NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

1.1 Obecabtagene autoleucel (obe-cel) can be used as an option to treat relapsed or refractory B-cell precursor acute lymphoblastic leukaemia in people aged 26 years and over. Obe-cel can only be used if the company provides it according to the commercial arrangement (see section 2).

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 must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Obe-cel must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that obe-cel provides benefits and value for money, so it can be used routinely across the NHS in this population.

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Why the committee made these recommendations

Usual treatment for relapsed or refractory B-cell precursor acute lymphoblastic leukaemia is blinatumomab, inotuzumab ozogamicin or ponatinib. These can be followed by an allogeneic stem-cell transplant for some people. People 25 years and under can have tisagenlecleucel. Obe-cel would be another treatment option.

The results of comparisons of obe-cel with other treatments are uncertain. But they suggest that people who have obe-cel live longer than people who have blinatumomab, inotuzumab ozogamicin or ponatinib. They also suggest that obe-cel works about as well as tisagenlecleucel.

Compared with tisagenlecleucel, which is usually offered to people aged 18 to 25 years, the most likely cost-effectiveness estimates for obe-cel are above the range NICE considers an acceptable use of NHS resources. So obe-cel is not recommended for people aged 18 to 25 years.

For people 26 years and over, when considering the condition's severity and its effect on quality and length of life, the most likely cost-effectiveness estimates for obe-cel are within the range that NICE considers an acceptable use of NHS resources. So obe-cel is recommended for people aged 26 years and over.

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 (≥ 18 years) 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 (simple discount patient access scheme). This makes obe-cel available to the NHS with a discount. The size of the discount is commercial in confidence.

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 concluded that relapsed or refractory B-cell ALL has a high disease burden and is a severe condition that substantially affects people's lives.

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 (from here, 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 allogeneic 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 highly toxic 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 (SCTs) can be. They added that they had had quicker recovery from CAR T-cell therapy than ASCT. 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.

Company's proposed positioning

3.3 The company proposed that obe-cel would be offered to people with relapsed or refractory 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) 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, from here TA451) or
- inotuzumab (see TA541).

The company considered ASCT to be a subsequent treatment for both the Philadelphia-chromosome-negative and -positive groups. The clinical experts explained that some people would be offered ASCT earlier in the treatment pathway before relapse. Other people would have ASCT after ponatinib, inotuzumab or blinatumomab, which would be used as a bridge to ASCT for these people. 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 whether people would have ASCT after having obe-cel (see section 3.21). The clinical expert explained it could be considered for fit people with matched donors who have not already had an SCT. They emphasised 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

Overall population

3.4 The committee discussed the relevant comparators for each population of relapsed or refractory B-cell ALL. 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) is recommended for people 18 to 25 years and is considered a relevant comparator for this population (see section 3.7). The experts noted that in current clinical practice most people 26 years and over with relapsed or refractory B-cell ALL (regardless of Philadelphia chromosome status) have brexucabtagene autoleucel (see TA893). But this is only recommended through the Cancer Drugs Fund, so it cannot be considered a relevant comparator for this appraisal. The experts explained that it is difficult to predict what might happen in clinical practice for people over 26 if brexucabtagene autoleucel therapy were not available. People with relapsed or refractory B-cell ALL, regardless of Philadelphia chromosome status can have inotuzumab. The clinical experts agreed that inotuzumab would be the most commonly used if CAR T-cell therapies were not available for adults aged 26 years or older. The committee concluded that, inotuzumab and tisagenlecleucel (for people 18 to 25 years) are relevant comparators regardless of Philadelphia chromosome status.

Philadelphia-chromosome-negative population

3.5 For people with relapsed or refractory Philadelphia-chromosome-negative B-cell ALL, the company considered blinatumomab was another relevant comparator. The clinical experts explained that recent NICE guidance had 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 whose condition relapses will likely have already had blinatumomab earlier in the treatment

pathway. They explained that, currently, people with minimal residual disease-negative B-cell ALL usually have blinatumomab during consolidation treatment, which is used to maintain remission and prevent recurrence. But people with minimal residual disease-positive B-cell ALL have blinatumomab as a bridge to ASCT. The clinical expert said that an increase in early use of blinatumomab would be 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 acknowledged that most people would already have had blinatumomab earlier in the treatment pathway. It heard from the clinical experts that some people who had previously had blinatumomab in an earlier setting could have retreatment in the relapsed and refractory setting. The clinical experts noted that in the relapsed or refractory setting, blinatumomab and inotuzumab may be used as consolidation or palliative care for people who have had an ASCT or were ineligible for one. The clinical experts explained that they expect the outcomes for people having blinatumomab or inotuzumab to be similar when used in palliative care or as consolidation or a bridge to an ASCT. The committee concluded that blinatumomab is a relevant comparator for people with relapsed or refractory Philadelphia-chromosome-negative B-cell ALL. But it acknowledged that most of these people would have already had blinatumomab as part of consolidation treatment, so its use at this point in the pathway would reduce over time.

Philadelphia-chromosome-positive population

3.6 For people with relapsed or refractory Philadelphia-chromosome-positive B-cell ALL, the company proposed that ponatinib was another comparator. The clinical experts explained that ponatinib and inotuzumab are both used in this population. The committee was aware that ponatinib is a protein kinase inhibitor. It noted that it was associated with various severe side effects for some people, particularly an increased risk of serious cardiovascular occlusive events (see TA451). 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. The committee concluded that ponatinib is a relevant comparator for people with relapsed or refractory Philadelphia-chromosome-positive B-cell ALL.

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

3.7 The conditional marketing authorisation for obe-cel is for relapsed or refractory B-cell ALL in adults. 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). The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) explained that, currently, around 22.5% of people having tisagenlecleucel in the NHS are aged 18 to 25 years. The company's main clinical trial evidence comes from the FELIX study (see section 3.8). It explained that in FELIX there was only a small number of people in the 18 to 25 years age group. Because of this, it had expected its marketing authorisation to be restricted to a similar population to that for brexucabtagene autoleucel (people 26 years and over). The company noted the small sample size in 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 Cancer Drugs Fund lead noted 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 requested a comparison using FELIX data for obe-cel alongside real-world data from the Systemic Anti-Cancer Therapy (SACT) dataset for tisagenlecleucel. At draft guidance consultation the company did a matching-adjusted indirect comparison (MAIC) of obe-cel and tisagenlecleucel (see section 3.12).

The committee concluded that tisagenlecleucel was the relevant comparator in the 18 to 25 years age group.

Clinical effectiveness

Obe-cel data sources

3.8 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 and 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 more 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 more 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 thought that cohort 2A best reflects the population that obe-cel's marketing authorisation would cover. It also thought 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 dose of obe-cel. 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 anticancer 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 were more representative of what happens to people starting CAR T-cell therapy in the NHS. It also thought that these groups were more suitable for comparing efficacy against other treatments (see section 3.11). At consultation, the company provided results for the latest data cut-off from January 2025 using the committee's preferred cohorts 1A and 2A. The median overall-survival results are considered confidential by the company, so they cannot be reported here. The committee concluded that the company's updated data cut-off using cohorts 1A and 2A were suitable for decision making.

Preferred population

3.9 At the first committee meeting the company initially used the results from the infused mITT population from FELIX cohort 2A as the basis for all the economic modelling and comparisons (see sections 3.4 to 3.6). This population included people who had had at least 1 obe-cel infusion. The

EAG disagreed with this approach and preferred to use the ITT population from cohorts 1A and 2A. This included the pretreatment period, so captured people 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 (it can take up to 4 to 6 weeks to manufacture the cells for infusion and get them to the treatment centre) and bridging. The EAG explained that this is unlike comparator treatments, which begin immediately. The Cancer Drugs Fund lead explained that NHS England reimburses trusts for CAR T-cell therapy only after infusion. So, if a person has leukapheresis but does not have infusion, 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 EAG noted that the mITT population excludes people who discontinued treatment for reasons that may influence both costs and outcomes in real-world clinical practice. The EAG further noted that the mITT population may underestimate the full burden of treatment, while also ignoring the outcomes for people who do not have infusion. At the first committee meeting the committee concluded that its preferred population was the enrolled ITT population from cohorts 1A and 2A. At consultation, the company updated its base case using the latest FELIX data cut-off from January 2025, which included the committee's preferred population.

Generalisability of FELIX in NHS practice

3.10 FELIX is an ongoing, single-arm, open-label trial with a small sample size (see section 3.8). The EAG expressed concerns that, despite a large number of people being recruited 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 prioritises people with good performance status, that age is not a barrier, and that older people who have 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 outcomes were better in the population over 65 years in FELIX than in 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 trial was generalisable to NHS practice. It concluded that the trial was generalisable to NHS practice.

Indirect treatment comparison

MAIC for inotuzumab, blinatumomab and ponatinib

3.11 Because FELIX is a single-arm trial (see section 3.8), 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. It 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 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 it 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. At consultation, the company updated the MAIC using the January 2025 data cut-off for each of the 3 comparisons. These analyses were done for the committee-preferred infused and enrolled populations of cohorts 1A and 2A of the FELIX trial. The exact results are confidential, but the EAG noted that it resulted in minimal changes to the updated hazard ratios applied in the modelling. The committee was satisfied that the company's updated MAIC using the January 2025 data cut-off of FELIX comparing obe-cel with inotuzumab, ponatinib and blinatumomab was appropriate. But it noted that uncertainty remained because of the small sample sizes.

At the third committee meeting, the committee noted the following comments from the EAG about the similarities and differences between the included trials:

- People in INO-VATE had fewer lines of prior therapy than people in TOWER and FELIX.
- People in TOWER were more closely aligned to FELIX than to INO-VATE. The difference between FELIX and TOWER is less pronounced and causes less concern for adjustment than INO-VATE, which did not include people who had had 3 or more lines of prior therapy.
- INO-VATE involves a population earlier in the treatment pathway (prior induction), whereas TOWER is focused on salvage therapy, which is more aligned with FELIX.

The committee also noted that more people went on to have an SCT in INO-VATE than in the other trials. This possibly led to the treatment benefit of inotuzumab being overestimated. The clinical experts explained that most people with relapsed or refractory disease would already have had an SCT in clinical practice, so fewer people have an SCT in the relapsed or refractory setting. The committee was concerned that the people enrolled in INO-VATE probably represented a healthier population, with a larger proportion having a subsequent SCT than what would normally happen in clinical practice. The committee noted that INO-VATE may not be an appropriate comparable population compared with FELIX and TOWER.

The committee considered the results of the MAIC, which were considered confidential by the company. It noted that the hazard ratio for overall survival and event-free survival for the comparison of obe-cel with inotuzumab showed that inotuzumab had similar outcomes to obe-cel. The committee thought that the MAIC might be overestimating the true treatment effect of inotuzumab compared with obe-cel in the relapsed and refractory setting. It noted that the results of the MAIC for the comparison with blinatumomab may be more reflective of outcomes in NHS practice.

The committee recalled that the clinical experts did not think there would be a difference in outcomes between blinatumomab and inotuzumab (see section 3.5). The committee thought that, for the purposes of the economic modelling, the lower-bound confidence interval from the MAIC with inotuzumab may be more representative of current clinical practice. It is also similar to the hazard ratio for the comparison with blinatumomab. The committee concluded that the results of the MAICs were highly uncertain because of the small sample sizes, and the comparison with inotuzumab may overestimate inotuzumab's true treatment effect.

MAIC for tisagenlecleucel

3.12 At consultation, the company did a MAIC to compare obe-cel with tisagenlecleucel for people aged 18 to 25. The MAIC was based on the infused modified ITT population from cohort 2A of FELIX using the 2024 data cut-off (only for people aged 18 to 25) and data from Stackelberg et al. (2023). This study combined the populations of several tisagenlecleucel studies, including a combination of trial and real-world populations. The MAIC compared the infused populations of both technologies. The results showed a non-significant overall-survival benefit with obe-cel compared with tisagenlecleucel for the adjusted analysis. But the company noted that the analysis was extremely uncertain. This was because of limited treatment-effect modifiers from the tisagenlecleucel trials, population differences and a low effective sample size. (The exact results from the MAIC are considered confidential by the company, so cannot be reported here.) The company also compared FELIX obe-cel data with SACT data for tisagenlecleucel for people aged 18 to 25, provided by NHS England. The company noted that although the results showed improved survival with obe-cel, these should be interpreted with caution. The EAG noted that cohort-1A data could have been used in the MAIC, and that even small changes to the population may have influenced the results. It highlighted that the analysis was at risk of bias. It also highlighted that it was unclear why no separate MAIC was done using characteristics specific to the SACT population, and that the naive

comparison with SACT follow up was highly uncertain. At the second committee meeting, the clinical expert said there was no reason to believe that obe-cel would be less effective in people 25 years and under. They highlighted that they would welcome its use in this group if it was approved over tisagenlecleucel. The committee noted that there were uncertainties in the data that the company presented for the comparison. It acknowledged that the data was limited, but it noted that the company did not include both cohorts 1A and 2A in its comparison, as preferred by the committee. The committee also noted that the company could have used the data from Stackelberg et al. (2023) to compare against the NHS SACT data, to provide a more robust comparison. It noted that the EAG had also provided a cost comparison with tisagenlecleucel assuming equal effectiveness and resource use, which it took into consideration. The committee concluded that assuming similar treatment effect between obe-cel and tisagenlecleucel was appropriate, but the results of the company's analyses were highly uncertain.

Adverse events

3.13 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. This was not the case for cytokine release syndrome, for which 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 because of 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. At consultation, the company updated its base case to align with the committee's preference.

Economic model

Company's modelling approach

3.14 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 committee was aware that the model accounts for all costs and outcomes using the ITT population (see section 3.9). 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 (see section 3.17). The committee concluded that the model structure was appropriate for decision making.

Method for extrapolation

3.15 The results of the company's updated data cut from FELIX using the committee-preferred population (see section 3.8), were used to inform overall- and event-free-survival extrapolations in the model for obe-cel. For the comparators, the inverse hazard ratio approach was used (see section 3.16) and the EAG agreed that the updated hazard ratios from the MAIC were appropriate (see section 3.11). The EAG chose to use a more

flexible approach to fitting obe-cel event-free survival in the overall population and event-free survival and overall survival in the Philadelphia-chromosome-negative population. This approach was guided by goodness-of-fit statistics and plausibility of estimates where the cure model was applied. The EAG noted that the differences in the choice of survival curves between its approach and the company's had a very minimal impact on the results. The EAG noted that the rest of its preferred curve selections were identical to the company's. The committee noted that the choice of survival curve had minimal impact on the model results. It concluded that the company's updated survival extrapolation curves were acceptable.

Inverse hazard ratio approach

3.16 To inform the effectiveness of the comparators in the modelling the company used an inverse hazard ratio approach. This uses the inverse of the hazard ratio from the MAIC and applies it to the obe-cel overall- and event-free-survival extrapolations. The company said 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. At the first meeting 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 needed further justification. It considered that an inverse hazard ratio approach would be appropriate if FELIX was the best reflection of the NHS population. At the first committee meeting, the committee did not believe it had seen evidence that FELIX reflected the NHS population better than INO-VATE or TOWER. It requested 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.

At consultation, the company stated that it had kept the inverse hazard ratio approach. It noted that the suggestion by the EAG to fit parametric curves to each arm using the standard MAIC approach would not allow for an accurate incremental analysis in the Philadelphia-chromosome-negative subgroup. It highlighted that because no Philadelphia chromosome subgroup-specific data was available from INO-VATE, the hazard ratios are based on the overall populations of inotuzumab and obe-cel. So, applying this hazard ratio in the economic model to the inotuzumab curve to estimate obe-cel efficacy in the Philadelphia-chromosome-negative subgroup would introduce bias. This is because neither the obe-cel nor the inotuzumab curves would be representative of a Philadelphia-chromosome-negative subgroup. The company said that the inverse hazard ratio approach anchors the inotuzumab curve to the subgroup-specific obe-cel data. It said that this minimises bias arising from using the overall population data from INO-VATE. The company also noted that this approach is in line with the committee preference in TA893. The company noted that the Philadelphia-chromosome-negative subgroup represents the largest population, and it is an important subgroup for adopting this approach to enable a fully incremental analysis. The company noted that the approach it adopted ensures consistent baseline characteristics across all treatment arms when compared with inotuzumab and blinatumomab, enabling a comparison for both comparators. The EAG noted that the company's argument applies only to the Philadelphia-

chromosome-negative population, and there was no reason not to implement the analysis for the overall population. It also noted that the assumption of proportional hazards is not met and may influence where the curves diverge over a 3-year horizon. The company highlighted that FELIX is representative of people in the UK and noted that the inotuzumab and blinatumomab studies were done a long time ago, and clinical practice has since evolved.

At the second committee meeting, the committee noted that the company had not provided any new robust evidence on whether the FELIX study is a better source than INO-VATE or TOWER for reflecting the NHS population. The committee acknowledged that, although FELIX included a higher proportion of people from the UK, concerns remained about how representative its selected population was of real-world UK clinical practice. The committee concluded that there remains significant uncertainty with applying the inverse hazard ratio approach but that it could be used for decision making.

Cure assumption and standardised mortality ratio

3.17 The company's model included a cure assumption for people in any treatment arm alive 3 years after treatment (see section 3.14). 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 (SMR) 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 SMR of 3 used in both the EAG and company base cases 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 event-free and post-event health states). It said that this could introduce 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 have the same SMR as people who remained event-free. At the first committee meeting, the committee noted that in the original source data (Martin et al. 2010), the mortality risk ranged between 4 and 9 for people who survived without recurrence for at least 5 years. At the first committee meeting the committee requested further examination of the 3-year cure assumption and 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 SMR as people who had no events. At consultation, the company's base case kept a cure assumption of 3 years and applied an SMR of 3 to all people considered cured, regardless of prior events. It provided scenario analyses using an SMR of 4. The company noted that the plateaus seen in the event-free-survival and overall-survival curves for obe-cel support the 3-year cure assumption. It noted it had validated this with clinical experts and that it was in line with previous appraisals in this disease area. At the second committee meeting, the clinical expert reiterated that a cure assumption of 3 years was reasonable. The EAG also agreed that a cure assumption of 3 years was appropriate. It acknowledged that events beyond 3 years could occur, but it considered the assumption reasonable and broadly aligned with the approach taken in TA893. For the SMR of 3, the company noted that the data in Martin et al. (2010) was collected between 1970 and 2002. So, it explained that because experience with curative treatments had likely improved over time, an SMR toward the lower range of this dataset may better represent the current mortality risk. It also noted that a lack of divergence between event-free and overall survival in the plateau supports using the same SMR in both the event-free and progressed-

disease health states. They also noted that this was consistent with TA893. The committee noted the uncertainty in these assumptions, acknowledging both the lack of evidence and unknown duration of response. But it concluded that a 3-year cure point and an SMR of 3 applied to all people, regardless of whether they had experienced an event, was a suitable assumption for decision making.

Costs

Bridging therapies

3.18 At the first committee meeting, the committee asked for clarification on how the model accounts for bridging therapy with ponatinib and inotuzumab to improve outcomes before CAR T-cell therapy. It also requested information on their relevant costs. At consultation, the company stated that the costs associated with bridging therapy, including with inotuzumab and ponatinib, were captured in the model. This was done by calculating a weighted average based on the proportion of people who had each bridging chemotherapy from FELIX and the associated acquisition and administration costs. The company provided the estimates for the proportion of people in the pooled cohorts 1A and 2A who had inotuzumab and ponatinib. (The exact estimates are confidential and cannot be reported here.) The company also noted that the impact on clinical efficacy from bridging therapy had already been captured in the model because it was included in the efficacy data from FELIX. The EAG agreed that the model captures the influence of these treatments on CAR T-cell therapy outcomes by incorporating efficacy data from FELIX. But it identified an issue with the formula used in the model and corrected it to ensure accurate cohort-specific results. The EAG also highlighted a concern about the correction factor applied to bridging treatment costs. It noted that the company used a correction factor of less than 1 to account for people who have leukapheresis but do not have a CAR T-cell infusion. This results in double counting when the preferred ITT population is used. To avoid this duplication, the EAG preferred a correction factor of 1. At the

second committee meeting, the company accepted the EAG's approach to modelling the correction factor. The committee concluded that the company had provided sufficient evidence to show how the model accounts for comparators as bridging therapies. It also concluded that it preferred the EAG's approach and supported a correction factor of 1 in the model.

Hospitalisation and resource use for obe-cel

3.19 The company's economic model included the costs associated with leukapheresis, delivery of treatment, adverse events, hospital stay and intensive care unit (ICU) costs. In its original base case, the company used a bottom-up costing approach to calculate the administration cost of obe-cel in the model covering hospitalisation and ICU costs. Data on hospitalisation (length of hospital stay, proportion needing ICU care, 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 Cancer Drugs Fund 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, or
- 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 to 2025.

The Cancer Drugs Fund lead explained that a tariff cost of £60,462 now applies, which is the annual uplift figure for 2025 to 2026 applied to the 2024 to 2025 figure. The company explained that it had used resource-use data from people in the UK in the FELIX trial, because it believed that it better reflected 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 EAG presented a scenario based on a CAR T-cell tariff value of £41,101 which had been accepted in previous NICE evaluations for CAR T-cell treatments. But the Cancer Drugs Fund lead explained that this was outdated and that the current tariff represented more thorough cost calculations. The company accepted that 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. At consultation, the company updated its base case to include the CAR T-cell tariff. But it reiterated its concerns relating to several uncaptured benefits associated with using the tariff, which the committee took into consideration (see section 3.29). The committee concluded that the updated tariff cost of £60,462 should be applied in the model because this was the current cost of delivering CAR T-cell treatments in the NHS. But it agreed that there may be uncaptured benefits for obe-cel which it would consider in its decision making (see section 3.28).

Outcomes for ASCT after obe-cel

3.20 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 include 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 that around 10% of people are expected to have obe-cel as a bridging therapy to ASCT (see section 3.21). 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 noted that healthcare professionals now better understand the value of CAR T-cell persistence and are less likely to offer ASCT outside a clinical trial setting. The committee concluded that the numbers of people having ASCT after obe-cel would be low (see section 3.21). But it acknowledged that the results of FELIX captured the outcomes for people who had ASCT after obe-cel, so this should be reflected when modelling the costs of obe-cel.

Proportion having ASCT after obe-cel

3.21 In the original company submission, the company included the potential benefits of subsequent ASCT for obe-cel but did not include associated costs. The EAG considered that including outcomes of ASCT without associated costs introduces a bias. So the EAG's base case included the costs of ASCT for the proportion who had ASCT in the FELIX trial. The committee noted 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 (see section 3.3). 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 smaller 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, but that the outcomes modelled were based on the FELIX trial. At the first committee meeting, the committee

asked to see a range of scenarios in which the costs of ASCT are included for a proportion of people who had ASCT after obe-cel. It asked to see how this impacted the cost-effectiveness estimates. It noted that this proportion was likely to be less than 10% and concluded that a range of scenarios would help resolve the uncertainty. At consultation, the company updated its base case to assume 10% of the obe-cel ITT population have an ASCT after obe-cel. It also provided scenarios using 2.5% and 5%, noting that these had minimal impact on the incremental cost-effectiveness ratios. (The exact estimates are confidential and cannot be reported here.) The EAG used 10% in its base case and provided scenario analyses using 2.5% and 5%. At the second committee meeting, the clinical expert explained that it was reasonable to assume that less than 10% of people have ASCT. They noted it would be less common in clinical practice to have ASCT after obe-cel because most people who currently have a CAR T-cell therapy in the NHS have already had an ASCT. They also noted that very few people would go on to have ASCT after CAR T-cell therapy because of the CAR T-cell persistence seen in people who have obe-cel. They noted that this CAR T-cell persistence seems to be greater than that seen in other CAR T-cell therapies. The Cancer Drugs Fund lead noted that data on the proportion of people who have ASCT after CAR T-cell is not collected formally but estimated that the proportion is likely to be in the range of 5% to 10%. The committee recalled that the outcomes of ASCT after obe-cel in the model were based on the FELIX data (see section 3.20). It also noted it had not been provided with any robust evidence on the proportion of people having ASCT after obe-cel. It concluded it would accept the company and EAG base-case assumption that 10% of the ITT population has ASCT.

Costs associated with ASCT

3.22 The company and EAG both modelled the costs of ASCT using NHS reference costs consistent with TA893. At the second committee meeting the company identified a more recent data source on costs associated with ASCT in England in Ernst & Young LLP's analysis of hospital activity

and costs following allogeneic stem cell transplantation in England, 2021 (PDF only; from here referred to as the Ernst & Young LLP report). The report presents an analysis of hospital activity and costs associated with people who had ASCT 1 year after discharge. The analysis found that hospital resource use remained significant beyond 100 days, with estimated costs substantially higher than those used in the original company submission. The company noted that in the base-case cost estimates, the initial cost of SCT was £115,591 and the first 6-month follow up was £34,347. In the Ernst & Young LLP report, the initial cost was £82,197 and the first 6-month follow up was £88,808. The company incorporated these alternative costs in scenario analyses, noting that the report may provide a more up-to-date and accurate estimate of the long-term resource use and costs associated with ASCT. The clinical expert noted that transplants are complex procedures often associated with multiple infections, particularly in the first 6 months after transplant. They also noted that the associated costs of newer therapies to manage these complications can be substantial. The EAG noted that the Ernst & Young LLP report reflects higher follow-up costs and may better represent current NHS resource use but lacks details on how the costs were derived. It highlighted that both the company and EAG base case used cost estimates built from NHS reference costs, consistent with other appraisals, rather than SCT tariffs. The Cancer Drugs Fund lead confirmed that the tariff for SCT generally falls within the £85,000 to £105,000 range, covering the procedure and care for up to 100 days. The committee felt that the company and EAG had likely captured the increased follow-up costs in the first 6 months (as suggested by the Ernst & Young LLP report) in their base-case costs, which used NHS reference costs. This is because these costs were already included as part of the upfront costs. It also noted that the Ernst & Young LLP report may inflate costs for ASCT because it includes children, who typically have longer hospital stays and higher costs than adults. The report also used cost data from only 1 NHS trust. Although the costs were adjusted to account

for potential higher costs associated with the trust's location, the committee noted it may not reflect what ASCT typically costs across the country. The committee concluded that the alternate ASCT costs were not transparent or clearly reported. It was satisfied that the base-case costs used by the company and EAG were appropriate.

Modelling follow up after ASCT

3.23 In the original submission, 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 identified 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. At the first meeting, the committee asked for clarification from the company on how mortality had been addressed in the SCT tunnel states. At consultation, the company adopted the EAG approach in line with the committee's preferences. But, it suggested the costs may be slightly overestimated because mortality is only accounted for when a new follow-up period is reached instead of per cycle. The EAG noted this has a minimal impact on the incremental cost-effectiveness ratio (ICER). The committee concluded that it was satisfied with the company's explanation on how mortality had been addressed and accepted that any impact on overestimating costs has a minimal impact on the ICER.

Immunoglobulin resource use

3.24 The committee recalled the patient expert testimony on the potential for CAR T-cell therapy to weaken the immune system. The Cancer Drugs Fund 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 (IVIg) 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 IVIg 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 IVIg. They explained that the rising use of IVIg in CAR T-cell therapy may be linked to longer survival. This contrasts with the comparator groups, for which durable responses are less common. Another clinical expert highlighted that persistent B-cell aplasia tends to be shorter with comparators like inotuzumab and blinatumomab than for CAR T-cell therapies, resulting in lower IVIg 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 IVIg. The Cancer Drugs Fund lead noted that IVIg is costly and is not included in the CAR T-cell tariff. The company explained that it had modelled IVIg costs by linking them to the adverse event of hypogammaglobulinaemia, assumed to be 0% in the comparator arms and slightly higher for obe-cel. The committee discussed whether IVIg 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 IVIg. At the first committee meeting, the committee thought that the company's

model probably underestimated the proportion of people who have IVIg and the duration of treatment. It requested updated scenarios in the model exploring higher use and longer duration of IVIg.

In response to consultation, the company updated the model for IVIg use based on clinical expert opinion and real-world data from FELIX, 6 months after obe-cel infusion. The company reported the mean and median IVIg use for the infused pooled population (cohort 1A and 2A) and UK-specific cohort (figures are considered confidential by the company and cannot reported here). In the company's updated approach to modelling IVIg, its use was reevaluated every 6 months over the model's time horizon, and a 5% reduction applied at months 6, 12, and 18. This was followed by a 2% reduction every 6 months. The EAG noted several issues with the company's modelling of IVIg and was concerned that its approach had structural issues. This was because the undiscounted cost output from the model was lower than the total one-off IVIg cost calculated using the company's own input parameters, suggesting a potential underestimation. (The exact figures are considered confidential by the company and cannot reported here.) The EAG also noted that the company likely underestimated the proportion of people needing IVIg, which it based on the proportion of people in FELIX with hypogammaglobulinaemia. The EAG preferred to use data from the FELIX February 2024 cut-off, which showed a higher proportion of people having IVIg, and applied this in its base case. The EAG considered the company's assumed frequency of IVIg use to also be underestimated. It highlighted that its clinical expert noted that most people remain on IVIg for over 12 months. It noted the company's approach to reduction in IVIg over time was confusing and likely underestimated real-world IVIg use. So, the EAG modelled IVIg administration over a 12-month period, applied in the first model cycle. At the second committee meeting, the company accepted that its approach may have been an underestimate. But it noted that the percentage the EAG used from FELIX included all participants, not just people in the UK.

(For people in the UK the percentage who have IVIg was smaller, but the company considered the exact number confidential so cannot be reported here.) The committee recalled that in NICE's technology appraisal guidance on brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma (from here, TA677), the company reported that 32% have IVIg. The patient expert noted that they began IVIg treatment 6 months after CAR T-cell therapy because of recurrent infections and poor response to antibiotics. They explained that they currently have IVIg every 4 weeks and expect to continue long term, describing the regular hospital visits as burdensome. The committee noted that some people may need IVIg for longer than the 12 months modelled by the EAG, while others may not need it. The clinical expert explained that it is difficult to estimate the proportion of people who will need IVIg but highlighted that people with ongoing B-cell aplasia are likely to need it. They also noted that younger people may be more likely to need IVIg because of their immature immune systems, whereas this is less common in adults. The committee noted there was uncertainty around the company's and EAG's modelling of IVIg. It noted that the EAG base case modelled the proportion of IVIg using the data from people across all countries in FELIX. But, there was uncertainty around the correct proportion of people having IVIg to include in the modelling. The EAG base case included costs of IVIg for 12 months. But the committee noted it had heard that IVIg use was often long term, with some needing it for life. The committee then considered the EAG base case compared with IVIg use modelled in TA677. It recalled clinical experts explaining that prolonged B-cell aplasia seen with obe-cel is largely attributed to its sustained efficacy. It also noted that obe-cel may be more effective than other CAR T-cell therapies previously appraised by NICE. The committee considered it more appropriate to estimate a higher initial proportion of people having IVIg (as the EAG had done) modelled over 12 months than to use the lower proportion in the company base case. The committee concluded that the EAG approach to modelling IVIg use over time was more appropriate than

the company's approach. But it acknowledged that some uncertainty remained in the true cost of IVIg use over time.

Application of discount rate

3.25 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 in NICE's health technology evaluations manual. The committee concluded that the EAG's application of a per-year discount was acceptable for decision making. At consultation, the company updated its base case to align with the committee's preference.

Utilities

Incorporating ASCT utility effects into the economic model

3.26 In the company's original base case it 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 3.20). 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 NICE's technology appraisal guidance on blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. 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 and updated its base case at consultation. 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

3.27 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 also provided absolute and proportional QALY shortfall estimates for blinatumomab (for the Philadelphia-chromosome-negative population) and inotuzumab and ponatinib (for the Philadelphia-chromosome-positive population) based on age and sex distribution informed by the FELIX trial. 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 a 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, so it 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 of the company's estimates (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 overall population). The weighted analysis assumed that the remaining people have either blinatumomab (74%) or ponatinib (68%). This was based on the proportion of Philadelphia-chromosome-positive and -negative disease in England and Wales, as referenced in TA450. The results showed a weighted QALY weight of 1.2. Based on this result, and the 1.2 severity weighting across comparators in the EAG's base case, the EAG preferred to also apply a 1.2 QALY weight for comparisons with:

- inotuzumab and ponatinib for the Philadelphia-chromosome-positive population and
- inotuzumab and blinatumomab for the Philadelphia-chromosome-negative and overall populations.

At consultation, the company updated its base case to align with the committee's preference. The committee recalled its conclusion around the reduced use of blinatumomab in the Philadelphia-chromosome-negative population (see section 3.5). It noted that the EAG's threshold approach, which estimated that only 5% of people have inotuzumab in this population, is extremely conservative. The committee acknowledged that the condition has a significant impact on quality of life. It was not aware that outcomes were expected to be different across comparators or Philadelphia chromosome groups. The committee agreed that it would apply a 1.2 severity modifier. The committee concluded that it was satisfied that a severity weight of 1.2 should be applied for all the populations.

Uncaptured benefits

3.28 The committee considered whether there were any uncaptured benefits of obe-cel. The company and experts considered at the committee meetings that there were a number of benefits not captured in the modelling. These related to the reduction in adverse events and potential for outpatient

(ambulatory) treatment and monitoring not captured in the CAR Tcell tariff, quicker treatment times and lower ICU costs. The committee considered each uncaptured benefit in turn:

- The company noted that the existing CAR T-cell tariff is based on real-world costs associated with people on older CAR T-cell therapies currently available in the UK. The company noted that older CAR T-cell treatments have substantially worse safety profiles and poorer CAR T-cell persistence compared with obe-cel. The company highlighted that obe-cel has lower rates of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome than currently available CAR T-cell therapies (for example, brexucabtagene). The Cancer Drugs Fund lead highlighted that the CAR T-cell tariff is fixed and, although reduced toxicity may offer benefits, the lack of resource data makes them hard to quantify.
- The company argued that the favourable adverse-event profile of obe-cel allows for the potential to administer or monitor obe-cel in an outpatient setting. This makes administration less costly and the technology more accessible to people. The company noted that this had not been accounted for in the tariff. The company noted that recovery in non-hospital settings, such as in hotels or at home, could be more resource efficient than inpatient stays. The patient expert said that they spent 20 days in hospital followed by a month in a nearby hotel for outpatient visits 2 to 3 times a week. This highlighted that outpatient administration would be a major benefit for people and their families. The clinical expert noted that a significant proportion of people travel over 2 hours each way for treatment. They noted that if the company had considered ambulatory treatment as an alternative to inpatient stays then it had not incorporated these costs into the model.
- The company highlighted that the current tariff is substantially higher than the figure applied in earlier technology appraisals of CAR T-cell therapies. It said that its original submission had explored the potential for ambulatory care using a bottom-up costing approach based on UK

patient resource use. It said that this was notably lower than the CAR T-cell tariff. The committee recalled that it had previously noted that this analysis was highly optimistic (see section 3.19).

- The company noted that, because obe-cel is manufactured in the UK, it should allow for quicker treatment and less time in the bridging period. This may reduce the need for or the dose of bridging therapies. These people may be more likely to have their condition managed in outpatient settings, reducing the need for ICU-level monitoring and prolonged hospital stays. The clinical expert supported this, noting that obe-cel enables quicker discharge. The company also noted that the model does not capture the improvement in health-related quality of life because of reduced ICU admissions. It also noted that freeing up ICU capacity could improve outcomes for other critically ill people. The Cancer Drugs Fund lead explained that ICU costs are separate from the base CAR T-cell tariff, which only covers care on the ward where the treatment is administered. So, reductions in ICU stays do not impact the base tariff.

  The committee acknowledged that some potential benefits were not captured in the current modelling relating to the reduction in adverse events and the potential for outpatient administration and reduced ICU costs. The committee thought the company could have done exploratory modelling to better capture the potential benefits it believed were missing from the current model. This could have included incorporating lower ICU costs or exploring the use of IVIg in the comparator arm. The committee noted that the potential for outpatient administration of obe-cel is currently only being considered in a clinical trial setting. So, the committee said that it would need considerably more evidence before it could be considered for routine practice. It also noted that even if outpatient delivery of obe-cel could be implemented, it would take time for the cost savings to be realised in the NHS. This would happen, for example, through an updated CAR T-cell tariff cost. The committee had previously concluded that it preferred to use the

CAR T-cell tariff because it represents the cost to the NHS (see section 3.19). The committee concluded that it would take the potential uncaptured benefits of obe-cel into account in its decision making (see section 3.29). It would also consider the benefit of obe-cel as a potentially curative treatment option for people unable to have an ASCT because of fitness or lack of a matched donor. It noted that lack of a matched donor was more likely to affect people from ethnic minority backgrounds (see section 3.31).

Cost-effectiveness estimates

Acceptable ICER

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

- comparison of obe-cel with tisagenlecleucel (see section 3.12)
- comparison of obe-cel with inotuzumab, ponatinib and blinatumomab and applying the inverse hazard ratio approach (see section 3.11)
- cure assumption being applied equally for people who have had events and people who have not had events (see section 3.17)
- ASCT use after obe-cel (see section 3.21)
- IVIg use over time (see section 3.24).

But the committee noted that there were some uncaptured benefits in the modelling. It said that these included the expected lower rates of adverse events with obe-cel than for other CAR T-cell therapies and the impact this could have on its administration (see section 3.28). It

said that these also included the benefit for populations who are unable to have an ASCT because of fitness or lack of a matched donor.

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

Committee's preferred assumptions and cost-effectiveness estimates

3.30 The committee noted its preferred assumptions, which included:

- using the enrolled ITT population from cohorts 1A and 2A (see section 3.9)
- assuming equal efficacy and resource use with tisagenlecleucel (see section 3.12)
- accepting the EAG's approach of modelling adverse events using the data from the enrolled ITT population from cohorts 1A and 2A (see section 3.13)
- using the company's updated hazard ratios but applying the lower-bound hazard ratio adjusted confidence intervals for the comparison with inotuzumab (see section 3.11) and survival extrapolations for obe-cel (see section 3.16)
- applying a cure assumption at 3 years and an SMR of 3 (see section 3.17)
- applying a correction factor of 1 to account for bridging therapies (see section 3.18)
- using the latest NHS England CAR T-cell tariff costs of £60,462 (see section 3.19)
- 10% of people having ASCT after obe-cel in the ITT population (see section 3.21)
- using NHS reference costs to calculate the costs of follow up after ASCT (see section 3.22)
- using the EAG approach to IVIg use estimates (see section 3.24)
- using the EAG's per-year discount rate of 3.5% (see section 3.25)

- using utility values adjusted in the post-event health state using time-dependent utilities from TA541 (see section 3.26)
- applying a severity weight of 1.2 to the QALYs for all populations (see section 3.27).

The company presented cost-effectiveness results for the overall population and subgroup results for the Philadelphia chromosome-positive and -negative populations. The company used the Philadelphia chromosome subgroup-specific data from FELIX to estimate the obe-cel overall- and event-free-survival extrapolations. It also applied the hazard ratio to estimate the relative treatment effect for inotuzumab and blinatumomab, and a naive comparison was used for ponatinib (see section 3.16). The exact cost-effectiveness estimates are confidential and cannot be reported here.

The results of the cost-effectiveness analysis showed that the ICER for obe-cel compared with inotuzumab was below £30,000 per QALY gained in the overall population. The committee considered whether it was relevant to consider subgroup analyses for the comparison with inotuzumab. It recalled that the hazard ratios are based on the overall populations of inotuzumab and obe-cel. It noted the company response, which explained that using the inverse HR approach in the Philadelphia chromosome-positive population leads to a significant overestimation of overall and event-free survival compared with the published inotuzumab data. The committee were also aware that the subgroup data from FELIX for the Philadelphia chromosome-positive population was based on a small number of patients. The committee did not believe there was sufficient evidence to support differential cost-effectiveness results in the Philadelphia-chromosome-positive subgroup for the comparison with inotuzumab. So the committee agreed its decision should be based on the overall population results which included a larger sample size and were associated with greater certainty. The committee recalled its conclusion around the reduced use of blinatumomab in Philadelphia-chromosome-

negative population (see section 3.5) and that the comparison with ponatinib was highly uncertain. It agreed that it would weight its decision to recommend obe-cel around the comparison with inotuzumab. But, only as long as the cost-effectiveness results compared with blinatumomab and ponatinib did not suggest that a recommendation would harm the NHS as a whole.

The results of the of the cost-effectiveness analysis with tisagenlecleucel, assuming equal clinical effectiveness between the treatments, showed that obe-cel was above the range considered a cost-effective use of resources.

Equality

3.31 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, so no further adjustments could be made or addressed within the recommendation. The committee were also aware that lower toxicity of obe-cel may support its administration in ambulatory settings or homecare. This could address some geographical access, although CAR T-cell therapy would still be based out of specialist centres and this cannot be addressed within the recommendation. Age is a protected characteristics under the Equality Act 2010 and the committee were aware that tisagenlecleucel was the relevant comparator for those in the 18 to 25 year age range that was limited by the marketing authorisation for tisagenlecleucel. The committee considered whether making a recommendation limited to age would affect some people over others. It

concluded that there was higher unmet need in people aged 26 years and over who cannot have a CAR T-cell therapy as part of routine practice.

Conclusion

Recommendation

3.32 The committee considered the important uncertainties in the clinical effectiveness and the modelling. It agreed that obe-cel improved event-free and overall survival in relapsed and refractory B-cell ALL compared with inotuzumab, blinatumomab and ponatinib, and had similar effectiveness to tisagenlecleucel. But, there was a high degree of uncertainty in the clinical evidence and the economic modelling. When the committee's preferred assumptions were applied, the most likely cost-effectiveness estimates for obe-cel compared with tisagenlecleucel in people aged 18 to 25 are above what NICE considers a cost-effective use of NHS resources. So, obe-cel should not be used for treating relapsed and refractory B-cell ALL in people aged 18 to 25 years. The committee concluded that the cost-effectiveness evidence showed that obe-cel is a cost-effective use of NHS resources compared with inotuzumab, blinatumomab and ponatinib, because the ICERs for obe-cel were within the range that NICE considers a cost-effective use of NHS resources. So, obe-cel can be used for adults aged 26 years and over.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

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 routine commissioning, 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. Interim funding will end 90 days after positive final guidance is published at which point funding will switch to routine commissioning budgets. The NHS England 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 a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient aged 26 years or over has relapsed or refractory B-cell precursor acute lymphoblastic leukaemia and the healthcare professional responsible for their care thinks that obecabtagene autoleucel is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Janet Boadu
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Associate director

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