NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

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

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

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: June 2025

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using obecabtagene autoleucel in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: Friday 4 July 2025
- Second evaluation committee meeting: Thursday 21 August 2025
- Details of the evaluation committee are given in section 4

Issue date: June 2025

1 Recommendations

1.1 Obecabtagene autoleucel (obe-cel) should not be used to treat relapsed or refractory B-cell precursor acute lymphoblastic leukaemia in adults.

1.2 This recommendation is not intended to affect treatment with obe-cel 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 healthcare professional consider it appropriate to stop.

What this means in practice

Obe-cel is not required to be funded in the NHS in England to treat relapsed or refractory B-cell precursor acute lymphoblastic leukaemia in adults. It should not be used routinely in the NHS in England.

This is because there is not enough evidence to determine whether obe-cel offers value for money in this population.

Why the committee made these recommendations

Usual treatment for relapsed or refractory B-cell or B-cell precursor acute lymphoblastic leukaemia is ponatinib, inotuzumab ozogamicin, blinatumomab or tisagenlecleucel. This can be followed by an allogeneic stem cell transplant for some people. Obe-cel would be another treatment option.

There is no clinical trial evidence directly comparing obe-cel with any of the usual treatments. Indirect comparisons suggest that people who have obe-cel live longer than people who have ponatinib, inotuzumab ozogamicin or blinatumomab. But the evidence for this is highly uncertain. There has been no indirect comparison with tisagenlecleucel.

There are also important uncertainties in the economic evidence. These are caused by the assumptions used in the economic model. Because of the uncertainties in the clinical evidence and the economic model, it is not possible to determine the most likely cost-effectiveness estimates for obe-cel. So, it should not be used.

2 Information about obecabtagene autoleucel

Marketing authorisation indication

2.1 Obecabtagene autoleucel (obe-cel; Aucatzyl, Autolus Limited) is indicated for 'the treatment of adult patients (aged 18 years and older) with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for obe-cel.

Price

2.3 The list price for obe-cel is £372,000 per infusion (company submission).

2.4 The company has a commercial arrangement, which would have applied if obe-cel had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Autolus Limited, 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

Relapsed or refractory B-cell acute lymphoblastic leukaemia

3.1 Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing blood cancer. It happens when the bone marrow produces too many immature white blood cells, called lymphoblasts, which accumulate and interfere with normal blood cell production. This overproduction leads to

an abnormal increase in B- or T-lymphocytes, impairing the bone marrow's ability to produce healthy blood cells. ALL develops rapidly and in around 45% of adults with the condition it comes back after a period of remission (relapses) or it stops responding to treatment (becomes refractory). ALL is categorised based on the type of lymphoblast affected (B- or T-cells) and the presence or absence of the Philadelphia chromosome. When B-lymphoblasts are overproduced, the condition is sometimes referred to as B-cell precursor ALL, but this evaluation uses B-cell ALL from here. Philadelphia chromosome-positive B-cell ALL is more common in adults and carries a higher risk of relapsing or becoming refractory. The committee recognised that relapsed or refractory B-cell ALL has a high disease burden and is a severe condition that substantially affects people's lives. It concluded that people with relapsed or refractory B-cell ALL, would welcome a new treatment option.

Clinical management

Treatment options

3.2 Treatment for relapsed or refractory B-cell ALL varies by the person's Philadelphia chromosome status, age, general health and previous treatment. Current treatment options for people with Philadelphia chromosome-positive disease include immunotherapy with ponatinib or inotuzumab ozogamicin (inotuzumab). People with Philadelphia chromosome-negative disease can have immunotherapy with blinatumomab or inotuzumab. Tisagenlecleucel is offered to people 25 years and under. People 26 years and over can have brexucabtagene autoleucel through the Cancer Drugs Fund (see NICE's technology appraisal guidance on brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over, from here TA893). The clinical expert highlighted that allogenic stem cell transplant (ASCT), and chimeric antigen receptor (CAR) T-cell therapy are the only curative options for relapsed or refractory B-cell ALL. They explained that ASCT can be a highly toxic treatment and can lead to

graft-versus-host disease (an immune-mediated condition caused by a complex interaction between donor and recipient adaptive immunity). The committee heard from the patient experts about the severe side effects of chemotherapy and how invasive and debilitating stem cell transplants can be. They added that they had had quicker recovery from CAR T-cell therapy. They also believed that earlier access to CAR T-cell therapy could have prevented many long-term side effects, even though it can result in a weakened immune system. The committee concluded that people with relapsed or refractory B-cell ALL would welcome a new treatment option.

Companies proposed positioning

3.3 The company proposed that obe-cel would be offered to people with Philadelphia chromosome-negative B-cell ALL who usually have:

- blinatumomab (see NICE's technology appraisal guidance on blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia, from here TA450) or
- inotuzumab (see NICE's technology appraisal guidance on inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia, from here TA541).

It would also be offered to people who have Philadelphia chromosome-positive B-cell ALL who usually have:

- ponatinib (see NICE's technology appraisal guidance on ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia) or
- inotuzumab (see TA541).

The company considered ASCT to be a subsequent treatment for both groups. Clinical experts explained that some people would be offered ASCT earlier in the treatment pathway before relapse. Others would have ASCT after ponatinib, inotuzumab or blinatumomab. The clinical experts

also noted they would not offer a second ASCT and that ASCT use may decrease in favour of CAR T-cell therapy. The committee discussed if people would have ASCT after having obe-cel (see section 3.16). The clinical expert explained it could be considered for fit people with matched donors who have not already had a stem cell transplant (SCT). But they noted this would cause the loss of CAR T-cell persistence. If CAR T-cells are lost (within 6 months) without relapse, ASCT may be considered, but only in rare, closely monitored cases. They emphasized that this is a complex scenario, relevant to only a small number of people. The committee broadly accepted the company's proposed positioning in the treatment pathway.

Relevant comparators

3.4 The clinical experts explained that the recent introduction of blinatumomab to routine commissioning has changed the upfront management of B-cell ALL (see NICE's technology appraisal guidance on blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive minimal residual disease-negative B-cell precursor acute lymphoblastic leukaemia). They noted that, going forward, most people with Philadelphia chromosome-negative B-cell ALL who relapse, will likely have had blinatumomab earlier in their treatment pathway. They explained that, currently, people who are minimal residual disease-negative usually have blinatumomab during consolidation. But, people who are minimal residual disease-positive have blinatumomab as a bridge to ASCT. They highlighted that people with Philadelphia chromosome-positive status who relapse are offered ponatinib, while inotuzumab is offered regardless of Philadelphia chromosome status. The clinical experts noted that both are used as bridging treatments before ASCT (if not already offered) or CAR T-cell therapy, to control the condition, reduce toxicity and improve outcomes. Brexucabtagene autoleucel (see TA893) is recommended in the Cancer Drugs Fund so it was not considered a relevant comparator. The NHS England Cancer Drugs Fund clinical lead (from here, CDF lead) recalled

that a significant number of people (72.5%) have brexucabtagene autoleucel after ASCT, whether in first or second remission. The clinical expert explained that the high proportion of people having ASCT before CAR T-cell therapy reflects recent access. The clinical expert said that increased early use of blinatumomab is expected to reduce the number of SCTs in first remission. They explained that the aim is to improve outcomes and reduce the need for subsequent treatments caused by relapses. The committee noted that blinatumomab's use in relapsed or refractory B-cell ALL is expected to fall because of its earlier position in the treatment pathway. But, it concluded that blinatumomab remains a relevant comparator. The committee noted that most of the comparators are used as bridging therapies to ASCT or CAR T-cell therapy. The committee concluded that the comparators ponatinib, inotuzumab and blinatumomab were broadly acceptable if ASCT is included as a subsequent treatment. But, it added, tisagenlecleucel (see NICE's technology appraisal guidance on tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under) should be included as a comparator in the 18 to 25 years age group (see section 3.5).

Tisagenlecleucel as a comparator in the 18 to 25 years age group

3.5 The conditional marketing authorisation for obe-cel is for adults with relapsed or refractory B-cell ALL. The committee understood that the company had anticipated a narrower age range for its marketing authorisation and this had influenced its proposed positioning in the treatment pathway (see section 3.3). So it did not provide a comparison with tisagenlecleucel for people 18 to 25 years. The CDF lead explained that, currently, around 22.5% of people having tisagenlecleucel in the NHS are 18 to 25. The company's main clinical trial evidence comes from the FELIX study (see section 3.6). It explained that in cohort 2A of the FELIX study, there was only a small number of people in the 18 to 25 years age group (n=11). Because of this, it had expected that its marketing authorisation would be restricted to a similar population to

brexucabtagene autoleucel (people 26 years and over). The company explained that its initial submission therefore focused on people 25 years and over. But, it confirmed that all the evidence for people 18 and over from cohort 2A of FELIX had been included in the modelling. The company noted the small size of the 18 to 25 age group in the FELIX study and that individual patient data was not available for the tisagenlecleucel population. It explained that these limitations made a robust comparison difficult. The CDF lead noted that that there is data available from the NHS on overall survival and event-free survival for people 18 to 25 years having tisagenlecleucel. The committee acknowledged the challenges in extracting data from the FELIX study. But, it noted that a comparison may still be feasible despite the small trial population for obe-cel compared with the larger real-world cohort for tisagenlecleucel. It concluded that tisagenlecleucel was a suitable comparator in the 18 to 25 years age group. So, it would like to see a comparison using FELIX data for obe-cel alongside real-world data from the Systemic Anti-Cancer Therapy dataset (SACT) for tisagenlecleucel.

Clinical effectiveness

Obe-cel data sources

3.6 The company's main clinical trial evidence on the clinical effectiveness of obe-cel came from the FELIX study. FELIX is an ongoing, single-arm phase 1B/2, non-randomised, open-label multicentre trial. It is evaluating the safety and efficacy of obe-cel in adults with relapsed or refractory B-cell ALL in 2 phases (phase 1B and phase 2), across 5 cohorts:

- phase 1B, cohort 1A: people with morphological disease (5% or more blasts in the bone marrow; n=21 enrolled, n=13 infused)
- phase 1B, cohort 1B: people in morphological remission but with minimal residual disease (minimal residual disease of 10^{-4} or greater and less than 5% blasts; n=3 enrolled, n=3 infused)

- phase 2, cohort 2A: people with morphological disease (5% or more blasts in the bone marrow; n=112 enrolled, n=94 infused)
- phase 2, cohort 2B: people in morphological remission but with minimal residual disease (minimal residual disease of 10^{-4} or greater and less than 5% blasts; n=10 enrolled, n=10 infused)
- phase 2, cohort 2C: people with isolated extramedullary disease at screening (n=7 enrolled, n=7 infused).

In both phases, people went through the following 5 stages:

- screening
- leukapheresis
- lymphodepletion
- treatment and
- follow up.

The company identified the cohort 2A modified intention-to-treat (mITT) population as the cohort relevant for the submission that included people who had at least 1 obe-cel infusion (n=94). It felt that cohort 2A best reflects the population that obe-cel's anticipated licence would cover. It also felt that the mITT population best reflects who would have obe-cel in clinical practice, because obe-cel will only be reimbursed for people who have at least 1 dose. Of the 112 people enrolled in the cohort, 94 had at least 1 obe-cel dose. The company viewed progression-free survival to be equivalent to event-free survival in this setting. Event-free survival was defined as time from first obe-cel infusion to treatment failure, morphological relapse or death (whichever happens first). The median event-free survival was 9.03 months in the mITT population of cohort 2A, with censoring for SCT and other new anti-cancer treatments. Overall survival in the mITT population of cohort 2A was considered without censoring for SCT. The median overall-survival results are considered confidential by the company, so they cannot be reported here. The EAG thought the enrolled intention-to-treat (ITT) populations of cohorts 1A and

2A are more representative of what happens to people starting CAR T-cell therapy in the NHS. It also felt that these groups were more suitable for comparing efficacy against other treatments. The committee concluded that the enrolled ITT population from cohorts 1A and 2A was the most appropriate source of clinical evidence for obe-cel.

Generalisability of FELIX in NHS practice

3.7 FELIX is an ongoing, single-arm, open-label trial with a small sample size (see section 3.6). The EAG expressed concerns that, despite high recruitment in the UK, the FELIX trial may not reflect the NHS population. It gave 2 reasons for this. First, the trial population included a lower proportion of people 65 years and over with relapsed or refractory B-cell ALL than is seen in NHS practice. Second, the trial excluded people with an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or more, which represents a significant portion of the NHS treated population. The clinical expert noted that the age range may have reflected referral bias. They highlighted that current practice prioritizes those with good performance status and explained that age itself is not a barrier, and that older people who receive treatment often have higher performance status. Older people who are fit would be eligible to have obe-cel, and it may be a preferred option. This is because, compared with other CAR T-cell therapies, obe-cel is less likely to cause serious side effects like cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. To be eligible for CAR T-cell therapy in the UK, people must typically have an ECOG performance status of 0 to 1. The company highlighted that the population over 65 years in FELIX performed better than the younger population. The committee discussed how generalisable the results were across the age groups. The clinical experts agreed it was reasonable to assume no major differences in relative effects by age. The committee recalled the improved outcomes seen in people 65 years and over, which suggested that the FELIX trail is generalisable to NHS practice. It concluded that the trial was generalisable to NHS practice.

Indirect treatment comparison

Matching-adjusted indirect comparison

3.8 Because the FELIX trial is single arm trial (see section 3.6), the company did indirect treatment comparisons of obe-cel with inotuzumab, blinatumomab, and ponatinib. The company did a systematic literature review to identify studies that could provide comparator data to use in an indirect treatment comparison. The company updated the search strategy used in the systematic literature review for TA893. Studies for the indirect treatment comparisons were selected based on TA893 and clinical expert input. The studies included were:

- FELIX for obe-cel
- INO-VATE for inotuzumab, a phase 3, controlled, open-label trial in 164 people with relapsed or refractory B-cell ALL
- TOWER for blinatumomab, a phase 3, controlled, open-label trial in 271 people with Philadelphia chromosome-negative relapsed or refractory B-cell ALL, and
- PACE for ponatinib, a phase 2 singe-arm open-label trial in 32 people with Philadelphia chromosome-positive relapsed or refractory B-cell ALL.

Because there was no individual patient data in the comparator studies and FELIX is a single-arm trial, only unanchored population-adjusted indirect comparisons were feasible. The company did a matching-adjusted indirect comparison (MAIC) to estimate the relative effectiveness of obe-cel compared with inotuzumab (from INO-VATE) and blinatumomab (from TOWER) for overall survival and event-free survival. A MAIC was done with ponatinib, but the results were unreliable because of poor study overlap and a small effective sample size. So, the company presented a naive unadjusted comparison, which was used in its base case. Results from the MAIC, and the naive unadjusted comparison are considered confidential by the company, so they cannot be shown here. The

committee concluded that because of the small sample size, the results of the MAIC were highly uncertain.

Adverse events

3.9 The company derived the incidence of adverse events from the individual comparator trials. Grade 3 or higher adverse events that happened in 3% or more of the population in any arm were included in the model (apart from cytokine release syndrome, where the proportion of people with grades 2 and 3 were included). For obe-cel, the model included grade 3 or higher adverse events from the mITT population of cohort 2A in FELIX. The EAG noted concerns about the company's adverse event reporting. For example, key events such as immune effector cell-associated neurotoxicity were not included, despite being considered critical for CAR T-cell therapies by the company's clinical advisers. The EAG preferred to include all grade 3 or higher treatment-emergent adverse events for all people infused, as reported in the clinical study report, in the model. The company explained that the difference in numbers was due to the choice of population in the FELIX study. The company focused on the infused mITT population of cohort 2A (n=94). But, the EAG's preferred population was the broader enrolled ITT population of cohorts 1A and 2A (n=133). The company accepted the EAG's approach to modelling adverse events. The committee concluded that it preferred the EAG's approach and supported the use of broader data from the larger cohort.

Economic model

Company's modelling approach

3.10 The company used a partitioned-survival model to estimate the long-term costs and outcomes of treatments for relapsed or refractory B-cell ALL. The model included 3 states: event-free, post-event and death. All people enter the model in the event-free state and transition to the post-event or the death state upon disease progression. The event-free state captured the time at which people first have treatment to the time at which 1 of

either treatment failure, morphological relapse or death happens. The post-event state included people who experience disease progression or treatment failure. The death state accounted for people who died from any cause. The company's model also included a cure assumption for people in any treatment arm who were alive 3 years after treatment. The committee concluded that the model structure was appropriate for decision making.

Preferred population and method for extrapolation

3.11 The company used the infused mITT population from FELIX cohort 2A, which included people who had had at least 1 obe-cel infusion, as the basis for all comparisons (see section 3.6). The EAG preferred the enrolled ITT population from cohorts 1A and 2A. This included the pre-infusion period and so captured individuals who had leukapheresis. The EAG noted that an effective comparison should start at leukapheresis for CAR T-cell therapy. This is because excluding this phase introduces bias caused by treatment delays and bridging, unlike comparator treatments that begin immediately. The CDF lead explained that NHS England reimburses trusts for CAR T-cell therapy only after infusion. So, if a person has leukapheresis but is not infused, the cost is not covered. The clinical expert noted that bridging management had significantly improved during the FELIX study, with faster CAR T-cell manufacturing and more aggressive bridging therapies. The company noted that, although the inclusion criteria were consistent across cohorts 1A and 2A, people in cohort 1A had heavier pretreatment, which contributed to slightly worse outcomes. The committee considered the company's and EAG's preferred populations. It concluded that the EAG's preferred population, comprising the enrolled ITT population from cohorts 1A and 2A, was the most appropriate for decision making.

Inverse hazard ratio approach

3.12 For the comparisons with inotuzumab and blinatumomab, the company used an inverse MAIC approach in its base case. The company

highlighted that it used the inverse hazard ratio approach for inotuzumab and blinatumomab to enable fully incremental analysis across the different subgroups. It noted that its methods broadly aligned with those used in TA893. It also explained that it preferred to base the analysis on the characteristics of the FELIX study, rather than the MAIC-weighted extrapolations based on comparator trial populations. It noted that when matched to ponatinib, the effective sample size was small, indicating poor overlap between the 2 studies. So, it considered the results unreliable and preferred a naive approach. The EAG acknowledged that, despite its concerns with the FELIX trial, its high level of UK recruitment made it a reasonable choice. The EAG explained that, had the company used the standard MAIC approach without the inverse method, it could have relaxed the proportional hazards assumption by fitting separate parametric curves to each arm. The committee noted that the very small effective sample sizes contributed to considerable uncertainty in the results. It accepted that this uncertainty could not be fully resolved. But, it considered that the use of the inverse hazard ratio approach required further justification. It considered that an inverse hazard ratio approach would be appropriate if FELIX was the best reflection of the NHS population. The committee did not believe it had seen evidence that the FELIX study is better than INO-VATE or TOWER for reflecting the NHS population. It asked that the company provide a more robust rationale, based on the data submitted for this appraisal, for using the inverse hazard ratio approach in these analyses.

Cure assumption

3.13 The company's model included a cure assumption for people in any treatment arm alive 3 years after treatment (see section 3.10). This impacted the survival extrapolations in the model. The EAG also included a cure assumption at 3 years. The company explained that the model's cure assumption applied to people who had not experienced an event and to people who had (those in the post-event health state). It noted that a standardised mortality ratio of 3 was applied to people alive beyond

3 years. This reflected their higher mortality risk and reduced quality of life compared with the general population. The clinical expert supported the company's approach for people in the obe-cel arm and noted that relapses are generally not expected beyond that point. The committee concluded that a cure assumption at 3 years was appropriate in the event-free state. But, the standardised mortality ratio of 3 used in both the EAG and company base case was based on data from people in remission only. The committee noted that, while the cure assumption was applied across all treatment arms, a higher number of people remained alive in the obe-cel arm (across both even-free and post-event health states). This could introduces bias in favour of obe-cel. The committee considered whether it was appropriate to assume that people who experienced events could be considered cured and share the same standardised mortality ratio as people who remained event-free. It concluded that it wanted further clarification on the cure assumption applying to people in the post-event health state. The committee noted that in the original source data (Martin et al. 2010), the mortality risk had ranged between 4 and 9 for people who survived without recurrence for at least 5 years. So it requested further examination of the mortality risk applied after the cure assumption. The committee also requested further evidence that it would be reasonable for people who have had events to be considered cured and have the same standardised mortality ratio as people who had no events. Given the impact the cure assumptions had on survival extrapolations, additional analyses should explore any changes of these assumptions on survival extrapolations.

Costs

Hospitalisation and resource use for obe-cel

3.14 The company used a bottom-up costing approach to calculate the administration cost of obe-cel in the model, which consisted of hospitalisation and intensive care unit (ICU) costs. Data on hospitalisation (length of hospital stay, proportion needing ICU, length of ICU stay) was

originally based on TA893. After clarification, the company used UK-specific data from the FELIX trial's cohort 2A (n=36) to estimate length of hospital stay. The EAG preferred to use the latest NHS England CAR T-cell tariff cost, which is £60,462. This includes the costs associated with leukapheresis, delivery of CAR T-cell therapy, in-hospital adverse events, monitoring for 100 days and training. The CDF lead highlighted that the tariff did not include the cost of:

- administration, delivery and acquisition of conditioning and bridging chemotherapy
- CAR T-cell therapy product acquisition
- subsequent therapies and
- subsequent ASCT.

Recent NICE evaluations of CAR T-cell therapies (such as NICE's technology appraisal guidance on lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable) used a CAR T-cell tariff cost of £58,964 for the financial year 2024/25. The CDF lead explained that a tariff cost of £60,462 now applies, which is the annual uplift figure for 2025/26 applied to the 2024/25 figure. The company explained that it had used resource use data from UK patients in the FELIX trial, because it believed it better reflects NHS practice. The company highlighted that obe-cel has lower toxicity than other CAR T-cell therapies and may offer additional benefits not captured by the current tariff. The company accepted the tariff would apply and reflects the cost paid by NHS England to deliver CAR T-cell therapy. But, it highlighted that the tariff excludes ICU costs and may not reflect the value of ambulatory care for obe-cel. The committee concluded that the updated tariff cost of £60,462 should be applied in the model, but there may be uncaptured benefits associated with the costs of ambulatory care (see section 3.26).

Outcomes for ASCT after obe-cel

3.15 The company's analysis assumed that people in the comparator arms (blinatumomab, inotuzumab and ponatinib) who had an event after starting treatment were eligible to have a subsequent ASCT. But, it assumed that in the obe-cel treatment arm, people would not have an ASCT. The company explained that the model did not explicitly model the impact of ASCT on overall survival. But, it noted that the event-free-survival and overall-survival Kaplan–Meier curves used in the analysis did not censor people who had an ASCT. So, the utility for ASCT is inherently captured within the curves. The company explained that outcomes for people who had ASCT after obe-cel in the trial were poor, which may reflect the loss of CAR T-cell persistence. The EAG highlighted that obe-cel has the dual potential to be a curative therapy or a bridging therapy to ASCT. The EAG assumed a small proportion of people (around 10%) are expected to have obe-cel as a bridging therapy to ASCT. This reflected the FELIX trial, where a small number of people had an ASCT after having an infusion of obe-cel (the number is considered confidential by the company and cannot reported here). The committee noted that outcomes for people who had ASCT in FELIX may not reflect those seen in clinical practice. It concluded that healthcare professionals now better understand the value of CAR T-cell persistence and are less likely to offer ASCT outside a trial setting.

Costs associated with ASCT

3.16 The committee then considered how the associated costs of ASCT are included in the economic model. The EAG's base case included the costs of ASCT for the enrolled ITT population from cohorts 1A and 2A in the FELIX trial. That is, the proportion who had ASCT in the trial were included in the EAG base-case model. The committee recalled (see section 3.3) that for fit, SCT-naive people with matched donors, ASCT could be considered after obe-cel if CAR T-cells are lost (within 6 months) without relapse. But the proportion of people to whom this applies was likely to be small. The committee acknowledged that the proportion of people who would progress to ASCT would be fewer than had ASCT in

the FELIX trial. The committee noted that there is limited data to inform the appropriate proportion and costs associated with ASCT in the obe-cel arm. It concluded it would like to see a range of scenarios on the impact of changing the proportion of people having ASCT. It noted that this proportion is likely to be less than 10% of the ITT population and concluded that a range of scenarios would help resolve the uncertainty.

Costs of follow up after ASCT

3.17 The company modelled the costs of ASCT for the comparator arms only. The total cost of ASCT for the comparators included the cost of stem cell harvesting, the ASCT procedure and follow-up costs for 24 months. The EAG found an error in the company's model that overestimated follow-up costs. The EAG assumed that the total undiscounted costs for different components of ASCT should not exceed the proportion of people having ASCT multiplied by the corresponding cost. It corrected the error to ensure the maximum undiscounted total costs align with the proportion of people having ASCT. The company acknowledged the error in its model. But it noted that the EAG's approach did not account for tunnel states, meaning it did not consider the proportion of people considered in previous cycles. The committee concluded that the EAG's approach was acceptable for calculating the costs of follow-up after ASCT. But, it concluded that it wanted clarification from the company on how mortality had been addressed in the SCT tunnel states.

Immunoglobin resource use

3.18 The committee recalled patient expert testimony on the potential for CAR T-cell therapy to weaken the immune system. The CDF lead highlighted that previous CAR T-cell therapies, especially for leukaemia, required substantial and prolonged intravenous immunoglobulin therapy. The clinical expert noted that people with persistent CAR T-cells often develop B-cell aplasia, which does not always lead to infections. They explained that intravenous immunoglobulin is considered for people with severe infections requiring hospitalisation. It is also considered for those with

recurrent milder infections managed with oral antibiotics and an immunoglobulin G level below 3. They explained that current management involves trialling prophylactic antibiotics first, with intravenous immunoglobulin added if infections persist. The clinical expert explained that all therapies deplete B-cells, leading to reduced immunoglobulin levels and increased susceptibility to infections, which may require intravenous immunoglobulin. They explained that the rising use of intravenous immunoglobulin in CAR T-cell therapy may be linked to longer survival. This is in contrast to the comparator groups, where durable responses are less common. Another clinical expert highlighted that persistent B-cell aplasia tends to be shorter with comparators like inotuzumab and blinatumomab compared with CAR T-cell therapies, resulting in lower intravenous immunoglobulin use. The clinical expert highlighted that, in contrast, the prolonged B-cell aplasia seen with obe-cel is largely attributed to its sustained efficacy, which would explain the increased need for intravenous immunoglobulin. The CDF lead noted that intravenous immunoglobulin is costly and it is not included in the CAR T-cell tariff. The company explained that it modelled immunoglobulin costs by linking them to the adverse event of hypogammaglobulinemia, assumed to be 0% in the comparator arms and slightly higher for obe-cel. The committee discussed whether immunoglobulin would still be needed 3 years after treatment if a person is considered cured. The clinical experts noted that it may still be needed in some cases, depending on the clinical scenario. This is because the longer CAR T-cells persist, the higher the risk of infection and continued need for intravenous immunoglobulin. The committee considered that the company's model likely underestimated the proportion of people who have intravenous immunoglobulin and the duration of treatment. It requested updated scenarios in the model exploring higher usage and longer duration of intravenous immunoglobulin.

Application of discount rate

3.19 The company applied a per-cycle discount rate to calculate discount factors in the model. The cycle length was 28 days, and the discounting was applied at the end of each cycle. The EAG disagreed with the application of a per-cycle discount rate and preferred to use a per-year discount rate of 3.5%, as specified in the NICE reference case. The committee concluded that the EAG's application of a per-year discount was acceptable for decision making.

Utilities

Incorporating ASCT utility effects into the economic model

3.20 The company's base case did not include any disutility associated with ASCT for any comparator. It also assumed no one in the obe-cel treatment arm had subsequent ASCT (see section 3.15). But, in a scenario analysis it explored the impact of applying a post-SCT disutility. The scenario considered separate utility decrements associated with ASCT in addition to alternative health state utility values, in line with TA450. The EAG noted that the utility value applied for the 'post-event' health state in the company's base case (sourced from FELIX), does not reflect the utility impacts of ASCT. The EAG assumed that people who have an ASCT experience varying utility values depending on how much time has passed since the ASCT. This is consistent with the approach used in TA541. The EAG thought these values were appropriate because they reflect changes in health-related quality of life post-transplant and include the disutility associated with graft-versus-host disease. In its base case, the EAG adjusted utility values in the post-event health state using time-dependent utilities from TA541. This captured variations in post-SCT health-related quality of life and accounted for the proportion of people having ASCT across different treatments. The company accepted the EAG's approach to incorporating ASCT utility effects in the model. The committee acknowledged that a small number of people would progress to ASCT but the utility post-SCT should be captured in the model. It concluded that it preferred the EAG's base-case assumption that adjusted

utility values in the post-event health state using time-dependent utilities from TA541.

Severity

3.21 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) if technologies are indicated for conditions with a high degree of severity. This is called a severity modifier. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. It provided absolute and proportional QALY shortfall estimates for blinatumomab (for the Philadelphia chromosome-negative population), inotuzumab and ponatinib (for the Philadelphia chromosome-positive population) based on FELIX trial data. The company considers the results of its QALY shortfall analysis to be confidential, so they cannot be reported here. The company's shortfall analysis indicated that obe-cel meets the criteria for 1.7 severity modifier when compared with blinatumomab, and a 1.2 severity modifier when compared with inotuzumab and ponatinib. The company considered 1.7 to be the appropriate severity modifier, because it met the criteria for at least 1 comparator, and so applied it across all analyses. The EAG considered it inappropriate to apply the 1.7 severity modifier for all analyses, regardless of population and comparator. The EAG did a weighted analysis (including age, QALYs, and sex distribution) that assumed that inotuzumab is used by at least 5% of people with relapsed or refractory B-cell ALL. The results supported a 1.2 severity modifier across all populations, which was applied to the EAG's preferred cost-effectiveness results. The committee discussed the proportion of people with relapsed or refractory Philadelphia chromosome-negative B-cell ALL having inotuzumab compared with other treatments. The clinical expert noted that inotuzumab is often used as a bridge to ASCT or CAR T-cell therapy. The committee acknowledged that the condition has a significant impact on quality of life. It recalled the clinical expert (see

section 3.4) saying blinatumomab use is expected to fall because of its earlier placement in the treatment pathway following recent commissioning changes. The committee concluded that it was satisfied with the severity weight of 1.2 applied to the QALYs for all populations.

Cost-effectiveness estimates

Committee's preferred assumptions

3.22 The committee concluded that the cost-effectiveness estimates were uncertain and further justifications for assumptions are needed (see sections 3.4, 3.12, 3.13 and 3.17). It agreed that the company's overall model structure was acceptable for decision making (see section 3.10). The committee concluded that its preferred assumptions are to use:

- the EAG's approach of modelling adverse events using the data from the enrolled ITT population from cohorts 1A and 2A (see section 3.9)
- the EAG's choice of population, the enrolled ITT population from cohorts 1A and 2A (see section 3.11)
- the latest NHS England CAR T-cell tariff costs of £60,462 (see section 3.14)
- the EAG's approach for calculating the costs of follow up after ASCT (see section 3.17)
- the EAG's per-year discount rate of 3.5% (see section 3.19)
- utility values adjusted in the post-event health state using time-dependent utilities from TA541 (see section 3.20)
- a severity weight of 1.2 applied to the QALYs for all populations (see section 3.20)

Uncertainty in the cost-effectiveness estimates

3.23 The committee acknowledged the uncertainties in the company's and EAG's modelling assumptions. To help it to decide on the cost effectiveness of obe-cel, the committee requested the following:

- further clarification on how the model accounts for ponatinib and inotuzumab being used as bridging therapies to improve outcomes before CAR T-cell therapy, and their relevant costs (see section 3.4)
- a comparison using FELIX data for obe-cel alongside real-world data from NHS England for tisagenlecleucel (see section 3.5)
- further evidence and justification for applying the inverse hazard ratio to blinatumomab (see section 3.12)
- further clarification on the population included in the post-event health state, and the assumption that people who have had events can be considered cured (see section 3.13)
- further evidence to support the assumption that a standardised mortality ratio of 3 is appropriate, especially for those who have had an event (see section 3.13)
- a range of scenarios exploring a proportion of less than 10% of people having ASCT after obe-cel in the ITT population (see section 3.16)
- further clarification from the company on how mortality was addressed in the SCT tunnel states (see section 3.17)
- further evidence and justification on the proportion people having intravenous immunoglobulin in the model, and the duration of treatment (see section 3.18).

Managed access

3.24 Having concluded that obe-cel could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed access period. The committee acknowledged it had not seen a managed access proposal, but it considered managed access may be suitable if it could address uncertainties in the evidence.

Other factors

Equality

3.25 The committee noted that people from ethnic minority backgrounds are less likely to find a fully matched unrelated donor for ASCT. It noted that

additional alternatives to an unrelated donor SCT, such as CAR T-cell therapy, are important. It also noted that geographical access to CAR T-cell therapy specialist centres can be a barrier for people in lower socioeconomic groups. This is because they may be unable to afford to travel to have treatment or long-term monitoring. The committee noted these concerns but concluded that ASCT was not a direct comparator, and these concerns cannot be addressed within the recommendation.

Uncaptured benefits

3.26 The committee considered whether there were any uncaptured benefits of obe-cel. The patient expert highlighted that they tolerated treatment well despite being hospitalised and suggested it could be considered an outpatient treatment for others who respond similarly. The clinical experts noted that obe-cel has a more favourable toxicity profile than other CAR T-cell therapies. Because of this, people who have a lower disease burden could potentially have obe-cel in an outpatient setting, which would improve accessibility. The clinical expert noted that a significant proportion of people travel over 2 hours each way for treatment. They noted that if ambulatory treatment is considered as an alternative to inpatient stays, these costs had not been incorporated into the model. The committee concluded that it would take the potential uncaptured benefits of obe-cel into account in its decision making.

Conclusion

Recommendation

3.27 The committee noted the important uncertainties in the clinical effectiveness and the modelling. It decided that more evidence was needed to generate robust cost-effectiveness estimates. The committee could not conclude that obe-cel would represent a cost-effective use of NHS resources. So, obe-cel is not recommended

4 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology evaluation by the highly specialised technologies evaluation committee. The highly specialised technologies evaluation committee and the 4 technology evaluation committees are standing advisory committees of NICE.

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

Paul Arundel

Chair, highly specialised technologies evaluation committee

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 adviser, a project manager and an associate director.

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