unsure whether the company submission document is complete.

3.4 *R-BAC PFS*

Like for OS, the company combined extrapolations fitted to recreated data from Liebers et al.[3] and McCulloch et al.[2] to account for those who did and did not receive subsequent alloSCT respectively, with a separate scenario for non-infused people using the same approach as for OS. Log-normal extrapolations were used for both datasets, which the EAG accepts and uses in the EAG base case.
However, the EAG also applies the brexu-cel cure assumption to PFS, same as for OS.
The EAG notes several errors in this section of the company comments relating to the figures. Figure 18 is the PFS outcome for people who received alloSCT from McCulloch et al., however the company actually utilises the non-alloSCT data from this source. Figure 19 is incorrectly captioned as "Overall survival", when the plot and section are actually progression-free survival. Figure 19 is also for people who did receive alloSCT.
Figure 20 shows the extrapolations from Figure 18; however these are not used by the company, with the outcomes for people receiving alloSCT coming from Liebers et al.

4 EAG additional analyses

4.1 *Company's cost effectiveness results*

Table 5 and Table present the company's deterministic base-case cost-effectiveness results for brexu-cel compared with standard of care (SoC), as prepared by the EAG. Table 5 shows the results after the EAG amended the calculation of the severity modifier, while Table 6 presents the results after additionally correcting an error in progression-free survival (PFS) modelling, ensuring that PFS is always less than or equal to overall survival (OS).

Table 5: Company's deterministic base-case results (severity modifier amended)

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) (Without severity weighting)	ICER with severity weighting (x1.2)*
SoC (Placeholder)	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

* £[redacted] = £[redacted] ÷ ([redacted] × 1.2)

* In these results, the calculation of the severity modifier was amended by the EAG. The company's value for incremental QALYs, applying a severity modifier of 1.2, was [redacted], and the ICER with severity weighting was £[redacted]. (see section 2.13)

Table 6: Company's deterministic base-case results (severity modifier and PFS error amended)

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) (Without severity weighting)	ICER with severity weighting (x1.2)*
SoC (Placeholder)	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

* £[redacted] = £[redacted] ÷ ([redacted] × 1.2)

* In these results, the calculation of the severity modifier was amended by the EAG. Furthermore, PFS is always less than or equal to OS. (see section 2.13 for more details on these errors)

4.2 *Overview of the company and EAG's base case after AC1*

Table 7 summarizes the key changes in assumptions and approaches between the company's original model, the EAG's original assessment, and the company's updated model, along with the EAG's corresponding updates. It highlights modifications across multiple areas, including the population and extrapolation methods, time horizon, half-cycle correction, cure time points, costs and effects of alloSCT, mortality adjustment, IVIg therapy needs, adverse event sources, CAR T costs, and HRQoL estimates. The table also indicates whether a severity modifier was applied. Abbreviations used in the table are defined at the end for clarity. This comparison illustrates how the company's new approach incorporates additional real-world evidence, updated data sources, and revised assumptions to better align with the committee's preferred methodology and guidance.

Table 7: Overview of the company and EAG's base case after AC1

Area of change	Company's original Value/approach	EAG's original value/approach	Company's new approach	EAG's new approach	Related section
Population approach and extrapolation	Intervention: Using the mITT from ZUMA-2 Comparator: R-BAC based on McCulloch (2020)	Patient age - 66 years Intervention: Using the ITT population (leukapheresed patients) from real world sources. Comparator: Comparator: R-BAC based on McCulloch (2020) with using the updated extrapolation with excluding the alloSCT effects	Patient age - 66 years Intervention: Using a pooled dataset based on ZUMA-2 plus SACT (NDRS, 2024) for OS and ZUMA-2 plus UK RWE (O'Reilly 2024) for PFS Comparator: Updated R-BAC outcomes were estimated separately for patients not receiving subsequent alloSCT (estimated from McCulloch 2020) and patients receiving subsequent alloSCT (data from Liebers 2025).	Patient age - 66 years Intervention: The same as Company's new approach, but using all the SACT data Comparator: The same as company's new approach	2.1, 2.2, 2.4, 2.5, 2.6, 3.1, 3.2, 3.3
Time horizon	Using the company's approach (fixed 50-year time horizon)	Using the 100 years minus the starting age as a time horizon	Company's original approach	EAG's original approach	-
Half-cycle correction	Using cycle midpoints	Use of average health state occupancy for half-cycle correction	Company's original approach	EAG's original approach	-
Cure time point	Using the 48-month LTS timepoint.	Using the 60-month LTS timepoint	Company's original approach	Using the 60-month LTS timepoint (for the brexu arm and the SoC arm in patients who received alloSCT)	2.7

Area of change	Company's original Value/approach	EAG's original value/approach	Company's new approach	EAG's new approach	Related section
Costs of alloSCT	Including alloSCT in both arms ([redacted]% in brexu-cel and 31% in R-BAC) with updated costs	Including alloSCT in both arms ([redacted]% in brexu-cel and [redacted]% in R-BAC) with updated costs	Including alloSCT in both arms ([redacted]% in brexu-cel and 15% in R-BAC) with updated costs	The same as company's new approach	2.3
Mortality Rate Adjustment Factor (MRAF)	Using the MRAF of 1.09	Using the MRAF of 3.00	Company's original approach	EAG's original approach	2.8
IVIg Therapy Needs	Using [redacted]% for patients requiring IVIg therapy for a period of one year	Using 38% for patients requiring IVIg therapy for a period of one year	15% IVIg post brexu-cel (clinician advice) for 1 year	EAG's original approach	2.11
Adverse events source	Incidence rates that are reported in the main submission	Using the most updated incidence rates	Company's original approach	EAG's original approach	-
CAR T tariff costs	Using the tariff costs for CAR T infusion and monitoring, valued at £41,101	Using the tariff costs for CAR T infusion and monitoring, valued at £ £60,462 + ICU costs (with the probability of 27% for requiring ICU)	Company's original approach	EAG's original approach	2.9
Pre/Post-Progression, and LTS HRQoL Estimates	Pre-Progression; ZUMA-2 value ([redacted]), Post-Progression: [redacted], LTS: GPU	Pre-Progression; GPU, Post-Progression: Direct TA502 value (0.68), LTS: GPU	Pre-Progression; Original approach Post- Progression: weighted	EAG's original approach	2.10
Severity modifier	No	1.2	1.2	EAG's original approach	2.12
mITT: modified Intent-to-Treat; ITT: Intent-to-Treat; OS: Overall Survival; PFS: Progression-Free Survival; SACT: Systemic Anti-Cancer Therapy; NDRS: National Disease Registration Service; RWE: Real-World Evidence; LTS: Long-Term Survivor; alloSCT: Allogeneic Stem Cell Transplant; MRAF: Mortality Rate Adjustment Factor; IVIg: Intravenous Immunoglobulin; CAR T: Chimeric Antigen Receptor T-cell therapy; HRQoL: Health-Related Quality of Life; GPU: General Population Utility					

4.3 *Impact of EAG changes on the company's base-case results*

Table 8 presents the results of EAG's exploratory post-ACM1 analyses for brexu-cel versus standard of care (SoC), focusing on incremental costs, incremental QALYs, and ICERs (£/QALY) under various preferred assumptions. The company's base case (post-ACM1) serves as the reference scenario. Among the individual scenario analyses, the Mortality Rate Adjustment Factor (MRAF = 3.00) assumption led to the largest increase in ICER (+[redacted]%), while the half-cycle correction assumption resulted in the smallest ICER change (-[redacted]%). The CAR T tariff costs scenario also notably increased the ICER (+[redacted]%), while changes in the time horizon had minimal impact (+[redacted]%). In terms of incremental costs, the CAR T tariff costs scenario incurred the highest incremental cost (£[redacted]). Incremental QALYs ranged from [redacted] in the Population approach and extrapolation scenario to [redacted] for the half-cycle correction scenario. Overall, these analyses demonstrate the sensitivity of the ICER to key model assumptions and highlight which factors most strongly drive changes in cost-effectiveness.

Table 8: Results of EAG's exploratory analysis -post ACM1 analyses

EAG's preferred assumption based on issues		Brexu-cel vs SoC*			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Impact
Company's base case (post ACM1 results)		[redacted]	[redacted]	[redacted]	[redacted]
1	Population approach and extrapolation: The same as Company's new approach, but using all the SACT data (brexu-cel arm)	[redacted]	[redacted]	[redacted]	[redacted]
2	Time horizon: Using the 100 years minus the starting age as a time horizon	[redacted]	[redacted]	[redacted]	[redacted]
3	Half-cycle correction: Use of average health state occupancy for half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]
4	Cure time point: Using the 60-month LTS timepoint (for the brexu arm and the SoC arm in patients who received alloSCT)	[redacted]	[redacted]	[redacted]	[redacted]
5	Mortality Rate Adjustment Factor (MRAF): Using the MRAF of 3.00	[redacted]	[redacted]	[redacted]	[redacted]
6	IVIg Therapy Needs: Using 38% for patients requiring IVIg therapy for a period of one year	[redacted]	[redacted]	[redacted]	[redacted]
7	Adverse events source: Incidence rates that are reported in the main submission	[redacted]	[redacted]	[redacted]	[redacted]
8	CAR T tariff costs: Using the tariff costs for CAR T infusion and monitoring, valued at £60,462 + ICU costs (with the probability of 27% for requiring ICU)	[redacted]	[redacted]	[redacted]	[redacted]
9	Pre/Post-Progression, and LTS HRQoL Estimates: Pre-Progression; GPU, Post-Progression: Direct TA502 value (0.68), LTS: GPU	[redacted]	[redacted]	[redacted]	[redacted]
Combined 1-9 (EAG's base case-post ACM1)		[redacted]	[redacted]	[redacted]	[redacted]

ITC: Indirect Treatment Comparison; QALY: Quality-Adjusted Life Year; SCT: Stem Cell Transplant; EAG: External Assessment Group; LTS: Long-Term Survivor; IVIg: Intravenous Immunoglobulin; CAR T: Chimeric Antigen Receptor T-cell therapy; HRQoL: Health-Related Quality of Life; GPU: General Population Utility; MRAF: Mortality Rate Adjustment Factor; SACT: Systemic Anti-Cancer Therapy; ICU: Intensive Care Unit; ACM1: First Appraisal Committee;
*The severity modifier of 1.2 is applied for all exploratory analyses

4.4 *EAG* Deterministic and probabilistic base-case results

Table and Table present the deterministic and probabilistic base-case results for brexu-cel versus standard of care (SoC) post-ACM1.

In the deterministic analysis (Table), brexu-cel has total costs of £[redacted], total QALYs of [redacted], and an incremental cost of £[redacted] versus SoC, resulting in an ICER of £[redacted] per QALY. The incremental net health benefits (INHB) at a £20,000 and £30,000 willingness-to-pay (WTP) threshold are [redacted] and [redacted], respectively, indicating that the intervention is not cost-effective at these thresholds.

In the probabilistic analysis (Table), which incorporates parameter uncertainty, brexu-cel shows slightly lower total costs (£[redacted]) and slightly higher total QALYs ([redacted]) compared with the deterministic base case. The incremental cost is marginally lower at £[redacted], and the ICER is slightly reduced to £[redacted] per QALY.

Overall, the probabilistic analysis confirms the deterministic base-case findings, showing that while the ICER is slightly lower and total costs marginally reduced, [redacted]

Figure 2 presents the cost-effectiveness scatter plot for the post-ACM1 analysis. All sampled points are located in the [redacted], indicating that the intervention (brexu-cel) is [redacted]costly but also [redacted] effective compared with standard of care.

Figure 3 shows the cost-effectiveness acceptability curve (CEAC). Based on this curve, the probability that the intervention is cost-effective compared with standard of care at a £30,000 per QALY threshold in the UK is [redacted]%.

Table 9: EAG's deterministic base-case results -post ACM1

Technologies	Total costs	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay

*The severity modifier of 1.2 is applied for all exploratory analyses

Table 10: EAG Probabilistic results -post ACM1

Technologies	Total costs	Total QALY	Incremental costs (£)	Incremental QALYs*	ICER (£/QALY)	INHB (£20,000 WTP)	INHB (£30,000 WTP)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years; INHB: incremental net health benefit or incremental net benefit; WTP: willingness to pay
*The severity modifier of 1.2 is applied for all exploratory analyses

Figure 2: Cost-effectiveness scatterplot-post ACM1

Figure 3: Cost-effectiveness acceptability curve-post ACM1

4.5 *EAG's scenario analysis results*

Table 11 presents the results of EAG's scenario analyses post-ACM1, showing the impact of different model assumptions on incremental costs, incremental QALYs, and ICERs for brexu-cel versus standard of care. The EAG base case (post-ACM1) is used as the reference scenario, with an ICER of £[redacted] per QALY. Among the individual scenarios, the "No SMR adjustment" assumption produced the largest reduction in ICER (-[redacted]%), while the "Exponential OS distribution" and "MRAF = 5.00" scenarios resulted in the largest increases in ICER (+[redacted]% and +[redacted]%, respectively). Incremental costs varied across scenarios, with the population approach using pooled SACT/ZUMA-2 data producing the highest incremental cost (£[redacted]), and the CAR T tariff costs (company's approach) scenario producing the lowest incremental cost (£[redacted]). Incremental QALYs ranged from [redacted] to [redacted], reflecting differences in assumptions about survival, cure time points, and health-related quality of life. Overall, the table illustrates which assumptions have the greatest impact on cost-effectiveness and highlights the sensitivity of the ICER to key model parameters.

Table 11: EAG's Scenario analysis results-post ACM1

Scenario		Incremental costs (£)	Incremental QALYs*****	ICER (£/QALY)	Impact
EAG Base case (post ACM1)		[redacted]	[redacted]	[redacted]	[redacted]
Population approach*	Using a pooled dataset based on ZUMA-2 plus SACT (NDRS, 2024-not all SACT data) for OS and ZUMA-2 plus UK RWE (O'Reilly 2024) for PFS (company's new approach)	[redacted]	[redacted]	[redacted]	[redacted]
	Following the EAG approach by using the "Exponential" distribution for overall survival of brexu-cel.	[redacted]	[redacted]	[redacted]	[redacted]
	SACT-ITT-Leukapheresed population	[redacted]	[redacted]	[redacted]	[redacted]
	Using the log-normal for OS from pooling of SACT (whole) and ZUMA-2	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	Time horizon: 50 years (company's approach)	[redacted]	[redacted]	[redacted]	[redacted]
Half-cycle correction	Using cycle midpoints (company's approach)	[redacted]	[redacted]	[redacted]	[redacted]
Cure time point****	Using the 48-month LTS timepoint (company's approach-only for brexu-cel)	[redacted]	[redacted]	[redacted]	[redacted]
	Using the 48-month LTS timepoint (applying for both arms)	[redacted]	[redacted]	[redacted]	[redacted]
	Using the 36-month LTS timepoint (applying for both arms)	[redacted]	[redacted]	[redacted]	[redacted]
	Using the 72-month LTS timepoint (applying for both arms)	[redacted]	[redacted]	[redacted]	[redacted]
	Without applying any cure time point (applying for both arms)	[redacted]	[redacted]	[redacted]	[redacted]
Mortality Rate Adjustment Factor (MRAF)	Using the MRAF of 1.09 (company's approach)	[redacted]	[redacted]	[redacted]	[redacted]
	Using the MRAF of 5.00	[redacted]	[redacted]	[redacted]	[redacted]
	No SMR adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Scenario		Incremental costs (£)	Incremental QALYs*****	ICER (£/QALY)	Impact
EAG Base case (post ACM1)		[redacted]	[redacted]	[redacted]	[redacted]
IVIg Therapy Needs	Using 15% for patients requiring IVIg therapy for a period of one year (company's approach)	[redacted]	[redacted]	[redacted]	[redacted]
	Using 38% for patients requiring IVIg therapy for two years	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events source**	Incidence rates that are reported in the main submission (company's approach)	[redacted]	[redacted]	[redacted]	[redacted]
CAR T tariff costs	Using the tariff costs for CAR T infusion and monitoring, valued at £41,101 (company's approach)	[redacted]	[redacted]	[redacted]	[redacted]
Pre/Post-Progression, and LTS HRQoL Estimates	Pre-Progression: ZUMA-2 value ([redacted]), post-progression: weighted, LTS: GPU (company's approach)	[redacted]	[redacted]	[redacted]	[redacted]
	Pre-Progression: ZUMA-2 value ([redacted]), post-progression: [redacted], LTS: GPU*0.90	[redacted]	[redacted]	[redacted]	[redacted]
	Pre-Progression; TA502 value (0.78), Post-Progression: Direct TA502 value (0.68), LTS: GPU	[redacted]	[redacted]	[redacted]	[redacted]

mITT: Modified intention to treat; ITT: Intention to treat; OS: Overall survival; EFS: Event-free survival; GPU: general population utility; ICU: intensive care unit; IVIg: Intravenous immunoglobulin; MRAF: mortality rate adjustment factor; EAG: external assessment group; LTS: long term survivorship; HRQoL: health related quality of life;
* Baseline characteristics and other related data from each source are presented in the appendix 6.5 of original EAG report
**The new values are presented in the appendix 6.5 of original EAG report
***The company's value of cost of alloSCT in the original company submission was £47,508.32.
****In the scenarios with applying for both arms, in SoC arm this assumption is applied only for patients who received alloSCT.
*****The severity modifier of 1.2 is applied for all exploratory analyses.

5 References

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