NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in adults in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

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

The appraisal 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: December 2022

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 appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in adults in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 6 January 2023

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 4.

1 Recommendations

1.1 Autologous anti-CD19-transduced CD3+ cell treatment is not recommended, within its anticipated marketing authorisation, for relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over.

1.2 This recommendation is not intended to affect treatment with autologous anti-CD19-transduced CD3+ cells that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Standard treatment for B-cell acute lymphoblastic leukaemia includes inotuzumab, blinatumomab, and ponatinib. This can be followed by allogeneic stem cell transplant for some people. Autologous anti-CD19-transduced CD3+ cells would be offered as an additional treatment option.

Evidence from a study of autologous anti-CD19-transduced CD3+ cells does not compare the treatment with anything else. It suggests that people having it may live longer and have more time before their disease relapses, but this is uncertain. There is also not enough evidence to tell if this treatment can cure B-cell acute lymphoblastic leukaemia.

The most likely estimates are higher than what NICE normally considers an acceptable use of NHS resources and these results are uncertain. So, autologous anti-CD19-transduced CD3+ cells cannot be recommended for routine use.

The cost-effectiveness estimates are higher than what is normally considered an acceptable use of NHS resources. So autologous anti-CD19-transduced CD3+ cells cannot be recommended within its anticipated marketing authorisation for use in the Cancer Drugs Fund.

2 Information about autologous anti-CD19-transduced CD3+ cells

Marketing authorisation indication

2.1 Autologous anti-CD19-transduced CD3+ cells (Tecartus, Kite) is expected to be indicated for 'the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia'.

2.2 The dosage schedule will be available in the summary of product characteristics for autologous anti-CD19-transduced CD3+ cells.

Price

2.3 The list price for single infusion is £316,118 (excluding VAT, MIMS [Monthly Index of Medical Specialities] online, accessed October 2022).

The company has a commercial arrangement. This makes autologous anti-CD19-transduced CD3+ cells available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

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

Treatment pathway and clinical practice

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

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

26 years and over, because there are no CAR T-cell therapy options for this population. The committee concluded that people with relapsed or refractory B-cell acute lymphoblastic leukaemia, especially those 26 years and over, would welcome new treatment options such as CAR T-cell therapies that improve the chance of survival.

The company's positioning of autologous anti-CD19-transduced CD3+ cells in the treatment pathway is appropriate

3.2 The company proposed 3 potential positions for autologous anti-CD19-transduced CD3+ cells in the treatment pathway. Specifically, for people 26 years and over with relapsed or refractory B-cell acute lymphoblastic leukaemia:

- whose disease has relapsed after an allo-SCT or
- who are ineligible for an allo-SCT or
- who are unlikely to reach a point where they can have an allo-SCT via existing bridging therapies.

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

concluded that the company's positioning of autologous anti-CD19-transduced CD3+ cells in the treatment pathway is appropriate.

The relevant comparators are inotuzumab, blinatumomab and ponatinib

3.3 The company compared autologous anti-CD19-transduced CD3+ cells with all comparators in the NICE scope, that is, FLAG-IDA, inotuzumab, blinatumomab and tyrosine kinase inhibitors (ponatinib). Based on clinical advice, the company refined the list of comparators and categorised them by treatment group: overall population (irrespective of Philadelphia chromosome), Philadelphia chromosome negative, and Philadelphia chromosome positive. The clinical experts explained that FLAG-IDA-based chemotherapy is rarely used in the UK because of its toxicity, poor tolerance and poor outcomes. They further explained that inotuzumab is given to both subgroups (Philadelphia chromosome negative and Philadelphia chromosome positive), whereas blinatumomab is restricted to Philadelphia chromosome-negative relapsed or refractory B-cell acute lymphoblastic leukaemia. Ponatinib is restricted to Philadelphia chromosome-positive relapsed or refractory B-cell acute lymphoblastic leukaemia in people whose disease does not respond or who cannot tolerate a tyrosine kinase inhibitor before having an allo-SCT. The committee discussed if FLAG-IDA should be included as a comparator in light of the clinical experts' comments. It agreed that since FLAG-IDA is rarely used in clinical practice, it should not be included as a comparator The committee concluded that inotuzumab, blinatumomab and ponatinib were the appropriate comparators for people 26 years and over with relapsed or refractory B-cell acute lymphoblastic leukaemia.

Clinical effectiveness

Autologous anti-CD19-transduced CD3+ cells could be clinically effective, but a curative treatment effect is uncertain

3.4 The clinical-effectiveness evidence for autologous anti-CD19-transduced CD3+ cells came from ZUMA-3, a single-arm open-label study of relapsed

or refractory B-cell acute lymphoblastic leukaemia. The trial recruited people from 32 centres across 5 countries, but there were no centres in the UK. A total of 78 people with relapsed or refractory B-cell acute lymphoblastic leukaemia were included in the final analysis, which provided the clinical evidence for the company's base-case cost-effectiveness analysis. The trial population included people under 26 years, so restricting the analysis to people covered by the anticipated marketing authorisation reduced the number of people included. The exact number is confidential so cannot be shown here. The primary outcome of the trial was overall complete remission. Secondary outcomes included overall survival and relapse-free survival. The median overall survival and relapse-free survival results are considered confidential by the company, so they cannot be shown here. The results suggested that autologous anti-CD19-transduced CD3+ cells could be potentially curative. The ERG explained that results supporting an assumption of cure with autologous anti-CD19-transduced CD3+ cells were uncertain, because the analyses did not distinguish between people who had an allo-SCT before treatment with autologous anti-CD19-transduced CD3+ cells and those who did not. Therefore, it was unclear if any survival benefit resulted from treatment with autologous anti-CD19-transduced CD3+ cells or from an allo-SCT. The clinical experts expressed concerns about how to interpret the relapse-free survival curve given the uncertainties. They added that curative outcomes can be seen in real-world evidence from people with relapsed or refractory B-cell acute lymphoblastic leukaemia who have had multiple different treatments before the CAR T-cell therapy. One of the clinical experts stressed that relapses after 12 months are infrequent and that this should be considered. The committee concluded that treatment with autologous anti-CD19-transduced CD3+ cells could be clinically effective, but a curative treatment effect is uncertain.

Autologous anti-CD19-transduced CD3+ cells are expected to be clinically effective in both subgroups

3.5 The company had proposed autologous anti-CD19-transduced CD3+ cells for Philadelphia chromosome-positive and -negative relapsed or refractory B-cell acute lymphoblastic leukaemia. The clinical experts stated that the treatment is expected to have similar efficacy in both populations. This is because the mechanism of action is not related to Philadelphia chromosome status. They noted that tisagenlecleucel is equally clinically effective in Philadelphia chromosome-negative and -positive. The committee concluded that autologous anti-CD19-transduced CD3+ cells are expected to be clinically effective in both Philadelphia chromosome-negative and Philadelphia chromosome-positive disease.

The inverse hazard ratio analysis is preferred over matching-adjusted indirect comparisons and naive comparisons

3.6 Because ZUMA-3 is a single-arm trial, an indirect treatment comparison was needed to estimate the efficacy of autologous anti-CD19-transduced CD3+ cells compared with the comparators. The company did an unanchored analysis using naive indirect comparisons and matching-adjusted indirect comparisons (MAICs). ZUMA-3 was used as the evidence source for autologous anti-CD19-transduced CD3+ cells. The evidence sources for the comparators were as follows: INO-VATE (inotuzumab); TOWER and SCHOLAR-3 (blinatumomab); pooled data from INO-VATE and TOWER (FLAG-IDA) and PACE (ponatinib). The company did 3 types of comparative analysis – a naive unadjusted comparison, a matched comparison via SCHOLAR-3, and a MAIC:

- For the naive unadjusted comparison, the company presented comparisons with ponatinib, inotuzumab, blinatumomab and FLAG-IDA.

- For the matched comparison via SCHOLAR-3, it used the synthetic control arm from SCHOLAR-3 to compare autologous anti-CD19-transduced CD3+ cells with blinatumomab.
- For the MAIC, it compared autologous anti-CD19-transduced CD3+ cells with inotuzumab, blinatumomab, FLAG-IDA. A MAIC against ponatinib was deemed unsuitable because of the small numbers of people with Philadelphia chromosome-positive disease in the ZUMA-3 study.

The committee considered that autologous anti-CD19-transduced CD3+ cells could potentially improve event-free survival compared with blinatumomab and inotuzumab, but this is uncertain. The company's base-case economic analyses used the naive comparisons against all comparators except for blinatumomab. The company preferred the naive comparison because it believes ZUMA-3 is more aligned with the target population in UK practice, whereas TOWER and INO-VATE are not. It said that using a MAIC would not adjust to the population of interest. The ERG noted that the populations in TOWER and INO-VATE are different to that in ZUMA-3, and so a naive comparison would be at risk of high bias. So, this comparison would not reflect the true relative treatment effect. It preferred a MAIC approach to adjust for the differences between the trials. The ERG was not able to look at the MAIC analysis for the Philadelphia chromosome-positive and -negative subgroups because the company used the overall population data. This is because it did not have subgroup data from the INO-VATE study for the comparisons of FLAG-IDA and inotuzumab. Therefore, the ERG had to adjust the MAIC analysis to the ZUMA-3 study data. The ERG also suggested using inverse hazard ratios derived from the MAIC analysis applied to the ZUMA-3 arm as baseline (an inverse hazard ratio method). This was an alternative method used to minimise bias associated with the other analysis methods. It considered this a reasonable approach since the company believes that matching

patients to other studies rather than ZUMA-3 would be inappropriate. The company had included this analysis in its updated economic model after technical engagement but had not given the ERG sufficient time to critique it, so it was not possible to present this evidence to the committee. However, the ERG was able to review this analysis after the first committee meeting. The committee concluded that it preferred the inverse of the hazard ratios method, over the MAIC and naive comparisons.

The company's economic model

The company's economic model is appropriate for decision making

3.7 The company used a partitioned survival model that included 3 mutually exclusive health states: event-free, progressed disease and death. The company modelled the cost effectiveness of treatment with autologous anti-CD19-transduced CD3+ cells using data from ZUMA-3 and data from INO-VATE, TOWER, PACE and SCHOLAR-3 for the comparators. After technical engagement the company updated its economic model to include a recent data cut of ZUMA-3, revised clinical-effectiveness data for people 26 years and over (the population in the anticipated marketing authorisation) and data from SCHOLAR-3. The committee agreed that the model was appropriate for decision making.

People having autologous anti-CD19-transduced CD3+ cells are likely to be at a higher risk of mortality than the general population

3.8 The company's model assumed a standardised mortality ratio of 1.09 to model the mortality risk of people whose cancer was considered cured compared with that of the age- and sex-matched general population in the UK. The ERG considered this to be an underestimate. It noted that this value was from a study of people with diffuse large B-cell lymphoma rather than B-cell acute lymphoblastic leukaemia. The ERG proposed a standardised mortality ratio of 4, sourced from a study in relapsed or refractory B-cell acute lymphoblastic leukaemia in which the mortality risk

ranged between 4 and 9. It noted that it had chosen the lowest value in the study, which was a conservative approach. The company noted that the study used by the ERG was in people who had allo-SCT, which is more burdensome and has longer-term treatment requirements than CAR T-cell therapy. The clinical expert explained that there is no long-term survival data for people with relapsed or refractory B-cell acute lymphoblastic leukaemia who have had autologous anti-CD19-transduced CD3+ cells. But he noted that he expected it to be similar to data for tisagenlecleucel, in which many people have been followed up for 5 to 10 years. The clinical expert highlighted that the main risk of the disease relapsing is during the first year after treatment and that after that, relapse is unlikely. He further explained that the risk of dying was associated with having an allo-SCT. This is because of the risk of graft-versus-host disease. The clinical expert added that it is rare that people who have had a CAR T-cell therapy develop graft-versus-host disease. The committee understood that the risk of dying was linked to allo-SCT before the CAR T-cell therapy. So, it considered that the true standardised mortality ratio for this population would be aligned to the value proposed by ERG (a standardised mortality ratio of 4). The committee concluded that people having autologous anti-CD19-transduced CD3+ cells are likely to be at a higher risk of mortality than the general population and the ERG approach should be used in decision making.

People who have had autologous anti-CD19-transduced CD3+ cells do not have the same quality of life as the general population

3.9 The company's model assumed that people who had autologous anti-CD19-transduced CD3+ cells and whose disease had not progressed after 3 years of treatment would have the same health-related quality of life as that of the same age- and sex-matched general population in the UK. The ERG had received clinical advice that there is cumulative toxicity from previous therapies, and that the disease itself reduced quality of life. Therefore, the ERG proposed a utility multiplier of 0.92 applied to the

general population utility values to adjust for lower quality of life. This was a midpoint between the utility value after the infusion and before relapse, and the general population of a similar age. The clinical experts explained that there is not enough evidence in CAR T-cell therapies to support either approach. But they explained that reduced quality of life in this population is likely to be related to previous treatments. People can live a near-normal life after treatment with the new technology and can return to daily activities soon after having a CAR T-cell therapy. The clinical expert also explained that CAR T-cell therapy can lead to better quality of life because the treatment is given in an outpatient setting and so people need less time in hospital. The patient expert stated that the condition had a huge emotional and financial impact on her and her family after she was diagnosed. She explained that she has a sustained risk from infections and so has to have regular follow-up appointments in the immunology department. The committee understood that people whose disease has not progressed will have a worse health-related quality of life than the general population because of the risks associated with CAR T-cell treatments and the effect of previous therapies. Therefore, it concluded that people having autologous anti-CD19-transduced CD3+ cells do not have the same quality of life as the general population and the ERG approach should be used in decision making.

Allo-SCT costs and QALY loss should be included in the model for people having autologous anti-CD19-transduced CD3+ cells

3.10 In ZUMA-3, 14 out of 78 people had an allo-SCT. But, the company did not account for the costs or quality-adjusted life year (QALY) impact of allo-SCT use in the autologous anti-CD19-transduced CD3+ cells arm in the economic model. The company stated that the technology is not planned to be used after an allo-SCT in UK clinical practice. It had done a sensitivity analysis adjusting for overall survival, censoring for allo-SCT, and no statistical difference was found. The ERG stated that the sensitivity analysis was not sufficiently powered to detect a difference. It also noted that an allo-SCT could have provided a survival advantage to

the people who had had one. The clinical experts stated that allo-SCT would be considered for some people whose disease had relapsed after having a CAR T-cell therapy and who were well enough to have this procedure. The committee concluded that allo-SCT costs and a QALY loss should be included in the model for people having autologous anti-CD19-transduced CD3+ cells.

CAR T-cell delivery costs of about £60,000 are most appropriate for decision making

3.11 The company used a bottom-up costing approach to calculate the cost of administering autologous anti-CD19-transduced CD3+ cells. The ERG considered that the company's approach likely underestimated the true cost based on expert advice it had received. The committee was aware that the tariff was developed after NICE recommended tisagenlecleucel, the first CAR T-cell therapy to be appraised, for use in the Cancer Drugs Fund in December 2018. NHS England stated that the tariff includes all costs of care from when a person is identified for CAR T-cell therapy to 100 days after infusion. It does not include acquisition costs of autologous anti-CD19-transduced CD3+ cells. The original tariff was £96,016. The tariff is subject to ongoing review and will be updated periodically. For use in NICE appraisals, NHS England provided a revised estimate of £65,415. NHS England explained that it worked with 1 NHS trust to provide a reasonable distribution of the total tariff costs across the different phases of treatment. The revised tariff also had an adjusted length of stay and an adjusted proportion of people who have care in an outpatient setting and outside the hospital. It also removed overheads that are legitimate costs incurred in the NHS but are not in line with NICE methods. The NHS England estimate is subject to ongoing review and will be updated periodically. NHS England explained that there is not a Healthcare Resource Group (HRG) that captures CAR T-cell therapies. It also commented that a key difference between its estimate of costs and the company's costs is the number of staff who look after people who have had CAR T-cell therapy. The company commented that is it not

appropriate to use the tariff in the modelling because it is a mechanism for NHS England to fund hospitals for providing CAR T-cell therapy and is not designed for technology evaluation. It is concerned that the evidence underlying the estimated cost has not been transparently shared and that it may not reflect the true cost of treatment. The ERG stated that the NHS England costing exercise had been a rapid review and that micro-costing had not been implemented. So, it had been unable to critique the cost components robustly because of the lack of alternative data sources for some costs. The NHS England Cancer Drugs Fund Clinical Lead commented that the company's costs were underestimated because some people need high intensity care after treatment, and because there are additional costs related to monitoring (such as paying for people to stay in hotels near hospitals). The committee was concerned that the company's costs underestimated the true cost of delivering autologous anti-CD19-transduced CD3+ cells. It noted that the company's cost was significantly less than the figure provided by NHS England. It noted that it was difficult to compare the company's cost with the NHS England tariff because they were reported differently. In the absence of an HRG, the NHS England estimate was the best available source for the costs of delivering CAR T-cell therapy. The committee considered that some costs included in the NHS estimate of £65,415 were already captured in the company's model. It concluded that a CAR T-cell administration cost of £60,000 was more relevant for decision making, but this value should be reviewed if any new evidence is presented.

End of life

Autologous anti-CD19-transduced CD3+ cells meets the criteria to be considered a life-extending treatment at the end of life

3.12 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The literature showed that median overall survival with the comparator treatments ranged from 5.3 to 8 months. The clinical

experts stated that life expectancy is the same for people with Philadelphia chromosome-negative and -positive disease. The company's model predicted that mean overall survival with the comparator treatments was more than 24 months, but the percentage of people alive at 2 years ranged from 13% to 22%. So, the committee was reassured that people are unlikely to live for longer than 24 months and that the short life expectancy criterion was met. The clinical experts explained that it is likely that autologous anti-CD19-transduced CD3+ cells will extend life for more than 3 months. Also, the model estimated a mean overall survival gain for autologous anti-CD19-transduced CD3+ cells compared with the comparators of more than 3 months. The exact data is confidential and so cannot be shown here. The committee concluded that the end of life criteria were met for people 26 years and over with relapsed or refractory B-cell acute lymphoblastic leukaemia.

Cost-effectiveness estimate

The most plausible ICERs are higher than those normally considered a cost-effective use of NHS resources

3.13 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted that the ERG's base-case analysis was more closely aligned with several of its preferred assumptions for both Philadelphia chromosome subgroups, specifically:

- using the inverse of hazard ratios derived from the MAIC analysis to model inotuzumab in the ZUMA-3 population (see section 3.6)
- including costs and QALY loss associated with allo-SCT for people who have autologous anti-CD19-transduced CD3+ cells (see section 3.10)

- using a standardised mortality ratio of 4 for people alive at 3 years (see section 3.8)
- using a utility multiplier of 0.92 applied to age-and sex-matched to the general population (see section 3.9)
- assuming adverse events related costs for autologous anti-CD19-transduced CD3+ cells to be the same as that for inotuzumab (this had very little effect on the cost-effectiveness results, so the committee considered the ERG's approach more appropriate)
- removing the costs of FLAG-IDA for people having ponatinib (this had very little effect on the cost-effectiveness results so the committee considered the ERG's approach more appropriate)
- assuming a NHS tariff of £60,000 for CAR T-cell delivery costs (see section 3.11).

Using these assumptions, and considering the confidential discounts for autologous anti-CD19-transduced CD3+ cells and comparator treatments, the ICERs for autologous anti-CD19-transduced CD3+ cells compared with the comparators for both the Philadelphia positive and negative subgroups were above £50,000 per QALY gained. Because there are confidential discounts for autologous anti-CD19-transduced CD3+ cells and some of the comparator treatments, the exact ICERs cannot be reported here. For the Philadelphia chromosome-negative subgroup, the ERG base case uses the SCHOLAR-3 data adjusted to a ZUMA-3 population to model blinatumomab. For the Philadelphia chromosome-positive subgroup, it assumes no adjunctive chemotherapy use with ponatinib. The fully incremental cost-effectiveness analysis for the Philadelphia negative subgroup showed that inotuzumab was extendedly dominated by autologous anti-CD19-transduced CD3+ cells and blinatumomab. That is, inotuzumab is less effective and has a higher ICER than the other treatments. Similarly, in the Philadelphia positive subgroup, inotuzumab was extendedly dominated by autologous anti-CD19-transduced CD3+ cells and

ponatinib. In both Philadelphia subgroups, the ICERs for autologous anti-CD19-transduced CD3+ cells compared with the comparators were above £50,000 per QALY gained. The committee did not consider that the technology represented a cost-effective use of NHS resources, even when taking into account the end of life criteria.

Conclusion

Autologous anti-CD19-transduced CD3+ cells are not recommended for routine use in the NHS

3.14 The committee recalled the uncertainties in the evidence for this technology (see section 3.13). It agreed that its preferred ICERs were likely to be above what NICE considers to be a cost-effective use of NHS resources. So, it concluded that autologous anti-CD19-transduced CD3+ cells cannot be recommended for routine use within its anticipated marketing authorisation for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over.

Cancer Drugs Fund

Autologous anti-CD19-transduced CD3+ cells cannot be recommended for use in the Cancer Drugs Fund

3.15 The committee considered if autologous anti-CD19-transduced CD3+ cells could be recommended for use within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee discussed if the uncertainties identified in the company's cost-effectiveness evidence could be addressed by collecting more data in the Cancer Drugs Fund. The ongoing single-arm ZUMA-3 trial will provide further data on the follow up of people after 15 years of autologous anti-CD19-transduced CD3+ cells. But the committee agreed that this would not address any of the substantial uncertainty in the comparative clinical-effectiveness

evidence. Other issues, such as the uncertainties in the mortality rate value (see section 3.8) and the utility value (see section 3.9), could not be resolved through further data collection in the Cancer Drugs Fund. The committee noted that the technology does not have plausible potential to be cost effective because the ICERs were still higher than what NICE considers acceptable use of NHS resources (see section 3.13). It concluded that autologous anti-CD19-transduced CD3+ cells did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Equality issues

3.16 The equalities issues cannot be addressed through this technology appraisal The clinical expert noted that people from minority ethnic backgrounds can sometimes find it difficult to identify a suitable match for a curative allo-SCT. For this reason, autologous anti-CD19-transduced CD3+ cells could potentially offer improved outcomes in this population. The committee noted that the company had not positioned autologous anti-CD19-transduced CD3+ as an alternative for people who are eligible for allo-SCT (such as people from minority ethnic backgrounds). The committee was also aware that this technology appraisal cannot change how suitable matches are identified. It agreed that this could not be addressed in this technology appraisal given the information available at this time. The committee noted that the company's anticipated marketing authorisation states that this technology is for people 26 years and over. The patient and clinical expert noted that if this technology is not recommended it would leave people above this age without access to a potentially curative treatment option. The committee acknowledged this issue and recalled that NICE can only make recommendations within the marketing authorisations. It was also aware that some religious groups such as Jehovah's witnesses may not accept technologies or procedures derived from blood (such as allo-SCT). These people would normally have best supportive care. The committee acknowledged that if autologous anti-CD19-transduced CD3+ cells does become an available treatment option, some people may choose not to have this treatment because it

contains human blood products. Accordingly, this is not viewed as an equality issue. For these reasons, the committee concluded that the equality issues cannot be addressed through this technology appraisal.

Stephen O'Brien
Chair, appraisal committee
October 2022

4 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

Anne Murray-Cota
Technical lead

Sally Doss
Technical adviser

Celia Mayer

Project manager

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