NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more lines of systemic treatment (review of TA677)

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using brexucabtagene autoleucel in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2025

Note that this document is not NICE's final guidance on brexucabtagene autoleucel. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using brexucabtagene autoleucel in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 13 August 2025
- Second evaluation committee meeting: 2 September 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Brexucabtagene autoleucel should not be used to treat relapsed or refractory mantle cell lymphoma in adults who have had 2 or more lines of systemic treatment that included a Bruton's tyrosine kinase inhibitor.

1.2 This recommendation is not intended to affect treatment with brexucabtagene autoleucel that was funded with managed access before final guidance was published. If this applies, NHS England and the company have an arrangement to make sure people who started treatment during the managed access period can continue the treatment process with brexucabtagene autoleucel.

What this means in practice

Brexucabtagene autoleucel is not required to be funded in the NHS in England to treat relapsed or refractory mantle cell lymphoma in adults who have had 2 or more lines of systemic treatment that included a Bruton's tyrosine kinase inhibitor. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that brexucabtagene autoleucel is value for money in this population.

Why the committee made these recommendations

This evaluation reviews the evidence for brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma (NICE technology appraisal guidance 677). It also reviews new evidence collected during the managed access period, which includes evidence from the company's clinical trial and from people having treatment in the NHS in England.

Standard care for relapsed or refractory mantle cell lymphoma in people who have had 2 or more lines of systemic treatment that included a Bruton's tyrosine kinase inhibitor is usually rituximab-containing chemoimmunotherapy (R-BAC).

Evidence comes from a single-arm study of brexucabtagene autoleucel that does not compare it with R-BAC. There are no trials directly comparing brexucabtagene autoleucel with R-BAC. An indirect comparison suggests brexucabtagene autoleucel may increase how long people have before their cancer gets worse and how long they live compared with R-BAC. But this is uncertain.

There are also uncertainties in the economic model because:

- there is not enough evidence to tell if the cancer can be 'cured' in people having brexucabtagene autoleucel treatment
- it is not known how long people live because the clinical trial is ongoing
- the age of people in the model does not represent the likely NHS population who would have brexucabtagene autoleucel treatment
- the model does not include outcomes for people who start leukapheresis but do not complete infusion with brexucabtagene autoleucel.

The cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. So, brexucabtagene autoleucel should not be used.

2 Information about brexucabtagene autoleucel

Marketing authorisation indication

2.1 Brexucabtagene autoleucel (Tecartus, Gilead Sciences) is indicated for 'the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for brexucabtagene autoleucel.

Price

2.3 The list price of a course of treatment with brexucabtagene autoleucel is £316,118 (company submission).

2.4 The company has a commercial arrangement, which would have applied if brexucabtagene autoleucel had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Gilead Sciences will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Gilead Sciences, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Mantle cell lymphoma

3.1 Mantle cell lymphoma is a subtype of non-Hodgkin lymphoma and can have debilitating symptoms. Rates of relapse after initial treatment are high. The condition has a substantial effect on quality of life and outcomes for people with refractory or relapsed disease are poor. Treatment options after a Bruton's tyrosine kinase inhibitor (BTKi) are normally associated with poorer responses than treatment at earlier lines and rapid disease progression. The patient expert explained that the disease always has the potential to relapse and that the side effects of existing treatments significantly reduce quality of life. They also explained that people with the condition often experience considerable psychological stress because of the constant fear of relapse and the knowledge that there are few effective treatments available. 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 that had given them back a high

quality of life. The clinical experts explained the potential for improved survival and the possibility of a functional cure for some patients who have a long-term response to brexucabtagene autoleucel. The committee concluded that there is an unmet need in this population and that patients and healthcare professionals would welcome new treatments.

Clinical management

Treatment pathway

3.2 First-line treatment of mantle cell lymphoma is usually rituximab-containing chemoimmunotherapy, most commonly rituximab, bendamustine and cytarabine (R-BAC). For fitter people, autologous stem-cell transplantation is an option. Second-line treatment is usually ibrutinib, a BTKi. Treatment options after relapse on a BTKi include more rituximab-containing chemoimmunotherapy (typically R-BAC) or, if this is not suitable, palliative care. For a small number of eligible people, consolidating a BTKi response with allogeneic stem-cell transplant (alloSCT) can be considered, but only while they are still responding to treatment with a BTKi. Treatment with brexucabtagene autoleucel is proposed as an option for people whose disease has relapsed or is refractory after a BTKi. The committee concluded that there are very limited treatment options for relapsed or refractory mantle cell lymphoma when the disease progresses after second-line treatment with a BTKi. The clinical experts explained that people who are considered fit enough for treatment with brexucabtagene autoleucel would also be considered fit enough to have R-BAC. The committee concluded that R-BAC is the appropriate comparator for brexucabtagene autoleucel for treatment of mantle cell lymphoma that is relapsed or refractory after 2 or more lines of systemic treatment that included a BTKi.

Clinical effectiveness

ZUMA-2

3.3 The clinical-effectiveness evidence for brexucabtagene autoleucel came from ZUMA-2, an ongoing, phase 3, multicentre single-arm study. The company presented results from the study for a modified intention-to-treat (mITT) group that consisted of 68 people who had completed treatment with brexucabtagene autoleucel, adjusted from 74 in the whole ITT population. The mITT group was used in the economic analysis of brexucabtagene autoleucel. The company explained this is because not everyone who begins the treatment process will be successfully infused with brexucabtagene autoleucel. The primary outcome measure was overall response rate, defined as complete response or partial response. Of the 68 people in the mITT group, 62 (91%) had an objective response (95% confidence interval [CI] 50.1 to 73.2) and, of these, 46 (68%) had a complete response (95% CI 55.2 to 78.5). Duration of response was a secondary outcome. Median duration of response was 28.2 months among the 62 responders, 46.7 months for those with a complete response (n=46) and 2.2 months for those with a partial response (n=16). Other secondary outcomes were progression-free survival (PFS) and overall survival (OS). Median PFS was 25.3 months (95% CI 12.7 to 46.6 months), and, at the time of analysis, median follow up was 67.8 months (95% CI 58.2 to 88.6 months) and 44 people (65%) had disease progression or died. Median OS was 46.5 months (95% CI 24.9 to 60.2 months) and 44 people (65%) had died at the time of analysis. The committee concluded that treatment with brexucabtagene autoleucel is clinically effective, with a high overall response rate.

Generalisability of ZUMA-2

3.4 The committee noted that ZUMA-2 did not include anyone from the UK. It included people who had had a median of 3 prior therapies, all with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (which means that their activities are relatively unrestricted by their disease) and had a mean age of 63.2 years. The clinical experts said people having treatment with brexucabtagene autoleucel would need to have a good performance status to tolerate the treatment's toxicity. The

EAG thought that the ZUMA-2 population is likely to be younger and in better health than people with relapsed or refractory mantle cell lymphoma in the NHS who have had 2 prior lines of treatment, including a BTKi such as ibrutinib. The company agreed that the mean age of 63.2 years is younger than would be expected for people with relapsed or refractory mantle cell lymphoma in the UK, but this is probably reflective of people who would be eligible for treatment with brexucabtagene autoleucel in clinical practice. The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) explained that for the most recent 3-year period up to May 2025, the Systemic Anti-Cancer Therapy (SACT) dataset showed that the mean age of people having treatment with brexucabtagene autoleucel was 66. They also explained that with ibrutinib now established as second-line standard care in the NHS, people in the NHS with relapsed or refractory mantle cell lymphoma will have had fewer treatments before treatment with brexucabtagene autoleucel than people in ZUMA-2. The SACT data was limited to people with ECOG performance status of 0 or 1, as was the case with ZUMA-2. The committee noted that other evidence is available for brexucabtagene autoleucel (see section 3.7). The committee concluded that results from ZUMA-2 were generalisable to patients in the NHS but it preferred to use the mean age of 66 from SACT as the starting age in the economic model.

Real-world evidence for R-BAC

3.5 For the comparator treatment, R-BAC, the company used data from a retrospective cohort study by McCulloch et al. (2020). This provided outcomes for people with mantle cell lymphoma that progressed after treatment with a BTKi in the UK and Italy. The study included 36 people who had R-BAC across 23 centres between October 2015 and March 2019. The median age was 66 years (range 43 to 81 years) and the median number of previous systemic therapies was 2 (range 1 to 6). The overall response rate to R-BAC was 83%, with a complete response rate of 60%. The median PFS was 10.1 months (95% CI 6.9 to 13.3) and the

median OS was 12.5 months (95% CI 11.0 to 14.0). The EAG agreed with the company that this real-world evidence was the most appropriate source of data for the safety and efficacy of R-BAC. But it had concerns about potential uncertainties because of the small sample size, retrospective nature of the study and, especially, the risk of bias towards selecting younger people for treatment. Because of this potential risk of selection bias, the EAG had concerns that the naive comparison with McCulloch (2020) is likely to overestimate the real-world efficacy of R-BAC. But in the absence of more suitable evidence, the EAG agreed with the company that McCulloch et al. (2020) is the most appropriate source of data for R-BAC in people with relapsed or refractory mantle cell lymphoma. The committee concluded that McCulloch et al. (2020) was the most appropriate source of data to enable a naive comparison with brexucabtagene autoleucel. But it noted that the outcomes from McCulloch were uncertain and would welcome further clinical input on whether these are generalisable to the NHS.

Real-world evidence for brexucabtagene autoleucel

3.6 In the first appraisal of brexucabtagene autoleucel (NICE's technology appraisal on brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma, from here TA677), the company did a naive comparison between brexucabtagene autoleucel and R-BAC because of a lack of any direct comparative evidence. The committee recalled that a matching-adjusted indirect comparison was done for TA677 comparing ZUMA-2 PFS and OS with McCulloch et al. (2020). But this was limited by its small sample size and limited number of matching covariates, and was not used to inform the company's economic model in that evaluation. The company noted that other sources of real-world evidence for the safety and effectiveness of brexucabtagene autoleucel had become available since TA677, including SACT data collected as part of the managed access agreement. The company preferred to use only data from ZUMA-2 in its economic model. The company accepted that survival estimates in its economic model were more optimistic than those derived from the

SACT data. But it suggested this was because of early production-related problems that had resulted in delays to starting treatment with brexucabtagene autoleucel for some people. The EAG did not agree with the company's choice to use data from ZUMA-2 only, and preferred to include data from SACT and other real-word sources for brexucabtagene autoleucel in its base case. This is because the naive comparison would then be between ZUMA-2 with pooled real-world evidence and the real-world evidence from the McCulloch et al. (2020) study, rather than comparing real-world evidence with ZUMA-2 only. The EAG explained that it used a pooled analysis from real-world sources to increase the overall sample size, overcome issues with the generalisability of ZUMA-2 and provide more robust survival estimates for brexucabtagene autoleucel. The EAG also used the longer follow-up data from ZUMA-2 to inform the most appropriate extrapolation. In addition to SACT data, the EAG used the following studies:

- a UK study by O'Reilly et al. (2024) that reported real-world outcomes for brexucabtagene autoleucel in patients from 12 treatment centres between February 2021 and June 2023. The median follow up was 13.3 months. The EAG noted that this population had considerable overlap with the SACT dataset. But it explained that while the SACT dataset contained OS outcomes, it did not collect data on progression events. So, the EAG used O'Reilly et al. (2024) to obtain PFS data for inclusion in the economic model
- the DESCAR-T registry that details the intention-to-treat (ITT) population in France, enrolled after European Medicines Agency approval for brexucabtagene autoleucel. This registry included 181 people from 24 French treatment centres, with a median follow up of 14.2 months. The population who were successfully infused with brexucabtagene autoleucel comprised 152 people, while those who had leukapheresis (the process of collecting the white blood cells from which T-cells are isolated) but were not infused comprised 26 people (3 were excluded from analysis because of ongoing manufacture at date

of cutoff). Many people in this registry would not have met the ZUMA-2 eligibility criteria. This was because of factors such as the necessity of a bridging therapy other than corticosteroids or a BTKi (61.1%), a performance status of 2 or more (12%) or a prior malignancy (8.3%)

- the US Lymphoma CAR T Consortium of people who had leukapheresis between August 2020 and December 2021 at 16 treatment centres. Of the 189 people who had leukapheresis, 168 had brexucabtagene autoleucel infusion. As with DESCAR-T, many people in this registry would not have met the ZUMA-2 eligibility criteria for reasons such as disease severity or clinically significant comorbidities.

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. The company explained that the French and US datasets contained a substantial number of people with an ECOG performance score of 2 or more, and that these populations had more severe disease and poorer outcomes than would be expected in UK clinical practice. The clinical experts agreed that the French and US datasets need to be interpreted with caution because of these differences, and because the treatment pathways in France and the US might differ from the pathway in the UK. The EAG explained that the Kaplan–Meier OS plots from each of these real-world studies showed a high degree of consistency, and it did not consider that the observed differences in their populations justified their exclusion from the pooled analysis. The committee noted that the real-world evidence from SACT and O'Reilly et al. (2024) did not provide longer follow up than that provided by ZUMA-2, but it may provide greater generalisability to the UK population. The committee agreed that the US Lymphoma CAR T Consortium and DESCAR-T studies were likely to be less generalisable to the UK than the data from SACT for OS and from O'Reilly et al. (2024) for PFS. It concluded that it would prefer for

these UK real-world evidence datasets to be combined with data from ZUMA-2 to provide a pooled analysis for brexucabtagene autoleucel clinical outcomes in the economic model.

Subsequent allogenic stem cell transplant after R-BAC

3.7 The EAG suggested that the rate of subsequent alloSCT after treatment with R-BAC in McCulloch et al. (2020) was likely to be higher than would be seen in the NHS. The EAG explained that the study focused on younger, transplant-eligible people, in part to demonstrate the efficacy of R-BAC bridging to alloSCT, resulting in a high proportion (31%) of subsequent alloSCT. Clinical expert advice to the EAG noted that only a small subset of young, fit people will have alloSCT within the NHS, typically in first remission or sometimes immediately after second-line BTKi treatment to consolidate response. By the third line of treatment, most eligible people would have already had alloSCT earlier in the treatment pathway. The company explained that very few people had subsequent alloSCT after brexucabtagene autoleucel in ZUMA-2 (this value is commercial in confidence and cannot be reported here). It also explained that it had not adjusted for the rate of subsequent alloSCT after R-BAC, but that it had explored the issue in scenario analyses, with subsequent alloSCT rates of 15% and 40% after R-BAC. The EAG explained that McCulloch et al. (2020) reported the outcomes of people who had had alloSCT separately. The EAG preferred to use the datasets for PFS and OS with the effect of alloSCT removed because they considered these outcomes to be more likely to represent the outcomes for people having R-BAC in the NHS. The company disagreed with the EAG's approach, and suggested that the whole population from McCulloch et al. (2020) should be used because this represents the pathway in the NHS in the absence of brexucabtagene autoleucel. The clinical experts agreed with the company that in the absence of brexucabtagene autoleucel more people would have alloSCT because of a lack of any other effective treatment options. The clinical experts outlined that around 15% of people may have alloSCT after R-BAC in

NHS practice. They also agreed with the company that only a very small number of people would have alloSCT after having brexucabtagene autoleucel. The EAG preferred to use the much smaller value from ZUMA-2 for alloSCT after brexucabtagene autoleucel for both model arms. This is because the EAG's clinical expert stated it was not clear why this rate would differ from the rate of alloSCT after brexucabtagene autoleucel. It also clarified that the effects of subsequent alloSCT could not be removed from the brexucabtagene autoleucel arm, but that the costs would be equal across both treatment arms. The committee agreed with the EAG that subsequent alloSCT after R-BAC would not be as high as 31% in the NHS because of the relatively poor fitness of people at third relapse. But it did not accept that the value would be as low as the EAG had preferred to use in its economic model. The committee concluded that the outcomes for R-BAC would probably fall between the McCulloch et al. (2020) study curves for the full population (31% having alloSCT) and the EAG's preferred subpopulation curve (0% having alloSCT). So, it preferred a value of 15% of people having subsequent alloSCT after R-BAC, and for alloSCT costs and outcomes in the model to reflect this. The committee would welcome additional data and clinical input on the proportion of people having subsequent alloSCT after R-BAC. For the brexucabtagene autoleucel arm, the committee agreed that the value for subsequent alloSCT from ZUMA-2 was appropriate.

Cost effectiveness

The company's model

3.8 The company used a partitioned survival model with 3 health states (progression free, progressed disease and death). PFS and OS estimates were modelled independently, with the proportion of progressed patients at each cycle calculated as the difference between the values for the OS and PFS curves. The company explained that the model also differentiates long-term survivorship (LTS) in the preprogression state, specifically for the brexucabtagene autoleucel arm. This means that

people in the brexucabtagene autoleucel arm are assumed to be long-term survivors (effectively assuming that they are cured) if they have not progressed after 48 months, at which point they follow age-adjusted general population survival data, adjusted by a standardised mortality ratio (SMR; see section 3.10). The committee concluded that the company's model structure is appropriate, but that it was uncertain about some of the model assumptions (see sections 3.9 to 3.13).

Modelling of pre-infusion period

3.9 The EAG explained that the company's model used a mITT population, comprising everyone who completed treatment with brexucabtagene autoleucel. But it noted that infusion with brexucabtagene autoleucel was not successful for everyone who began the treatment process, and that the company had included pre-infusion costs, but not clinical outcomes, for these people in its model. Reasons for not having an infusion include manufacturing failure, disease progression and subsequent ineligibility, and patient preference. Of the 71 people who had leukapheresis in ZUMA-2, 68 (92%) were infused with brexucabtagene autoleucel. The committee noted that this was in the context of a strictly controlled clinical trial, and a higher attrition rate would be expected in real-world clinical practice. The EAG cited infusion rates of 70.4% from SACT data (95 infused from 135 applications) and 69.7% from O'Reilly et al. (2024; 83 infused from 119 applications). The Cancer Drugs Fund lead explained that during the 3-year period until May 2025 during which brexucabtagene autoleucel was made available through the Cancer Drugs Fund, about 25% of applications did not reach infusion. The company explained that although the number of people not completing infusion with brexucabtagene autoleucel observed in ZUMA-2 could be expected to be lower than in real-world clinical practice, it also expected that real-world rates of people not completing infusion with brexucabtagene autoleucel would fall as improvements are made to the process of production and delivery of the treatment. But the Cancer Drugs Fund lead clarified that the 3-year SACT data did not include the first 12 months in which there

were manufacturing problems that would have increased the pre-infusion period and inflated the attrition rate. The EAG preferred to use the ITT population from O'Reilly et al. (2024) because this would provide a more realistic cost-effectiveness analysis that would better reflect what would be expected to happen in NHS clinical practice. The company disagreed with the EAG's preferred approach and explained that the NHS does not pay for brexucabtagene autoleucel if the person does not have an infusion. But the EAG explained that removing the clinical outcomes for people who have leukapheresis but do not have infusion with brexucabtagene autoleucel from the economic model potentially introduces bias in favour of brexucabtagene autoleucel. This is because it effectively removes the outcomes of people who would likely have more severe disease from the brexucabtagene autoleucel treatment arm. The EAG preferred to include these outcomes. ZUMA-2 did not collect these outcomes, so the EAG used the DESCAR-T study to estimate the survival outcomes of people who had leukapheresis but did not have an infusion (ITT population from 181 people in France, 26 of whom did not complete infusion). This was the only source identified by the EAG that reported this information. The committee concluded that it preferred to include both the costs and outcomes for the whole ITT population, including the people who had leukapheresis but not an infusion. It also agreed that data from SACT should be used to inform the exact proportion who do not go on to infusion (about 25%) and to estimate the survival outcomes for this population. If survival outcomes data is not available from SACT for this population, then the EAG's method of estimating survival outcomes for this population using the DESCAR-T study is preferred.

Cure assumption

3.10 The committee recalled that the company's economic model includes LTS in the preprogression state (see section 3.8). The company explained that there were only a few disease-related deaths or progressions beyond 48 months in ZUMA-2, which suggests this is an appropriate timepoint to assume that people are effectively cured of the condition. The EAG

disagreed, stating that there is no evidence to support a plateau in survival curves before 60 months, based on the observed Kaplan–Meier data. The EAG also noted that the risk of death remains substantially higher than background mortality between 48 and 88 months. The company applied an SMR to adjust for excess mortality compared with background population mortality. But the EAG noted that the value of 1.09 was taken from a study of diffuse large B-cell lymphoma (not treated with chimeric antigen receptor [CAR] T-cell therapy) and does not adequately account for the difference in mortality. It also noted that in TA677 the company used a 60-month LTS timepoint, which the EAG considers more appropriate. The committee also recalled that the assumption of a functional cure at 60 months was not accepted in TA677 because more data was needed from ZUMA-2. The EAG suggested that it was more appropriate to base the mortality adjustment on data from people with mantle cell lymphoma than on data from people with diffuse large B-cell lymphoma. Comparing ZUMA-2 data over the 60- to 88-month period with general population mortality produces an average SMR that is substantially higher than 1.09 (the value is commercial in confidence and cannot be reported here), which suggests that the company's selected value of 1.09 underestimates the mortality risk in this population. But the EAG acknowledged that the SMR would be expected to reduce over time, so it preferred a value of 3.0, which was accepted in NICE's technology appraisal guidance for brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. The committee noted that in the original appraisal, the calculated SMRs on previous ZUMA-2 data were estimated to be in the range of 2.36 to 4.37. The SMR estimated by the EAG in the current appraisal was above this range. The committee decided there was insufficient evidence presented from ZUMA-2 to assume a functional cure has been achieved at either 48 or 60 months, so it was difficult to know which SMR was most appropriate for the economic model. It noted that the company's preferred value was taken from an appraisal for a different condition and with a

different intervention, and that the EAG's preferred value was previously accepted for brexucabtagene autoleucel (but not for mantle cell lymphoma) and was based on a functional cure timepoint of 3 years. The committee had concerns about both the company's and the EAG's base cases, but thought the EAG's analysis was more plausible, despite its limitations. It concluded that it would prefer to see additional analyses from the company to explore the possibility of no functional cure point (standard parametric modelling) and potential use of mixture cure modelling. It would also like to see any additional data that could be used to support the assumption of a functional cure and at which timepoint, and data about the most appropriate SMR to use.

CAR T-cell therapy tariff and intensive care unit costs

3.11 The company's economic model included a cost for the CAR T-cell therapy tariff calculated by NHS England to cover the costs of leukapheresis, delivery of the intervention, adverse events experienced in hospital, monitoring and training. The company's model did not include separate costs for intensive care unit (ICU) care. The EAG explained that the cost used by the company was outdated and there was a revised tariff cost for the 2025 to 2026 financial year. The company suggested that the value of £41,101 used in its economic model was in line with that accepted in previous NICE evaluations for CAR T-cell treatments. But the Cancer Drugs Fund lead explained that this value was outdated by several years and had only ever been intended to be an approximate figure that would serve until more thorough cost calculations could be done. These calculations had produced a figure of £58,964 for the 2024 to 2025 financial year, and this had been revised in line with inflationary pressures for 2025 to 2026, giving a tariff of £60,462. Information from NHS England also confirmed that ICU costs are not included in the tariff and should be modelled separately. The committee agreed that this was the current cost of delivering CAR T-cell treatments in the NHS, so the most recent tariff should ideally be included in the economic model. But it also agreed that all costs in the economic model should be from the same

financial year, and that it might not be possible to update all costs to the 2025 to 2026 period. So, the committee concluded that all costs in the model should be updated to those for the 2025 to 2026 financial year for consistency. But if this is not possible, all costs in the model should be for the 2024 to 2025 financial year. It also concluded that ICU costs should be incorporated separately.

Utility values

3.12 The company explained that it derived a utility value for the preprogression health state directly from EQ-5D-5L data in the ZUMA-2 trial, using regression analysis and the van Hout algorithm to convert the data to EQ-5D-3L utility values (the value is commercial in confidence and cannot be reported here). Because of the limited postprogression data from ZUMA-2, the company explained that its preferred postprogression utility of 0.724 was derived from the difference between pre- and postprogression utilities reported from NICE's technology appraisal guidance on ibrutinib for treating relapsed or refractory mantle cell lymphoma (from here, TA502). The committee recalled the company's functional cure assumption for long-term survivors in the model (see section 3.10). To estimate a utility value for this health state, the company assumed an age- and sex-adjusted general population-equivalent utility. The EAG explained that it was not clinically plausible that the company's preprogression utility value should exceed the value for the general population and that it should be capped at this value. Regarding the company's choice of utility value for the long-term survivors in the model, the EAG noted again its concerns about the validity of a functional cure assumption based on survival data from ZUMA-2, for either the 48- or the 60-month timepoints. It suggested that it was highly uncertain whether people in the long-term survivor health state would fully regain the quality of life of the general population. This is because an increased mortality risk remains, which suggests a likelihood of persistent health complications that would affect quality of life. The EAG agreed with the company about the lack of postprogression quality-of-life data, but

disagreed with the methods used to derive a utility value from the absolute difference between pre- and postprogression values from TA502. The EAG instead preferred to either calculate this proportionally or use the TA502 postprogression value of 0.68 directly. The committee agreed with the EAG that the preprogression utility should not exceed the general-population utility at the baseline age and that for the postprogression health state the model should directly adopt the value of 0.68 from TA502. The committee concluded that the model's proposed utility value for long-term survivors needs further justification given that evidence of a functional cure from ZUMA-2 is uncertain and there remains a higher risk of death than for the general population.

Intravenous immunoglobulin therapy costs

3.13 The company noted that adverse-event costs were included within the CAR-T tariff, except for those associated with hypogammaglobulinaemia of grade 3 or above, which requires long-term intravenous immunoglobulin (IVIg) therapy. The company derived the proportion of people having IVIg after brexucabtagene autoleucel directly from ZUMA-2 (the rate is commercial in confidence and cannot be reported here). It assumed IVIg treatment for 1 year. The EAG explained that clinical expert advice had suggested that approximately 30% to 40% of patients will require IVIg for 1 to 2 years. It recalled that a rate of 32% had been previously accepted in TA677. It also noted that Wang et al. (2023) had reported 38% of people in ZUMA-2 having IVIg for any cause, not just for hypogammaglobulinaemia of grade 3 or above. The EAG preferred to assume that 38% of people had IVIg for 1 year in its base case. The clinical experts explained that there is likely to be regional variation because of different thresholds for treating infections and in some cases some centres may opt for antibiotics rather than IVIg. Both clinical experts stated that between 10% and 20% IVIg use for 1 year aligned with their own experiences. The committee concluded that the figure from Wang et al. (2023) was representative of the extent of IVIg use in ZUMA-2 and that 38% of people having IVIg for 1 year was appropriate for the economic

model. This was because it was observed data. It added that it would prefer to see data from SACT to quantify IVIg use after brexucabtagene autoleucel in the NHS.

Severity

3.14 Brexucabtagene autoleucel was originally assessed under the end-of-life criteria and was considered to have met these criteria, as outlined in TA677. But the committee noted that NICE's methods and process manual changed in 2022 and that the severity modifier has replaced the end-of-life criteria. The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The committee noted that in the company's base case, the absolute QALY shortfall is 10.51 and the proportional QALY shortfall is 88.32%. The EAG stated that the proportional QALY shortfall was higher (around 92%) in its preferred analysis. The committee noted that, based on its preferred assumptions (see section 3.16), the proportional shortfall was likely to be between the company's and the EAG's estimates. The committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate in the current analysis. But it will consider the QALY shortfall in the new analysis and appropriate severity weighting to be used at the second committee meeting.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.15 Because of confidential commercial arrangements for brexucabtagene autoleucel and some of the comparators, the exact cost-effectiveness results are confidential and cannot be reported here. Both the company's

and the EAG's base-case incremental cost-effectiveness ratios (ICERs) were substantially above the range NICE normally considers to be a cost-effective use of NHS resources.

Committee's preferred assumptions

3.16 The committee agreed that neither the company's nor the EAG's base case included all its preferred assumptions, which were as follows:

- mean age of 66 from SACT as the starting age in the economic model (see section 3.4)
- SACT data for OS and O'Reilly (2024) for PFS to be combined with data from ZUMA-2 to provide a pooled analysis for brexucabtagene autoleucel clinical outcomes (see section 3.6)
- 15% of people having subsequent alloSCT after R-BAC, and for alloSCT costs in the model to reflect this (see section 3.7)
- rate of subsequent alloSCT after brexucabtagene autoleucel to be taken from ZUMA-2 (see section 3.7)
- costs and outcomes included for people who had leukapheresis but not an infusion (see section 3.9)
- proportion of people having leukapheresis but not completing infusion with brexucabtagene autoleucel to be taken from SACT data (see section 3.9)
- clinical outcomes for people who had leukapheresis but not an infusion to be taken from SACT data. But if this is not available, to use the EAG's approach for estimating clinical outcomes for this population using data from the DESCAR-T study (see section 3.9).
- the most recent CAR T-cell therapy tariff for 2025 to 2026 to be used if other costs in the model can be updated to the same financial year. If not, all costs in the model to be for the 2024 to 2025 financial year. ICU costs to be incorporated separately (see section 3.11)
- the preprogression utility to be capped at the general-population utility at the baseline age, and the value of 0.68 from TA502 to be used for postprogression (see section 3.12)

- 38% of people have IVIg for 1 year after brexucabtagene autoleucel, based on data from ZUMA-2, if real-world evidence is not available from SACT (see section 3.13)
- calculation of absolute and proportional QALY shortfalls with these preferred assumptions to be considered at the next committee meeting (see section 3.14)

Acceptable ICER

3.17 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. The committee noted the high level of uncertainty, specifically about:

- how long people live
- whether it is appropriate to assume a functional cure timepoint and, if so, at what timepoint
- what is the most appropriate SMR to use
- how many people would have alloSCT after R-BAC.

So, the committee was unable to state an acceptable ICER threshold until these uncertainties have been addressed.

Other factors

Equality

3.18 The committee did not identify any equality issues.

Uncaptured benefits

3.19 The committee considered whether there were any uncaptured benefits of brexucabtagene autoleucel. It did not identify additional benefits of

brexucabtagene autoleucel not captured in the economic modelling. So, the committee concluded that all additional benefits of brexucabtagene autoleucel had already been taken into account.

Additional analyses

3.20 The committee would like the company to provide:

- additional analyses that explores the possibility of no functional cure point (standard parametric modelling) and the potential use of mixture cure modelling
- additional evidence that could be used to support the assumption of a functional cure and at which timepoint
- additional evidence about the most appropriate SMR to use
- additional evidence on how many people would have subsequent alloSCT after R-BAC
- additional evidence on the clinical outcomes for people who had leukapheresis but not an infusion.

Conclusion

Recommendation

3.21 The committee considered that the cost-effectiveness estimates presented by the company and EAG were uncertain, so it would like to see additional analyses. But the committee decided that, given its preferred assumptions and based on the analysis it had seen, the cost-effectiveness estimates were highly likely to be above the range that NICE considers a cost-effective use of NHS resources. The committee concluded that brexucabtagene autoleucel could not be recommended for treating relapsed or refractory mantle cell lymphoma.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical, a project manager and an associate director.

Luke Cowie

Technical lead

Alan Moore

Technical adviser

Jeremy Powell

Project manager

Emily Crowe

Associate director

ISBN: [to be added at publication]