NICE National Institute for Health and Care Excellence

NICE guidance

Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Brexucabtagene autoleucel is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. It is recommended only if the conditions in the managed access agreement for brexucabtagene autoleucel are followed.

1.2 This recommendation is not intended to affect treatment with brexucabtagene autoleucel that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Standard treatment for B-cell acute lymphoblastic leukaemia includes inotuzumab, blinatumomab, and ponatinib. This can be followed by an allogeneic stem cell transplant for some people. Brexucabtagene autoleucel would be offered as an additional treatment option.

Evidence from a study of brexucabtagene autoleucel does not compare the treatment with anything else. It suggests that people having the treatment may live longer and have more time before their disease relapses, but this is uncertain. There is also not enough evidence to tell if this treatment can cure B-cell acute lymphoblastic leukaemia.

The most likely cost-effectiveness estimates are uncertain, and some of them are higher than what NICE considers an acceptable use of NHS resources. So brexucabtagene autoleucel cannot be recommended for routine use.

Evidence collected in the Cancer Drugs Fund would help reduce some of the uncertainties in the clinical evidence. Brexucabtagene autoleucel has the potential to be cost effective, so it is recommended for use in the Cancer Drugs Fund.

2 Information about brexucabtagene autoleucel

Marketing authorisation indication

2.1 Brexucabtagene autoleucel (Tecartus, Kite) is indicated for 'the treatment of adult patients 26 years of age and above with relapsed or refractory B cell precursor acute lymphoblastic leukaemia'.

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

Price

2.3 The list price for single infusion is £316,118 (excluding VAT, MIMS [Monthly Index of Medical Specialities] online, accessed February 2023).

2.4 The company has a commercial arrangement. This makes brexucabtagene autoleucel available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Kite, a Gilead company, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway and clinical practice

People with relapsed or refractory B-cell acute lymphoblastic leukaemia would welcome a new treatment

3.1 Outcomes for people with relapsed or refractory B-cell acute lymphoblastic leukaemia are poor. The disease has low levels of response to treatment and is associated with limited survival. Common symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever and sweating. The clinical and patient experts noted that people with relapsed or refractory B-cell acute lymphoblastic leukaemia have limited treatment options. This is because the current treatments do not provide a cure and can only extend life for less than a year. This has a serious impact on the quality of life of people with the disease, and could affect their families. The only potentially curative option is an allogeneic stem cell transplant (allo-SCT), which not many people can have because of the eligibility requirements such as remission, age, fitness levels and donor availability. They further explained that stem cell transplants are associated with a slow and laborious recovery over around a year. The clinical expert explained that people from minority ethnic family backgrounds are less likely to find a matching donor. Chimeric antigen receptor (CAR) T-cell therapies are a new generation of personalised cancer immunotherapies in which the patients' own immune cells are collected and modified to treat their cancer. The clinical expert said that CAR T-cell therapy causes less severe, short-term and more manageable side effects than allo-SCT. They also said that the technology could potentially lead to a cure in some people. This type of technology is currently recommended for people 25 years and under (see NICE technology appraisal guidance on tisagenlecleucel for treating

relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years). So, there is an unmet need for people older than 25. The clinical expert explained that clinicians in the UK are in a difficult position when treating B-cell acute lymphoblastic leukaemia in people 26 years and over, because there are no CAR T-cell therapy options for this population. The committee concluded that people with relapsed or refractory B-cell acute lymphoblastic leukaemia, especially those 26 years and over, would welcome new treatment options such as CAR T-cell therapies that improve the chance of survival.

The company's positioning of brexucabtagene autoleucel in the treatment pathway is appropriate

3.2 The company proposed 3 potential positions for brexucabtagene autoleucel in the treatment pathway; specifically, for people 26 years and over with relapsed or refractory B-cell acute lymphoblastic leukaemia:

- whose disease has relapsed after an allo-SCT or
- who are ineligible for an allo-SCT or

- who are unlikely to reach a point at which they can have an allo-SCT via existing bridging therapies.

  The clinical experts stated that currently there are no curative treatment options for people 26 years and over whose disease has relapsed after having an allo-SCT. CAR T-cell therapy is not available for this group of people in the NHS. They also explained that in the UK, clinicians would not give a second allo-SCT and that allo-SCT use may decrease in favour of CAR T-cell therapy. This is because allo-SCT is a highly toxic treatment and can lead to graft-versus-host disease (an immune-mediated condition resulting from a complex interaction between donor and recipient adaptive immunity). The clinical experts also stressed the importance of having this treatment option for people who are ineligible for allo-SCT. The committee noted that the treatment pathway proposed by the company included Philadelphia chromosome-negative and Philadelphia chromosome-positive relapsed or refractory B-cell acute lymphoblastic leukaemia. It further noted that the marketing authorisation covered people both with and without the Philadelphia chromosome. The committee concluded that the company's positioning of brexucabtagene autoleucel in the treatment pathway was appropriate.

The relevant comparators are inotuzumab, blinatumomab and ponatinib

3.3 The company compared brexucabtagene autoleucel with all comparators in the NICE scope, that is, FLAG-IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin), inotuzumab, blinatumomab and tyrosine kinase inhibitors (ponatinib). Based on clinical advice, the company refined the list of comparators and categorised them by treatment group: overall population (irrespective of Philadelphia chromosome status), Philadelphia chromosome negative, and Philadelphia chromosome positive. The clinical experts explained that FLAG-IDA-based chemotherapy is rarely used in the UK because of its toxicity, poor tolerance and poor outcomes. They further explained that inotuzumab is given to both subgroups (Philadelphia chromosome-negative and -positive), whereas blinatumomab is restricted to Philadelphia chromosome-negative relapsed or refractory B-cell acute lymphoblastic leukaemia. Ponatinib is restricted to Philadelphia chromosome-positive relapsed or refractory B-cell acute lymphoblastic

leukaemia in people whose disease does not respond or who cannot tolerate a tyrosine kinase inhibitor before having an allo-SCT. The committee discussed if FLAG-IDA should be included as a comparator in light of the clinical experts' comments. It agreed that since FLAG-IDA is rarely used in clinical practice, it should not be included as a comparator. The committee concluded that inotuzumab, blinatumomab and ponatinib were the appropriate comparators for people 26 years and over with relapsed or refractory B-cell acute lymphoblastic leukaemia.

Clinical effectiveness

Brexucabtagene autoleucel could be clinically effective, but a curative treatment effect is uncertain

3.4 The clinical-effectiveness evidence for brexucabtagene autoleucel came from ZUMA-3, a single-arm open-label study of relapsed or refractory B-cell acute lymphoblastic leukaemia. The trial recruited people from 32 centres across 5 countries, but there were no centres in the UK. A total of 78 people with relapsed or refractory B-cell acute lymphoblastic leukaemia were included in the final analysis, which provided the clinical evidence for the company's base-case cost-effectiveness analysis. The trial population included people under 26 years, so restricting the analysis to people covered by the marketing authorisation reduced the number of people included. The exact number is confidential so cannot be shown here. The primary outcome of the trial was overall complete remission. Secondary outcomes included overall survival and relapse-free survival. The median overall survival and relapse-free survival results are considered confidential by the company, so they cannot be shown here. The results for overall survival suggested that brexucabtagene autoleucel could be potentially curative. The ERG explained that the results supporting an assumption of cure with brexucabtagene autoleucel were uncertain. It explained that, over time, relapse-free survival decreased, and that this indicated that brexucabtagene autoleucel may not be curative. It also noted that because the analyses did not distinguish between people who had an allo-SCT before treatment and those who did not, it was unclear if any of the survival benefit resulted from allo-SCT treatment before treatment with

brexucabtagene autoleucel. The clinical experts were concerned about how to interpret the relapse-free survival curve given the uncertainties. They noted that it was unlikely that survival after treatment with brexucabtagene autoleucel would be influenced by prior allo-SCT. They added that curative outcomes can be seen in real-world evidence from people with relapsed or refractory B-cell acute lymphoblastic leukaemia who have had multiple different treatments before the CAR T-cell therapy. One of the clinical experts stressed that relapses after 12 months are infrequent and that this should be considered. The committee concluded that treatment with brexucabtagene autoleucel could be clinically effective, but a curative treatment effect is uncertain.

Brexucabtagene autoleucel is expected to be equally effective in both subgroups

3.5 The company proposed brexucabtagene autoleucel for treating Philadelphia chromosome-positive and -negative relapsed or refractory B-cell acute lymphoblastic leukaemia. The clinical experts stated that the treatment is expected to have similar efficacy in both populations. This is because the mechanism of action is not related to Philadelphia chromosome status. They noted that tisagenlecleucel is equally clinically effective in Philadelphia chromosome-negative and -positive disease. The committee concluded that brexucabtagene autoleucel is expected to be equally effective in both Philadelphia chromosome-negative and Philadelphia chromosome-positive disease.

For the comparison with blinatumomab and ponatinib, the company and ERG's methods are acceptable

3.6 Because ZUMA-3 is a single-arm trial, an indirect treatment comparison was needed to estimate the efficacy of brexucabtagene autoleucel compared with the comparators. ZUMA-3 was used as the evidence source for brexucabtagene autoleucel. The evidence sources for blinatumomab were TOWER and SCHOLAR-3, and the evidence source for ponatinib was PACE. For the comparison with blinatumomab, the company presented:

- a matched comparison via SCHOLAR-3, using the synthetic control arm from SCHOLAR-3 to compare brexucabtagene autoleucel with blinatumomab (used in its base-case economic analysis)
- a naive unadjusted comparison
- a matching-adjusted indirect comparison (MAIC).

The ERG used the company's matched comparison via SCHOLAR-3 for the comparison with blinatumomab in its base case. But it highlighted that the company did this analysis with ZUMA-3 phase 2 data only, and matching with pooled phase 1 and 2 data would have been preferred. For the comparison with ponatinib, the company presented a naive unadjusted comparison only and used this in its base case. The company deemed a MAIC against ponatinib unsuitable because of the small numbers of people with Philadelphia chromosome-positive disease in ZUMA-3. The ERG agreed that a MAIC against ponatinib was unsuitable and that a naive comparison was needed. The committee considered that the treatment comparisons indicated that brexucabtagene autoleucel could potentially improve event-free and overall survival compared with blinatumomab and improve overall survival compared with ponatinib, but this was uncertain. It concluded that the company's and the ERG's methods of using a matched comparison via SCHOLAR-3 for blinatumomab and an unadjusted comparison for ponatinib were acceptable.

For the comparison with inotuzumab, the inverse hazard ratio analysis is preferred

3.7 For the comparison with inotuzumab, the company presented a naive unadjusted comparison and a MAIC. It used ZUMA-3 as the evidence source for brexucabtagene autoleucel and INO-VATE as the evidence source for inotuzumab. The company's base case used the naive unadjusted comparison. It preferred this comparison because it believed ZUMA-3 was more aligned with the target population in UK practice, whereas INO-VATE was not. It said that using a MAIC would not adjust to the population of interest. The ERG noted that the population in INO-VATE was different to that in ZUMA-3, and so a naive comparison would be at a high risk of bias. So, this comparison would not reflect the true relative treatment effect. It preferred a MAIC approach to adjust for the differences between the trials. The company used the overall

population data for the MAIC, so the ERG was not able to look at the MAIC analysis for the Philadelphia chromosome-positive and -negative subgroups. This is because it did not have subgroup data from the INO-VATE study. So the ERG had to adjust the MAIC analysis to the ZUMA-3 study data. The ERG also suggested using inverse hazard ratios derived from the MAIC analysis applied to the ZUMA-3 arm as baseline (an inverse hazard ratio method). This was an alternative method to minimise bias associated with the other analysis methods. The ERG considered this a reasonable approach because the company believed that matching patients to studies other than ZUMA-3 would be inappropriate. The ERG had not been given enough time to review this analysis before the first committee meeting, but was able to review it before the second meeting. At the second committee meeting, the ERG's base-case economic analysis used the inverse hazard ratio method for the comparison with inotuzumab. The committee considered that brexucabtagene autoleucel could potentially improve event-free survival compared with inotuzumab, but that this was uncertain. It concluded that it preferred the inverse of the hazard ratios method for the comparison with inotuzumab, over the MAIC and naive comparisons.

The company's economic model

The company's economic model is appropriate for decision making

3.8 The company used a partitioned survival model that included 3 mutually exclusive health states: event-free, progressed disease and death. The company modelled the cost effectiveness of treatment with brexucabtagene autoleucel using data from ZUMA-3 and data from INO-VATE, TOWER, PACE and SCHOLAR-3 for the comparators. After technical engagement the company updated its economic model to include a recent data cut of ZUMA-3, revised clinical-effectiveness data for people 26 years and over (the population in the marketing authorisation) and data from SCHOLAR-3. The committee agreed that the model was appropriate for decision making.

A standardised mortality ratio of 3 is appropriate in the absence

of evidence, but this is highly uncertain

3.9 The company's model assumed a standardised mortality ratio of 1.09 to model the mortality risk of people whose cancer was considered cured after 3 years of relapse-free survival. This was compared with the mortality of the age- and sex-matched general population in the UK. The ERG considered this to be an underestimate. It noted that this value was from a study of people with diffuse large B-cell lymphoma rather than B-cell acute lymphoblastic leukaemia. The ERG proposed a standardised mortality ratio of 4, sourced from Martin et al. (2010), which included people with relapsed or refractory B-cell acute lymphoblastic leukaemia in which the mortality risk ranged between 4 and 9. It noted that it had chosen the lowest value in the study, which was a conservative approach. The company noted that the Martin et al. study was in people who had allo-SCT, which is more burdensome and has longer-term treatment requirements than CAR T-cell therapy. During consultation, the company provided a scenario using a standardised mortality ratio of 2.2. This was a weighted average based on the proportion of people who had received allo-SCT before brexucabtagene autoleucel in ZUMA-3, with a standardised mortality ratio of 4 applied to people who had received an allo-SCT and 1.09 applied to the remaining proportion. The ERG also provided a threshold analysis that applied various standardised mortality ratios to the ERG base case, ranging from 1.09 to 4. The clinical experts explained that there is no long-term survival data for people with relapsed or refractory B-cell acute lymphoblastic leukaemia who have had brexucabtagene autoleucel. But they expected it to be similar to the data for tisagenlecleucel, for which many people have been followed up for 5 to 10 years. The clinical experts highlighted that the main risk of the disease relapsing is during the first year after treatment, and that after that, relapse is unlikely. They further explained that the increased risk of dying was associated with having an allo-SCT. This is because of the risk of graft-versus-host disease. The clinical experts added that it is rare that people who have had a CAR T-cell therapy develop graft-versus-host disease. They suggested that the appropriate standardised mortality ratio was highly uncertain, but that it was likely to be greater than 1.09 and lower than 4, and likely closer to the ERG's estimate than the company's. The committee understood that the risk of dying was linked to allo-SCT before the CAR T-cell therapy and that the population

in Martin et al. included only people who had had allo-SCT. So the population in Martin et al. was likely to be at a higher risk of death than the population who would be treated in clinical practice, who would not all have had allo-SCT. But the committee also noted that the ERG had used the lower end of the range of the standardised mortality ratio in Martin et al., which may be appropriate given the differences in the populations. The committee considered the company's weighted average standardised mortality ratio of 2.2. There was no evidence from people with B-cell acute lymphoblastic leukaemia that supported using a standardised mortality ratio of 1.09 in the weighted average for people who have not had an allo-SCT. So this was highly uncertain. The committee also noted that the standardised mortality ratio of 4 applied in the weighted average to people who have had allo-SCT was at the lower end of the range in Martin et al. and so may be an underestimate for this population. Given this, and the high level of uncertainty, the committee agreed that it was appropriate to consider a standardised mortality ratio higher than 2.2. It concluded that in this case and given the lack of evidence, a standardised mortality ratio of 3 was appropriate, as this was the midpoint between the company's scenario analysis of 2.2 and the ERG's base-case value of 4. It further concluded that the true standardised mortality ratio for this population was highly uncertain and may be as high as the ERG's estimate of 4.

People who have had brexucabtagene autoleucel do not have the same health-related quality of life as the general population

3.10 The company's model assumed that people who had brexucabtagene autoleucel and whose disease had not progressed after 3 years of treatment would have the same health-related quality of life as that of the same age- and sex-matched general population in the UK. The ERG had received clinical advice that there is cumulative toxicity from previous therapies, and that the disease itself reduced health-related quality of life. So the ERG proposed applying a utility multiplier of 0.92 to the general population utility values to adjust for lower quality of life. This was calculated from a ratio between the utility value reported in ZUMA-3 after the infusion and before relapse (0.82), and the general population of a similar age (0.89). The ERG also noted that if a standardised mortality ratio was being applied to account for an increased risk of

death in this population (see section 3.9), it was logical to also assume a decrease in health-related quality of life. The company disagreed that mortality and health-related quality of life would be correlated, because acute events that do not affect quality of life may lead to death. It also stated that the ERG's approach underestimated the health-related quality of life of the cured population, because it was partly based on utility values measured shortly after CAR T-cell treatment, which would be lower than the utility values expected 3 years after treatment. The company also noted that the general population included people who had weakened immune systems and who have had cancer, and so the general population utility values reflected the population whose relapsed or refractory acute lymphoblastic leukaemia was cured. The ERG explained that the proportion of people with a weakened immune system or who have had cancer was much lower in the general population than it would be in this population. The clinical experts explained that there is not enough evidence in CAR T-cell therapies to support either approach. But they explained that reduced quality of life in this population is likely to be related to previous treatments. People can live a near-normal life after treatment with the new technology and can return to daily activities soon after having a CAR T-cell therapy. The clinical experts also explained that CAR T-cell therapy can lead to better quality of life than other treatments, because it is given in an outpatient setting and so people need less time in hospital. The patient expert stated that the condition had a huge emotional and financial impact on them and their family after they were diagnosed. They explained that they have a sustained risk from infections and so have to have regular follow-up appointments. However, this monitoring provides reassurance and does not affect the ability to perform daily activities. They stated that the benefits of treatment outweighed the negative impacts. The committee understood that people whose disease has not progressed after 3 years will have a worse health-related quality of life than the general population, even though CAR T-cell treatment is better tolerated than some other treatments for acute lymphoblastic leukaemia. This is because of the risks associated with CAR T-cell treatments, the effect of previous therapies including chemotherapy and allo-SCT, and the effects from the disease itself, all of which are more prevalent in this population than in the general population. It noted that the ERG's approach appeared plausible and that the company had not provided an analysis

during consultation using a utility value based on trial data recorded after a longer follow up. It concluded that people having brexucabtagene autoleucel do not have the same quality of life as the general population, and the ERG approach should be used in decision making.

Allo-SCT costs and QALY loss should be included in the model for people having brexucabtagene autoleucel

3.11 In ZUMA-3, 14 out of 78 (18%) people had an allo-SCT. But the company did not account for the costs or quality-adjusted life year (QALY) impact of allo-SCT use in this proportion of people in the brexucabtagene autoleucel arm in the economic model. The company stated that the technology is not planned to be used before an allo-SCT in UK clinical practice. It had done a sensitivity analysis adjusting for overall survival, censoring for allo-SCT, and no statistical difference was found. The ERG stated that the sensitivity analysis was not sufficiently powered to detect a difference. So it could not be determined if an allo-SCT could have provided a survival advantage to the people who had had one. The ERG stated that it was therefore also appropriate to include the associated costs and QALYs in the model for the 18% who received brexucabtagene autoleucel in ZUMA-3 and went on to receive allo-SCT. The clinical experts stated that allo-SCT after CAR T-cell treatment would not be standard practice, and that brexucabtagene autoleucel would likely be used as a standalone therapy. The committee noted that it was unclear how often allo-SCT would be used in practice. But it noted the ERG's opinion that because the clinical-effectiveness evidence in the model included some people who received allo-SCT after CAR T-cell treatment, the associated costs and QALYs of allo-SCT should also be included. The committee concluded that allo-SCT costs and a QALY loss should be included in the model for people having brexucabtagene autoleucel.

CAR T-cell delivery costs of £41,101 are most appropriate for decision making

3.12 NHS England has established a single tariff to capture the costs of delivering CAR T-cell therapy. The tariff was developed after NICE recommended the first CAR T-cell therapy, tisagenlecleucel, for use in the Cancer Drugs Fund in December 2018. NHS England explained that

the tariff includes all costs of care from the decision to have CAR T-cell therapy to 100 days after the infusion. NHS England explained that there is not a healthcare resource group (HRG) code that adequately captures the administration of CAR T-cell therapies. As part of the NICE technology appraisal guidance on axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (TA872), the company (also the company in this appraisal) submitted an analysis using a CAR T-cell therapy delivery cost of £41,101. This was informed by an ERG scenario analysis in the NICE technology appraisal guidance on axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy. NHS England considered that, although the company's cost of £41,101 differs from the NHS England tariff for CAR T-cell therapy, it was an acceptable cost to use in the cost-effectiveness analysis. This is because although the NHS England tariff represents the high hospital costs of establishing the infrastructure of a CAR T-cell therapy service and delivering a relatively new type of treatment, economies of scale may be expected over time, particularly with clinical developments that reduce toxicity and the intensity of monitoring and treatment. At the second committee meeting, the company included the CAR T-cell delivery cost of £41,101 in its base case, and excluded the costs for the following from the model, which it believed should be covered by the delivery cost:

- leukapheresis
- CAR T-cell administration
- adverse events
- monitoring
- training

- conditioning and bridging chemotherapy acquisition, administration and delivery.

  NHS England's clinical lead for the Cancer Drugs Fund noted that the costs of conditioning and bridging chemotherapy are not included in the £41,101 delivery cost. The ERG also included the CAR T-cell delivery cost of £41,101 in its base case and excluded most of the same costs that the company excluded. But the ERG included the costs of conditioning and bridging chemotherapy separately in the model. NHS England confirmed that the ERG's approach was appropriate and in line with the approach agreed for TA872. The committee noted NHS England's comments and was satisfied that the ERG's costs were a reasonable projection of the cost to the NHS of delivering CAR T-cell therapy.

End of life

Brexucabtagene autoleucel meets the criteria to be considered a life-extending treatment at the end of life

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The literature showed that median overall survival with the comparator treatments ranged from 5.3 to 8 months. The clinical experts stated that life expectancy is the same for people with Philadelphia chromosome-negative and -positive disease. The company's model predicted that mean overall survival with the comparator treatments was more than 24 months, but the percentage of people alive at 2 years ranged from 13% to 22%. So the committee was persuaded that people are unlikely to live for longer than 24 months and that the short life expectancy criterion was met. The clinical experts explained that it is likely that brexucabtagene autoleucel will extend life for more than 3 months. Also, the model estimated a mean overall survival gain for brexucabtagene autoleucel compared with the comparators of more than 3 months. The exact data is confidential and so cannot be shown here. The committee concluded that the end of life criteria were met for people 26 years and over with relapsed or refractory B-cell acute lymphoblastic leukaemia.

Cost-effectiveness estimate

Because of the uncertainty, the maximum acceptable ICER would be substantially less than £50,000 per QALY gained

3.14 NICE's guide to the methods of technology appraisal (section 6) notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, decisions 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. The committee noted the high level of uncertainty, specifically associated with:

- the clinical-effectiveness estimates and the assumption of cure (see section 3.4)
- long-term mortality rates compared with the general population (see section 3.9)
- long-term quality of life compared with the general population (see section 3.10).

The committee also agreed that the end of life criteria applied, which allows it to consider ICERs of up to £50,000 per QALY gained (see section 3.13). NICE's guide to the methods of technology appraisal also notes that the appraisal committee does not use a precise maximum acceptable ICER. Given the level of uncertainty, the committee concluded that the maximum acceptable ICER for routine commissioning would be substantially lower than £50,000 per QALY gained.

Brexucabtagene autoleucel is not recommended for routine use in the NHS

3.15 The committee noted that the ERG's base-case analysis was more closely aligned with its preferred assumptions for both Philadelphia chromosome subgroups, specifically:

- using the inverse of hazard ratios derived from the MAIC analysis to model inotuzumab in the ZUMA-3 population (see section 3.7)
- including costs and QALY loss associated with allo-SCT for people who have brexucabtagene autoleucel (see section 3.11)
- applying a utility multiplier of 0.92, to age and sex-matched general population utilities (see section 3.10)
- assuming adverse event-related costs for brexucabtagene autoleucel would be the same as those for inotuzumab
- removing the costs of FLAG-IDA for people having ponatinib
- assuming a CAR T-cell delivery cost of £41,101 plus the costs associated with conditioning and bridging chemotherapy (see section 3.12).

The committee also concluded that it was appropriate to apply a standardised mortality ratio to the general population mortality rate after 3 years in the model. It was highly uncertain what the true standardised mortality ratio should be. It concluded that it was appropriate to consider a value of 3 for decision making, noting that it could plausibly be as high as 4 (see section 3.9). The committee considered the ICERs using standardised mortality ratios of 3 and 4 applied to the ERG's base case, using the confidential discounts for brexucabtagene autoleucel and the comparator treatments. Because there are confidential discounts, the exact ICERs cannot be reported here. The committee noted that the ICERs were not all substantially below £50,000 per QALY gained in deterministic analysis, compared with both comparators, in the Philadelphia-positive and -negative subgroups. It noted that the ICER was highest when using a standardised mortality ratio of 4. The ERG highlighted that these ICERs were based on deterministic analyses and that it was likely that the probabilistic ICERs in a fully incremental analysis would be higher. The committee recalled that a maximum acceptable ICER for routine commissioning would be substantially below £50,000 per QALY gained (see section 3.14). Given the high levels of uncertainty in the model and the fact that the ICERs using the committee's preferred assumptions were not all substantially below £50,000 per QALY gained, the committee concluded that brexucabtagene autoleucel could not be recommended for routine use in the NHS.

Cancer Drugs Fund

Brexucabtagene autoleucel meets the criteria for inclusion in the Cancer Drugs Fund

3.16 The committee considered if brexucabtagene autoleucel could be recommended for use within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016. The committee discussed if the uncertainties identified in the company's cost-effectiveness evidence could be addressed by collecting more data in the Cancer Drugs Fund. The ongoing single-arm ZUMA-3 trial will provide further data on the follow up of people having brexucabtagene autoleucel and may help resolve some clinical uncertainties around overall survival, relapse-free survival and whether this treatment is curative. The committee noted that even with further data collection from ZUMA-3, there would still be uncertainty in the comparative clinical-effectiveness evidence. This was because ZUMA-3 was a single-arm study and so comparative evidence relied on indirect treatment comparisons. Other issues, such as the uncertainties in the standardised mortality ratio value (see section 3.9) and the utility value (see section 3.10), would be unlikely to be resolved through further data collection in the Cancer Drugs Fund. The committee noted that brexucabtagene autoleucel does have the potential to be cost effective because some plausible scenarios resulted in ICERs below what NICE considers an acceptable use of NHS resources (see section 3.15). It concluded that brexucabtagene autoleucel did meet the criteria for inclusion in the Cancer Drugs Fund.

Equality issues

With the evidence available, this technology appraisal cannot address the equalities issues

3.17 The committee considered multiple equalities issues:

- The clinical experts noted that people from minority ethnic family backgrounds can have difficulty finding a suitable match for a curative allo-SCT. They also noted that older people are less likely to be eligible for allo-SCT, but could be eligible for brexucabtagene autoleucel. For people who are unable to have an allo-SCT, brexucabtagene autoleucel could offer improved outcomes over existing treatments. The committee noted that this was a population with a particular unmet need. But it was not presented with any clinical or cost-effectiveness evidence allowing this population to be considered separately. So it was only able to make a decision based on the full population in the decision problem. The committee agreed that this could not be addressed in this technology appraisal given the information available.

- The committee noted that the marketing authorisation states that this technology is for people 26 years and over. The patient and clinical experts noted that if this technology is not recommended, it would leave people above this age without access to a potentially curative treatment option. They highlighted that a different CAR T-cell treatment (tisagenlecleucel) is available through the Cancer Drugs Fund for people aged under 26. The committee acknowledged this issue and that people 26 years and over have a particular unmet need. It noted that the decision to recommend brexucabtagene autoleucel was based on the clinical and cost-effectiveness evidence available for this appraisal. The committee concluded that it could not recommend a technology for a particular population based on the fact that another technology appraisal did not include that population.

- The committee was also aware that some religious groups such as Jehovah's witnesses may not accept technologies or procedures derived from blood (such as allo-SCT). These people would normally have best supportive care. The committee acknowledged that if brexucabtagene autoleucel does become available, some people may choose not to have this treatment because it contains human blood products. So, this is not viewed as an equality issue in this appraisal.

  The committee concluded that given the information available, the equality issues cannot be addressed through this technology appraisal.

Conclusion

Brexucabtagene autoleucel is recommended for use in the Cancer Drugs Fund

3.18 The committee recalled the uncertainties in the evidence for this technology (see section 3.14) and that the population has high unmet needs (see section 3.1). Taking this into account, the ICERs based on its preferred assumptions were still higher that what was considered cost effective. So, it concluded that brexucabtagene autoleucel could not be recommended for routine use. But, the committee considered that brexucabtagene autoleucel did have plausible potential to be cost effective, and that some of the clinical uncertainties may be resolved with further data collection (see section 3.16). So brexucabtagene autoleucel is recommended for use in the Cancer Drugs Fund for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has relapsed or refractory B-cell acute lymphoblastic leukaemia and the doctor responsible for their care thinks that brexucabtagene autoleucel is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for use in the Cancer Drugs Fund, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Review of guidance

5.1 The data collection period is expected to end as outlined in the data collection arrangement, when more data from the ZUMA-3 trial is available. Once enough evidence is available, the process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

5.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in section 6 of NICE's guide to the processes of technology appraisal.

Stephen O'Brien
Chair, appraisal committee
March 2023

6 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

Anne Murray-Cota and Albany Chandler
Technical leads

Sally Doss and Christian Griffiths
Technical advisers

Celia Mayers
Project manager

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Accreditation