NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

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 and should not be used routinely in the NHS in England for the condition and population in the recommendations.

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

Issue date: December 2025

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 TA677). 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 trial in which all participants had brexucabtagene autoleucel and there was no comparison group. 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 the extent of brexucabtagene autoleucel's clinical benefit 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
- it is not known how long people live after having brexucabtagene autoleucel.

The cost-effectiveness estimates are substantially 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 rare 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 experts highlighted that people who had had 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. They outlined that this treatment helped people to return to work and enabled them to engage in a wide range of activities that would not be possible without this treatment. The clinical experts explained the potential for improved survival and the possibility of a functional cure for some people 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 an allogeneic stem-cell transplant (alloSCT) can be considered, but only while the person's cancer is still responding to BTKi treatment. Treatment with brexucabtagene autoleucel is proposed as an option for people whose cancer has relapsed or is refractory to 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 treating 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 intention-to-treat (ITT) population. The company used the mITT group in its economic analysis of brexucabtagene autoleucel (see section 3.9). The company explained this is because not everyone who begins the treatment process will have a successful infusion of brexucabtagene autoleucel. This may be because of disease progression, deterioration in Eastern Cooperative Oncology Group (ECOG) performance status, or manufacturing failure. 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). 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 people with a response, 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). 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 At the first meeting, the committee noted that ZUMA-2 did not include anyone from the UK. It included people who had had a median of 3 therapies, all with an 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 was likely to be younger and in better health than people with relapsed or refractory mantle cell lymphoma in the NHS who have had 2 lines of treatment, including a BTKi. The company agreed that the mean age of 63.2 years was younger than would be expected for people with relapsed or refractory mantle cell lymphoma in the UK, but this probably reflected 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 was available for brexucabtagene autoleucel (see section 3.6). It concluded that results from ZUMA-2 were sufficiently generalisable to people in the NHS to be

used to model outcomes for people having brexucabtagene autoleucel. But the committee recalled from NICE's first technology appraisal of brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma (from here, TA677) that even small variations in mean baseline age have a significant impact on the cost-effectiveness estimates. So it preferred to use the mean age of 66 from SACT as the starting age in the economic model. At consultation, the company accepted the committee's preference to use 66 as the starting age in its base case.

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 mantle cell lymphoma that progressed after treatment with a BTKi. The study included 36 people who had R-BAC across 23 centres in the UK and Italy between October 2015 and March 2019. It focused on fitter, transplant-eligible patients to demonstrate the use of R-BAC for subsequent bridging to alloSCT. 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 highlighted some uncertainties including the small sample size, the retrospective nature of the study and, especially, the risk of bias caused by selecting fitter transplant-eligible people for treatment. Because of this potential risk of selection bias, the EAG considered that the naive comparison with McCulloch (2020) was 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) was the most appropriate source of data for R-BAC in 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 this study were uncertain.

Real-world evidence for brexucabtagene autoleucel

3.6 In TA677, the company did a naive comparison between brexucabtagene autoleucel and R-BAC because of a lack of any direct comparative evidence. TA677 also included a matching-adjusted indirect comparison 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 was published, including SACT data collected as part of the managed access agreement. The company preferred to use data from ZUMA-2 only 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 when it was initially available through the Cancer Drugs Fund.

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 was because the naive comparison would then be between ZUMA-2 with pooled real-world evidence and the real-world evidence for R-BAC 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 people 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 to include in the economic model.
- The DESCAR-T registry, the ITT population of which included 181 people from 24 French treatment centres, with a median follow up of 14.2 months. 152 people had a brexucabtagene autoleucel infusion. People who had leukapheresis (the process of collecting the white blood cells from which T-cells are isolated) but did not have an infusion of brexucabtagene autoleucel comprised 26 people (3 were excluded from analysis because of ongoing manufacture at the cutoff date). Many people in the DESCAR-T 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%), an ECOG performance score 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 a 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) represented people who would have

brexucabtagene autoleucel in the NHS, but it 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 these countries might differ from the treatment 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 with the company 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. So it concluded that it would prefer for the SACT and O'Reilly et al. (2024) data to be combined with data from ZUMA-2 to provide a pooled analysis for brexucabtagene autoleucel clinical outcomes in the economic model.

At consultation, the company provided updated survival analyses using these UK real-world evidence datasets. For brexucabtagene autoleucel, a pooled dataset was created using ZUMA-2 plus SACT data for OS, and ZUMA-2 plus O'Reilly et al. (2024) for PFS. But, the company used SACT OS data only from September 2022 and onwards. The company explained that this was to account for the impact of new guidelines for the treatment of mantle cell lymphoma issued in 2022 by the British Society for Haematology. These

guidelines advocate for earlier identification and referral of people with high-risk mantle cell lymphoma for chimeric antigen receptor T-cell (CAR-T) treatment. The company explained that these guidelines are expected to enable treatment at an earlier disease stage, improving infusion rates and outcomes. The company cited data in O'Reilly et al. (2024) that showed increased infusion rates from 59.8% (2022) to 69.7% (2024). These improvements were attributed to earlier referral, better disease control and reduced manufacturing failure rates. A study by Boyle et al. (2023) also showed similarly improved CAR-T outcomes over time in large B-cell lymphoma. The company suggested that using post-August 2022 SACT data also avoided confounding from earlier cohorts affected by manufacturing delays and adverse impacts on clinical trial outcomes during the COVID-19 pandemic.

At the second committee meeting, the EAG did not agree with the company's approach of pooling real-world evidence from SACT (restricted to the cohort after August 2022) with data from ZUMA-2. By limiting the SACT data used in the model to people who had brexucabtagene autoleucel after August 2022 (n=43), rather than the whole SACT dataset (n=92), the SACT dataset carried a lower weighting when combined with the ZUMA-2 data (n=68). Instead, the EAG preferred to use the whole SACT dataset combined with ZUMA-2 data to estimate OS outcomes in the economic model. A covariate was used to distinguish between SACT and ZUMA-2 data, with the longer follow up in the trial data used to inform the shape of the long-term extrapolation. The EAG also provided a scenario analysis that used the company's approach of pooling data from both sources in the model but using the full SACT dataset and without a covariate. The committee considered the relative merits of the 3 approaches to modelling OS for brexucabtagene autoleucel:

- ZUMA-2 plus SACT data, with SACT data limited to September 2022 onwards (the company's preferred analysis). In this analysis a single

survival extrapolation was obtained by fitting a model to the pooled data, and the model does not distinguish between the source of the data

- ZUMA-2 plus SACT data, with the full SACT dataset and a covariate used so that ZUMA-2 informed the shape of the long-term extrapolation (the EAG's preferred analysis). In this analysis, a model was fitted to the pooled data, but the model distinguished between the sources so that 2 extrapolations for OS were obtained, one for each source of data. The extrapolations shared one parameter, so the longer follow-up of ZUMA-2 could influence the longer term OS modelled for the SACT extrapolation whilst reflecting the difference between trial and real-world outcomes
- ZUMA-2 plus SACT data, with the full SACT dataset but no covariate used (an EAG scenario). In this analysis a single survival extrapolation was obtained by fitting a model to the pooled data from both sources, and the model does not distinguish between the source of the data.

The committee agreed there was some evidence for a recent trend towards earlier identification, improved manufacturing and delivery of brexucabtagene autoleucel, and improved CAR-T outcomes for people with relapsed or refractory mantle cell lymphoma. So, it agreed with the company that it might be reasonable to exclude data for people treated with brexucabtagene autoleucel before September 2022. But it also agreed with the EAG that the SACT data was the most representative of treatment in the NHS and that using the restricted dataset gave it a lower weight than ZUMA-2 data in the analysis. The committee concluded that it would consider all 3 analyses in its decision making.

Subsequent allogenic stem-cell transplant after R-BAC

3.7 At the first meeting, 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 fitter, transplant-eligible people, in part to demonstrate

the efficacy of R-BAC bridging to alloSCT, resulting in a high proportion (31%) of subsequent alloSCT. The committee recalled that selection bias towards fitter patients in McCulloch et al. (2020) may have overestimated the efficacy of R-BAC compared with outcomes that would be expected in clinical practice (see section 3.5). Clinical expert advice to the EAG noted that only a small subset of people are well enough to have alloSCT in 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 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 it 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 after R-BAC 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 (the company considers this value to be commercial in confidence so it cannot be reported here). The EAG 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, and agreed with the clinical experts that 15% was appropriate. 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. For the brexucabtagene autoleucel arm, the committee agreed that the value for subsequent alloSCT from ZUMA-2 was appropriate.

At consultation, the company agreed to use the committee's preferred value of 15% having subsequent alloSCT after R-BAC in its updated base case, but it suggested that there was no clinical evidence to support this assumption. It also agreed to model outcomes for people separately depending on whether they had or did not have subsequent alloSCT after R-BAC. To do this it used a similar approach to that used by the EAG before the first committee meeting, in which people who did not have subsequent alloSCT were removed from the R-BAC cohort based on the subgroups reported in McCulloch et al. (2020). But the company preferred an alternative source of data, Liebers et al. (2025), for modelling outcomes for people who did have alloSCT after R-BAC. It suggested that the subgroup data from McCulloch et al. (2020) was limited to a small number of people (n=11), with a short follow up and a limited number of

observed events. Data from Liebers et al. (2025) included outcomes for 64 people who had alloSCT for relapsed or refractory mantle cell lymphoma. Median follow up was 34.1 months. This alloSCT cohort also had a similar ECOG performance status and BTKi exposure to people in McCulloch et al. (2020), supporting comparability between the 2 sources of data. The EAG agreed that using this data improved the robustness of estimated outcomes for this subgroup, but cautioned that there remained a high risk of bias when comparing trial data (even when pooled with SACT data) for brexucabtagene autoleucel with real-world data for R-BAC. The committee again concluded that approximately 15% of people would be expected to have alloSCT after R-BAC in NHS practice. It also concluded that Liebers et al. (2025) was the preferred source of data for estimating clinical outcomes in people who had alloSCT after R-BAC.

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 people with progressed disease at each cycle calculated as the difference between the values for the OS and PFS curves. The company explained that the model also differentiated long-term survivorship (LTS) in the preprogression state, specifically for the brexucabtagene autoleucel arm. This meant that people in the brexucabtagene autoleucel arm were assumed to be long-term survivors (effectively assuming that they were cured) if they had not progressed after 48 months, at which point they followed age-adjusted general population survival data, adjusted by a standardised mortality ratio (SMR; see section 3.12). The committee concluded that the company's model structure is appropriate, but it was uncertain about some of the model's assumptions (see sections 3.8 to 3.12).

Modelling of pre-infusion period: population

3.9 At the first meeting, the company's model used a mITT population, comprising everyone who completed treatment with brexucabtagene autoleucel. But not everyone who is approved for treatment with brexucabtagene autoleucel completes the infusion process. The committee noted 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. The EAG suggested that, by using the mITT population, the company effectively removed people with the most severe disease from its analysis.

At consultation, the company suggested that using an ITT approach was not a like-for-like comparison with R-BAC, because McCulloch et al. (2020) reflected only the outcomes for people in whom R-BAC treatment was started and completed. The company explained that R-BAC is an intensive and toxic chemotherapy regimen, so in a real-world population a substantial proportion of people may not be eligible or may stop R-BAC treatment early. It cited clinical expert estimates suggesting that treatment was not likely to proceed in 20% to 30% of people considered for R-BAC because of frailty or rapid disease progression. The EAG disagreed with the company's reasoning and explained that treatment with R-BAC was stopped early in 28% of the population in McCulloch et al. (2020) because of progressive disease or toxicity. So, it may not be correct to interpret that it reflected only the outcomes of people in whom R-BAC treatment was started and completed. The EAG noted that because the company had not provided any robust evidence or analyses to show that McCulloch et al. (2020) was effectively a mITT population, no adjustment to the outcomes of that population was justified.

The committee asked the clinical experts to describe the different pathways for brexucabtagene autoleucel and R-BAC from the point at

which the decision is made to start one of these treatments. The clinical experts explained that it takes between 4 and 6 weeks after leukapheresis to have an infusion of brexucabtagene autoleucel. This is the time it takes to manufacture the cells for infusion and transport them to the treatment centre. During this waiting time people will usually have bridging immunochemotherapy with R-BAC to improve their CAR-T outcomes. R-BAC bridging therapy will be given shortly after leukapheresis, which occurs 1 to 2 weeks after the clinical decision to offer CAR-T treatment. But during the period leading up to infusion, even with bridging therapy, the disease can progress and a person's condition can deteriorate, making them ineligible for the CAR-T infusion. But the clinical experts added that the same disease characteristics that cause rapid progression might also prevent someone being eligible for R-BAC, although the time between the decision to start treatment with R-BAC and having it is usually shorter, at between 2 and 4 weeks. The committee asked the clinical experts about the relative fitness of people having leukapheresis and those in the McCulloch et al. (2020) study. The clinical experts explained that the population in that study was broadly the same as the population considered suitable for brexucabtagene autoleucel. They suggested that if someone is considered fit enough for leukapheresis, this would be a fair point at which to begin a comparison with the population represented in McCulloch et al. (2020). At this point, the time from decision to treat is similar between the 2 treatments. The committee agreed with the clinical experts that the point of leukapheresis was the appropriate point at which to start the comparison with R-BAC. It noted that it was important to model the period between leukapheresis and infusion for brexucabtagene autoleucel because if people are considered fit enough for R-BAC then they would also be considered fit enough for leukapheresis. So the committee concluded that the population starting leukapheresis should be used to model both the cost and efficacy estimates for brexucabtagene autoleucel.

Modelling of pre-infusion period: attrition rates

3.10 Of the 71 people who had leukapheresis in ZUMA-2, 68 (92%) had a brexucabtagene autoleucel infusion. At the first meeting, the committee noted that this was in the context of a strictly controlled clinical trial, and that 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 available through the Cancer Drugs Fund, about 25% of applications did not result in someone having an infusion. The company explained that although the number of people not having an infusion of brexucabtagene autoleucel observed in ZUMA-2 was expected to be lower than in real-world clinical practice, it also expected that real-world rates of people not having an infusion of brexucabtagene autoleucel would fall as the processes of producing and delivering the treatment are improved. 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 inflated the attrition rate.

At consultation, the company provided more information on attrition rates at different stages of the CAR-T process. It provided data from its own ordering system (Kite Konnect) that showed a lower attrition rate between leukapheresis and infusion than that suggested by the SACT data. It explained that because this data was similar to the attrition rate between leukapheresis and infusion in ZUMA-2, it preferred the value from ZUMA-2 in its base case (Kite Konnect values are considered commercial in confidence and cannot be reported here). The company noted that information is collected in SACT using 2 forms: form A is a request for leukapheresis and form B is a request for infusion. But often there is a delay in leukapheresis taking place, so some people do not proceed to leukapheresis despite a request form being completed. So, data from form A includes people who drop out between approval and

leukapheresis, but also people who drop out between leukapheresis and the request for infusion. Data provided by NHS England at consultation (Blueteq, 4 August 2025 datacut) showed that 65 people were identified with a form A but no form B. Of these 65, CAR-T centres had confirmed that 5 had an infusion. Of the 60 not infused, 20 (a third) did not proceed to leukapheresis. So, 40 people were confirmed as having had leukapheresis but not an infusion.

At the second committee meeting, the committee asked the Cancer Drugs Fund lead whether more recent SACT data showed improved attrition rates, as would be expected given the expected improved manufacturing and delivery of CAR-T treatment, and of earlier referral and treatment for people with mantle cell lymphoma (see section 3.6). The Cancer Drugs Fund lead explained that in the last 12 months of available data, the attrition rate had decreased from around 30% to 20%. The committee preferred this more recent data from SACT, but acknowledged that it did not reliably inform the proportion of people who drop out between leukapheresis and infusion. The committee thought that the Blueteq data on the proportional split for attrition (a third of people who did not have an infusion did not have leukapheresis) was appropriate. So, the committee concluded that reducing 20% by a third provided its preferred attrition rate between leukapheresis and infusion of around 12%.

Modelling of pre-infusion period: outcomes

3.11 At the first meeting, 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 introduced bias in favour of brexucabtagene autoleucel. This was because it effectively removed the outcomes of people who would likely have more severe disease from the brexucabtagene autoleucel treatment arm (see section 3.10). The EAG preferred to include these outcomes. But ZUMA-2 did not report 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 have an infusion). This was the only source identified by the EAG that reported this information. At consultation, the company provided a scenario analysis using outcomes data from ZUMA-2 for people who had had leukapheresis but not had an infusion. It suggested that because SACT does not report outcomes for people who do not have infusions and because the DESCAR-T study was not generalisable to the UK population (see section 3.6), data from ZUMA-2 was the most robust. The EAG agreed to use this data in its base case in preference to using data from the DESCAR-T study. The committee concluded that outcomes for people who had had leukapheresis but not had an infusion should be estimated from ZUMA-2 data in the economic model.

Cure assumption

3.12 At the first meeting, the committee recalled that the company's economic model included 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 suggested this was an appropriate timepoint to assume that people are effectively cured. The EAG disagreed, stating that there is no evidence to support a plateau in survival before 60 months, based on the observed Kaplan–Meier data. The EAG also noted that the risk of death remained 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 company's value of 1.09 was taken from a study by Maurer et al. (2014) of diffuse large B-cell lymphoma (not treated with CAR-T treatment) and did 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 considered more appropriate. The committee also recalled that the assumption of a functional cure at 60 months was not accepted by the committee 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 the ZUMA-2 mortality data over the 60- to 88-month period with general population mortality produced an average SMR that was substantially higher than 1.09 (the value is commercial in confidence and cannot be reported here), which suggested that the company's value of 1.09 underestimated 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 (TA893). The committee noted that in TA677, the calculated SMRs from previous ZUMA-2 data were estimated to be in the range of 2.36 to 4.37. The committee decided there was insufficient evidence presented from ZUMA-2 to assume a functional cure 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 evaluation for a different condition and 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 requested exploratory mixture cure modelling and standard parametric modelling without a cure assumption after the first meeting. The company acknowledged this but did not provide these analyses. It argued that mixture cure modelling had already been explored in TA677, and that standard parametric modelling gave a clinically implausible SMR when calculated from tails of ZUMA-2 survival curves. The NICE technical team clarified that a preference for a LTS approach did not form part of the committee's preferred assumptions from TA677. They further highlighted that uncertainties around whether brexucabtagene autoleucel was curative was a key reason for its entry into the Cancer Drugs Fund, and that mixture cure modelling might have

helped to resolve this uncertainty. The EAG provided a scenario analysis using standard parametric modelling. The company restated its preference for a 48-month cure point, because of the limited number of events observed after this time. The EAG did not agree that the data from ZUMA-2 conclusively showed a cure from either 48 or 60 months. But it explained that it modelled a functional cure from 60 months because this was more conservative and maintained this for its base case.

At the second meeting, the clinical experts suggested that a proportion of people do seem to be cured by treatment with brexucabtagene autoleucel. The company also provided further information to justify maintaining its preferred SMR of 1.09 from Maurer et al. (2014). The company explained that people in the Maurer et al. (2014) study had a mean age of 63 years, which is the same as in ZUMA-2. But people in the EAG's preferred source of SMR (TA893) had a much lower mean age of 46. The company suggested that when the EAG's preferred SMR of 3 was applied in the economic model it gave an excess mortality that was clinically implausible because of the higher starting age in the economic model. But the EAG did not feel that the company's justification was correct; it did not agree that the starting age in the model was a relevant consideration for the calculation of an appropriate SMR, except that the SMR would be applied to a higher reference mortality rate from the general population. The committee noted that the SMR from Maurer et al. (2014) was taken from a population with diffuse large B-cell lymphoma and who had not had CAR-T treatment. The company also presented an SMR of 2.36 taken from a study by Eskelund et al. (2016) of people treated for mantle cell lymphoma, but this was also a population who had not had CAR-T treatment. The EAG noted that this value appeared to be a hazard ratio, and that it was reported alongside another hazard ratio of 4.37, with the true value likely to be in between. The EAG did not believe the difference in starting age to be a contributing factor to the choice of SMR.

The committee agreed that the company had not presented sufficient evidence for why the SMR from Maurer et al. (2014) was more clinically plausible than the EAG's preferred SMR of 3. It thought that it had not seen sufficient evidence to conclusively support the idea that modelling a cure point for brexucabtagene autoleucel was appropriate. But it noted that the incremental cost-effectiveness ratio (ICER) for the EAG's standard parametric modelling scenario (no assumption of a functional cure timepoint) was very similar to the ICER resulting from a 60-month cure assumption and an SMR of 3. The committee recalled that the clinical experts indicated that a proportion of people do seem to be cured with brexucabtagene autoleucel. So the committee concluded that a 60-month cure assumption timepoint was clinically plausible and was preferred, with an SMR of 3 to adjust to population mortality after this timepoint. The committee also recalled that 15% of people have subsequent alloSCT after R-BAC (see section 3.7), so further concluded that it was appropriate to apply the 60-month cure assumption to both arms of the economic model.

CAR T-cell treatment tariff and intensive care unit costs

3.13 The company's economic model included a cost for the CAR T-cell treatment tariff calculated by NHS England to cover the costs of leukapheresis, treatment delivery, 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 inflation 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. At consultation, the company restated its view that the tariff of £41,101 should be used, in line with previous CAR-T treatment evaluations. It suggested that NHS England had not been transparent in how the updated tariff for 2025 to 2026 had been calculated. But the committee agreed with the Cancer Drugs Fund lead that the updated tariff for 2025 to 2026 was the current cost of delivering CAR T-cell treatments in the NHS, so this tariff should be included in the economic model. It also concluded that ICU costs should be incorporated separately.

Utility values

3.14 At the first meeting, 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 3.12). 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 timepoint. 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 was because an increased mortality risk would remain, 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.

At consultation, the company did not provide further evidence to justify its preference for using the preprogression value from ZUMA-2. The committee agreed with the EAG and concluded that the preprogression utility should not exceed the general population utility at the baseline age. This was because it is not clinically plausible that people with mantle cell lymphoma would experience better quality of life than the age-matched general population. For the postprogression health state, the committee agreed that the company's approach of using the relative difference in utility values from TA502 was preferred. So the committee concluded that the postprogression utility should be calculated using a 13% decrement applied to the preprogression utility from ZUMA-2, capped at the utility of the age-matched general population.

Intravenous immunoglobulin treatment costs

3.15 At the first meeting, the company noted that adverse-event costs were included in the CAR-T treatment tariff, except for those associated with hypogammaglobulinaemia of grade 3 or above, which needs long-term intravenous immunoglobulin (IVIg) treatment. The company derived the proportion of people having IVIg treatment 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 people will need IVIg treatment for 1 to 2 years. It recalled that a rate of 32% had been accepted in TA677. It also noted that Wang

et al. (2023) had reported 38% of people in ZUMA-2 having IVIg treatment for any cause, not just for hypogammaglobulinaemia of grade 3 or above. The EAG preferred to assume that 38% of people had IVIg treatment 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 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.

At consultation, the company agreed to use the midpoint (15%) of these clinical expert estimates for its base case. It also noted that a rate of 16.5% was observed in the SACT data for diffuse large B-cell lymphoma. At the second committee meeting, the clinical experts suggested that it was likely that the rate of IVIg use would be similar between diffuse large B-cell lymphoma and mantle cell lymphoma populations. They also explained that the rates reported in Wang et al. (2023) were higher than would be seen in the UK. This is because ZUMA-2 included people from the US, where clinical guidelines on IVIg use for hypogammaglobulinaemia of grade 3 or above are less restrictive than those used in the NHS. Infection also needs to be present to start IVIg treatment in the NHS. The committee agreed that the figure of 38% from Wang et al. (2023) was probably too high. It noted that the SACT rate of 16.5% for diffuse large B-cell lymphoma was probably much closer to the real value for mantle cell lymphoma. So, the committee concluded that the company's choice of 15% for its base case was appropriate to model IVIg use after brexucabtagene autoleucel in the NHS.

Severity

3.16 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 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. At the first meeting, the committee noted that, in the company's original base case, the absolute QALY shortfall was 10.51 and the proportional QALY shortfall was 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 3.18), the proportional shortfall was likely to be between the company's and the EAG's estimates.

At consultation, the company requested flexibility from the committee to use a severity modifier of 1.7 rather than 1.2 to account for what it felt were uncaptured benefits of brexucabtagene autoleucel. These related to improvements made in the manufacturing and delivery of CAR-T treatments, along with quicker referrals leading to improved outcomes for people with mantle cell lymphoma in more recent years (see section 3.6). But the EAG noted that many of these claimed uncaptured benefits related to outcomes for brexucabtagene autoleucel rather than to outcomes for standard care, which is what informs the severity modifier. At the second meeting, the committee considered the particular circumstances in this evaluation, noting that the end-of-life criteria was applied in TA677. The committee considered if it could apply flexibility in terms of the severity modifier. It noted the absolute QALY shortfall of 9.22 in the company's updated base case, with a proportional QALY shortfall of 87.9%. It agreed that these were not close enough to the 1.7 severity modifier threshold (95% proportional QALY shortfall or higher) to warrant the flexibility of using a 1.7 severity modifier. It also agreed that the uncaptured benefits described by the company were accounted for in the committee's acceptable ICER (see section 3.19). The committee

concluded that a severity weight of 1.2 applied to the incremental QALYs was appropriate.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 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 ICERs were above the range NICE normally considers to be a cost-effective use of NHS resources.

Committee's preferred assumptions

3.18 The committee's preferred assumptions 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 for brexucabtagene autoleucel clinical outcomes (for OS, the committee concluded that it would consider the company's and EAG's preferred approaches and also the EAG's scenario analysis in its decision making, 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)
- data from Liebers et al. (2025) for estimating clinical outcomes in people who had alloSCT after R-BAC (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)
- 12% of people having leukapheresis but not having a brexucabtagene autoleucel infusion, from SACT data (see section 3.10)

- clinical outcomes for people who had leukapheresis but not an infusion to be taken from ZUMA-2 (see section 3.11)
- 60-month cure assumption timepoint, with an SMR of 3 to adjust to population mortality after this timepoint (see section 3.12)
- 60-month cure assumption to apply to both arms of the economic model (see section 3.12)
- the most recent CAR T-cell treatment tariff for 2025 to 2026 to be used and ICU costs to be incorporated separately (see section 3.13)
- preprogression utility to be capped at the general population utility at the baseline age, and postprogression utility 13% lower than preprogression utility (see section 3.14)
- 15% of people have IVIg treatment for 1 year after brexucabtagene autoleucel, based on the midpoint of clinical expert estimates (see section 3.15)
- a severity modifier of 1.2 applied to incremental QALYs (see section 3.16).

Acceptable ICER

3.19 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
- quality of life for people in the preprogression health state
- whether it is appropriate to assume a functional cure timepoint and, if so, at what timepoint
- the most appropriate SMR to use.

The committee considered these uncertainties. It also noted that the CAR-T tariff, the modelling of the ITT population and the assumption of a functional cure had substantial effects on the cost-effectiveness estimates. The committee further considered:

- the evidence for potential uncaptured benefits of brexucabtagene autoleucel (see section 3.21)
- the rarity of the condition (see section 3.1) and that committee considered that evidence generation can be more challenging in smaller populations
- potential equalities issues (see section 3.20)
- and that it was unable to allow a severity modifier of 1.7 to be used (see section 3.16).

It concluded that an acceptable ICER would be towards the upper end of the range NICE normally considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Other factors

Equality

3.20 The committee noted that people from ethnic minority backgrounds have fewer donor options and are less likely to have alloSCT. The committee concluded that this was not an equalities issue that could be addressed by this economic evaluation, but it was accounted for in its acceptable ICER.

Uncaptured benefits

3.21 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.

Conclusion

Recommendation

3.22 The committee considered that the cost-effectiveness estimates presented by the company and EAG were uncertain. 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 substantially 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

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