NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using axicabtagene ciloleucel 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: July 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 axicabtagene ciloleucel 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: 17 August 2022

Next appraisal committee meeting: 6 September 2022

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

1 Recommendations

1.1 Axicabtagene ciloleucel is not recommended, within its anticipated marketing authorisation, for treating relapsed or refractory follicular lymphoma after 3 or more systemic therapies in adults.

1.2 This recommendation is not intended to affect treatment with axicabtagene ciloleucel 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

There is no established treatment for relapsed or refractory follicular lymphoma after 3 or more systemic therapies. Treatment can involve trying previous treatments again. Axicabtagene ciloleucel is a CAR T-cell therapy. The therapy uses the person's own immune system cells (T cells), which have been modified to attach to and kill cancer cells.

The clinical evidence is from a small study that suggests that axicabtagene ciloleucel improves the amount of time people have before their condition gets worse and how long they live, but it is uncertain by how much.

Axicabtagene ciloleucel does not meet NICE's criteria to be considered a life-extending treatment at the end of life. This is because people having standard treatments for relapsed or refractory follicular lymphoma after 3 or more systemic therapies are likely to live longer than 2 years.

Because there are uncertainties in the economic model, the cost-effectiveness estimates are also uncertain. They are also all above the range NICE normally considers to be an acceptable use of NHS resources. So, axicabtagene ciloleucel is not recommended for routine use in the NHS.

Axicabtagene ciloleucel has not been reliably shown to have potential to be cost effective. So, axicabtagene ciloleucel is not recommended for use in the Cancer Drugs Fund.

2 Information about axicabtagene ciloleucel

Anticipated marketing authorisation indication

2.1 Axicabtagene ciloleucel (Yescarta, Kite) is indicated 'for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy'. Axicabtagene ciloleucel has not yet been granted a marketing authorisation from the Medicines and Heathcare products Regulatory Agency (MHRA). On 22 April 2022 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for axicabtagene ciloleucel, intended for treating relapsed or refractory follicular lymphoma after 3 or more lines of systemic therapy.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for axicabtagene ciloleucel.

Price

2.3 The list price for axicabtagene ciloleucel is £280,451. The company has a commercial arrangement. This makes axicabtagene ciloleucel 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 the 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.

The condition

Living with relapsed or refractory follicular lymphoma is physically and emotionally challenging

3.1 The clinical and patient expert's statements highlighted that follicular lymphoma can have a significant effect on the quality of life of people with the condition and their carers. They explained that people are concerned about relapse and the need for repeated courses of treatment is physically and psychologically challenging. They explained that the symptoms and unpredictable nature of the disease have a profound and devastating impact on all aspects of a person's life. People experience a wide variety of symptoms including enlarged lymph nodes, weight loss, fever, night sweats, constant itching, fatigue, neutropenia, anaemia, and thrombocytopenia. Low-grade lymphoma can transform into high-grade lymphoma, which can have serious symptoms requiring urgent treatment. These symptoms can lead to the inability to work, focus or concentrate and can affect mood and the ability to exercise, socialise, and have a relationship. They explained that people feel exhausted, tire easily and are unable to do daily activities. The committee understood that people with the disease often have difficulty doing day-to-day tasks, and fear relapse. In addition, treatment options become limited as the disease advances so courses of previous treatments are often repeated. There can be a negative impact on self-esteem and difficulties having relationships. A clinical expert explained that, with more effective treatment, there was potential for people with the condition to live longer and have a better quality of life. In addition, the patient expert statement

highlighted that caring for someone with follicular lymphoma is emotionally, practically and financially challenging. For example, carers often provide transport to and from hospital appointments and treatment sessions, requiring time off work. They also provide emotional support, while trying to deal with an emotionally difficult situation themselves. The committee concluded that living with the disease and caring for people with relapsed or refractory follicular lymphoma is physically and emotionally challenging.

People with relapsed or refractory follicular lymphoma would welcome a new treatment option

3.2 The clinical and patient experts explained that there is an unmet need for effective new treatments for people with relapsed or refractory follicular lymphoma. This is because for many people their disease does not respond well after 3 or more therapies. The only option for them is to repeat courses of previous treatments. These can have significant side effects which may impact their daily activities. The clinical and patient experts explained that if multiple treatments are available in the treatment pathway, it allows them to identify the best option as quickly as possible to achieve complete remission. The committee concluded that clinicians and people with the condition would welcome a new treatment option.

The treatment pathway

The proposed positioning of axicabtagene ciloleucel is appropriate

3.3 Follicular lymphoma is the most common type of indolent (low-grade) non-Hodgkin's lymphoma and is not considered curable. Treatment aims to induce response and control disease progression for as long as possible. The clinical experts explained that treatment is characterised by multiple lines of treatment as the disease responds and relapses. Rituximab monotherapy is used as a first-line treatment option for treatment of asymptomatic advanced (stage 3 or 4) disease. For symptomatic

advanced follicular lymphoma, NICE's technology appraisal guidance on rituximab for the first-line treatment of stage 3 to 4 follicular lymphoma recommends first-line treatment with rituximab in combination with either cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, vincristine and prednisolone (CVP), or mitoxantrone, chlorambucil and prednisolone (MCP) or cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alfa (CHVPi) or chlorambucil. At first relapse, if the disease had a good response to initial treatment, people are offered a different rituximab–chemotherapy combination followed by rituximab maintenance therapy. If the disease does not respond adequately or loses response, lenalidomide plus rituximab or obinutuzumab with bendamustine are offered. The clinical experts explained that if the disease relapses after obinutuzumab with chemotherapy it may be treated with a rituximab–chemotherapy combination, or with rituximab alone if there is resistance or intolerance to chemotherapy. The clinical experts also explained that when the disease becomes refractory, the available treatment options are limited, and people have a poor prognosis. Treatments are chosen based on the person's previous treatment and their fitness level. Rechallenge or reintroduction of previously used treatments is relatively common practice. The committee acknowledged that there is no established standard care for people with relapsed or refractory follicular lymphoma after 3 or more systemic therapies. The committee agreed with the company's positioning of axicabtagene ciloleucel after 3 or more previous therapies.

The company's blended comparator approach is acceptable for decision making

3.4 The company compared axicabtagene ciloleucel with various treatments based on the SCHOLAR-5 (an international external control cohort that was generated to provide comparative evidence in relapsed or refractory follicular lymphoma, see section 3.7). Treatments in the blended

comparator included rituximab with chemotherapy (CHOP, CVP or bendamustine), rituximab with lenalidomide, and obinutuzumab with bendamustine (from now on referred to as the blended comparator). A blended comparator was used because there is no established standard treatment after 3 or more systemic therapies. The company considered that rituximab monotherapy and best supportive care were not relevant comparators because these treatments would likely be used to treat people who are not well enough to have axicabtagene ciloleucel. Therefore, rituximab monotherapy and best supportive care were excluded from the comparator. The ERG and clinical experts broadly agreed that the company's blended comparator reflected clinical practice, but they highlighted a few differences. For example, in some cases CVP may be used after 3 treatments in clinical practice. The committee concluded that the company's blended comparator approach, and the treatments included in it, were suitable for decision making in the context of this appraisal.

Clinical evidence

The results of ZUMA-5 are generalisable NHS clinical practice

3.5 The clinical evidence for axicabtagene ciloleucel came from ZUMA-5, a single-arm, open-label, phase 2 study. The study was in people with relapsed or refractory B-cell indolent non-Hodgkin lymphoma (follicular lymphoma or marginal zone lymphoma). It included 125 people with relapsed or refractory follicular lymphoma. The committee noted that ZUMA-5 included people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, which means that their activities are relatively unrestricted by their disease. The clinical experts highlighted that the relevant population in the NHS is likely to be older and less fit than the trial population. However, they considered that the population included in ZUMA-5 would be generalisable to the people who would receive axicabtagene ciloleucel in clinical practice. The committee

concluded that ZUMA-5 is broadly generalisable to NHS clinical practice and appropriate for decision-making.

Axicabtagene ciloleucel is likely to be clinically effective but survival data is immature and uncertain

3.6 The primary outcome of ZUMA-5 was objective response rate. The secondary outcomes relevant to this appraisal were objective response rate, complete response, duration of response, best objective response, progression-free survival, and overall survival. Efficacy data was presented for people with follicular lymphoma with 2 or more lines of prior therapy because this was the predefined primary efficacy analysis set. However, to align with the anticipated marketing authorisation and decision problem, efficacy data was also presented for people with follicular lymphoma with 3 or more lines of prior therapy. Results showed that people with relapsed or refractory follicular lymphoma who had axicabtagene ciloleucel after 3 or more therapies, had a high objective response rate and complete response. Results are academic in confidence and cannot be reported here. Median overall survival and median progression-free survival are also academic in confidence and cannot be reported here. The committee noted that there is no evidence on the effectiveness of axicabtagene ciloleucel directly compared with standard care. At the latest data cut, the median follow-up in ZUMA-5 was short and the survival data was immature so there was uncertainty in the robustness of the results. The committee was aware that no plateau was observed in the Kaplan–Meier curves for overall survival and progression-free survival. It also noted that the curves were based on very few people having experienced an event by the data cut-off which means that the long-term outcomes are very uncertain. The committee also noted that some people included in ZUMA-5 received an allogeneic stem cell transplant after treatment with axicabtagene ciloleucel. The committee was aware that this may impact the overall mean survival for ZUMA-5.

The number of people who had allogeneic stem cell transplant is academic in confidence so cannot be reported here. The committee concluded that axicabtagene ciloleucel is likely to be clinically effective, but immature survival data, inclusion of subsequent therapies (such as allogenic stem cell transplant) in the trial, and the lack of comparator data mean the size of this benefit is uncertain.

ZUMA-5 is a single-arm study so comparator data was taken from SCHOLAR-5

3.7 Because ZUMA-5 was a single-arm study, the company used data from the SCHOLAR-5 study to inform comparative effectiveness. SCHOLAR-5 was a retrospective study with pooled data from 3 cohorts (A, B and C). Cohorts A and B included retrospective medical records from 7 sites in the UK, France, Spain, Portugal and the US. Cohort C included a single-arm, open-label phase 2 study (DELTA) for people with relapsed or refractory follicular lymphoma whose disease did not respond adequately or was refractory to rituximab and an alkylating agent and who had received idelalisib. The cohorts were restricted to people with follicular lymphoma who had received at least 3 prior therapies, in line with the anticipated marketing authorisation for axicabtagene ciloleucel. More treatments were included in SCHOLAR-5 than in the blended comparator (see section 3.4). Idelalisib, radioimmunotherapy, CVP and experimental treatments were excluded from the blended comparator because they were not considered representative of treatments used in the NHS. The committee noted the ERG's concerns that comparative effectiveness results from single-arm studies were prone to bias because of the lack of randomised comparators in the clinical data. The committee was aware that because of the lack of data for relapsed or refractory follicular lymphoma after 3 or more therapies, the company used a propensity-score weighted indirect comparison (see section 3.9). The committee concluded that using data

from the SCHOLAR-5 study was acceptable to inform comparative effectiveness.

The SCHOLAR-5 population is not fully aligned with the ZUMA-5 population

3.8 The committee discussed the differences between ZUMA-5 and SCHOLAR-5. The ERG noted that there were differences in the distribution of ECOG performance score (0 and 1) between ZUMA-5 and SCHOLAR 5. The committee was aware that the DELTA cohort of SCHOLAR-5 included people outside of the UK, and that some of the treatments they had are not recommended for routine use in clinical practice in England, including idelalisib, radioimmunotherapy, CVP and experimental treatments (see section 3.7). The ERG highlighted that people treated with idelalisib may have better outcomes than those not treated with idelalisib. The clinical experts agreed with the ERG that people who were treated with idelalisib had better outcomes. They explained that people treated with idelalisib had longer progression-free survival in the DELTA cohort. Therefore, the committee concluded that the SCHOLAR-5 population is not fully aligned with the ZUMA-5 population.

The company's approach to adjust the SCHOLAR-5 data is highly uncertain

3.9 Clinical inputs for the comparator arm, for treatment options after 3 or more therapies were derived using the propensity score weighted data from the SCHOLAR-5 study. To address the baseline imbalances between the ZUMA-5 and SCHOLAR-5 studies and to reduce bias in comparative effectiveness, the company applied propensity scoring methods (standardised mortality ratio weighting [SMR]). The ERG commented that it was not transparent how the SMR weighting had been applied to the propensity scoring. However, it considered that the weighting improved comparability between ZUMA-5 and SCHOLAR-5.

The results of pre-weighting and post-weighting baseline characteristics are academic in confidence and cannot be reported here. The committee noted that the company had access to individual person data from both the ZUMA-5 and SCHOLAR-5 studies, so other methods may have been more appropriate (as documented in NICE DSU Technical Support Document 18). The committee was aware that the company had not provided the individual person data to the ERG when requested. The company did an unanchored indirect comparison using both propensity score weighting and propensity score matching methods. The committee agreed with the ERG that propensity score weighting improved the comparability. However, the committee noted that some covariates had been excluded from the weighting; for example, follicular lymphoma subtype (grade 1, grade 2 and grade 3a) for which a large standardised mean difference was observed. The committee noted that stronger assumptions need to be met for an unanchored comparison. It also noted that propensity score weighting methods should adjust for all treatment effect modifiers and prognostic variables to better predict outcomes. The committee concluded that the company's approach and use of the propensity score weighting method was highly uncertain. It would like to see other methods explored in more detail or the uncertainties of the unanchored indirect comparison addressed.

Economic model

The company's model is appropriate for decision-making

3.10 The company used a partitioned-survival model to estimate the cost effectiveness of axicabtagene ciloleucel compared with standard care. It included 3 health states: pre-progression, progressed and death. The company's model structure was similar to those used in previous appraisals for relapsed or refractory follicular lymphoma. The ERG explained that the company had captured all relevant health states and that its model structure was appropriate but noted some uncertainties in

the assumptions used in its model. For example long-term survivor assumption, see section 3.12). The committee questioned whether the company had explored a mixture cure modelling approach. The company explained that because of the immaturity of the data it was not possible to use a mixture cure model or a spline model. The committee concluded that the company's model was appropriate for its decision-making.

Extrapolations for progression-free and overall survival benefits from SCHOLAR-5 for standard care are uncertain

3.11 The committee was aware that the company used SCHOLAR-5 to model the survival data for the blended comparator. Because there was no date of progression for people having the index therapy in the DELTA cohort, the ERG noted that these people were excluded from the progression-free survival analysis. This resulted in fewer people to inform progression-free survival post-weighting. The ERG explained that the results from SCHOLAR-5 could overestimate overall survival time in the post-progression state for standard care. At technical engagement, the company removed the DELTA cohort from the SCHOLAR-5 data before propensity weighting which improved the comparability with ZUMA-5. The committee noted the minimal impact of removing the DELTA cohort on the progression-free survival curves and that the company had selected gamma extrapolation in line with its original base case. The ERG explained that people from the DELTA cohort were included in SCHOLAR-5 from the point of progression representing people with prior exposure to idelalisib but not receiving idelalisib as fourth-line treatment. The ERG considered generalised gamma, log-logistic and lognormal distributions to provide the best statistical fits. The estimates of survival extrapolation for people with relapsed or refractory follicular lymphoma after 3 or more previous treatments in the NHS in England were noted by the ERG to be highly uncertain. The committee noted that the company did not justify using a gamma extrapolation as its chosen parametric

curve. It also noted that removing the DELTA cohort from SCHOLAR-5 had a large effect on cost-effectiveness results. The committee concluded that extrapolation of progression-free survival and overall survival for standard care after 3 or more therapies is uncertain..

The company and ERG long-term survivor assumption for ZUMA-5 and SCHOLAR-5 may not be appropriate

3.12 Progression-free survival and overall survival were the main effectiveness inputs included in the company's economic model. Progression-free survival and overall survival for axicabtagene ciloleucel and standard care after 3 or more therapies were estimated from time-to-event data from ZUMA-5 and SCHOLAR-5 respectively. The committee noted that both the company and ERG models assumed that a proportion of people who had axicabtagene ciloleucel could be considered long-term survivors from a future timepoint and thereafter experience zero risk of progression. The long-term survivors were also assumed to have a 9% higher probability of death than the general population from 5 years onwards. The company base case assumption was that 25% of people who had axicabtagene ciloleucel were long-term survivors and applied these extrapolation assumptions from 5 years. Non-long-term survivors continued to follow the hazards of progression and death based on a Weibull distribution fitted to the full ZUMA-5 dataset. The committee noted that the company's approach reflects a homogenous cohort of people, which is used at all timepoints for non-long-term survivors, but overridden by cure assumptions in the long-term survivor proportion at 5 years. The company clarified that based on clinical opinion and clinical validation of survival curves it assumed 25% of people who had axicabtagene ciloleucel as long-term survivors. The ERG agreed with the company that it was not possible to use a mixture cure model because the data from ZUMA-5 was immature. The ERG considered that because of the unique mechanism of action of axicabtagene ciloleucel, it would expect a proportion of people to

be long-term survivors but that the proportion could not be validated because of the lack of data after 3 therapies. The committee was aware that both the company and the ERG also presented scenario analyses with long-term survival proportions which varied up to 25%. The committee noted that the long-term survivor proportion assumption had little effect on the cost-effectiveness results. The committee noted that the company did not clearly present the model predictions for long-term survivors and non-long-term survivors separately. The committee concluded that based on the immature survival data from ZUMA-5 and the uncertainties in the SCHOLAR-5 data, it was uncertain if the company's long-term survival assumptions were appropriate.

The health state utility values used in the economic model are uncertain

3.13 In ZUMA-5 and SCHOLAR-5, no health-related quality of life data was collected. The committee noted that the company used health state utility values in the economic model from NICE's technology appraisal guidance on lenalidomide with rituximab for previously treated follicular lymphoma which were based on the AUGMENT study. The committee was aware that other sources of health state utilities were also available. However, the ERG was concerned that because most patients in the AUGMENT study were at an earlier stage in the disease pathway, they would be expected to have a higher quality of life than people having treatment after 3 or more therapies. The ERG therefore preferred to use utility values from Wild et al. 2006 in its base case which had EQ-5D data collected from people with relapsed or refractory follicular lymphoma. Long-term survivors (that is, people who were alive and free of progression at 5 years and beyond) were assumed to have a utility decrement compared with the general population for the rest of life. The ERG highlighted the limitations of the Wild et al. study but considered it better reflected the likely quality of life of people after 3 prior therapies than the AUGMENT study. In response to technical engagement, the company agreed with the

ERG and updated its base case using utility values from Wild et al. The company explained that it considered that health-related quality of life for long-term survivors would be equal to that of the general population in line with previous NICE technology appraisal guidance on axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies and autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma. To address uncertainty, the company also presented a scenario that assumed health state utility value for long-term survivors after axicabtagene ciloleucel treatment to be halfway between the Wild et al. progression-free estimate and the general population. The ERG broadly agreed with the company's updated base case. However, it considered it inconsistent that long-term survivors would attain a health state utility in line with the general population while experiencing an elevated mortality risk. Given the uncertainty, the ERG considered it important to consider the range of assumptions around long-term survivor's utility values. The committee noted that the source of utility values had a minimal effect on the cost-effectiveness results. The committee concluded that the ERG's approach of using a utility decrement for long-term survivors was more appropriate and it would consider the scenarios presented in its decision making.

Time on treatment and subsequent treatment costs for comparator therapies used in the economic model may not be appropriate

3.14 In its original model, for therapies used in the blended comparator, the company used the median number of treatment cycles reported in the relevant summary of product characteristics. The company fitted exponential distribution in its model to estimate time on comparator treatments. For simplicity, the company assumed equal subsequent therapy costs in both arms of the model. The ERG noted that the time on treatment curves were not consistent with the derived progression-free

survival and overall survival curves for the comparator arm. The ERG highlighted that the company capped the time on treatment so it could not exceed overall survival, assuming that treatment continues beyond progression. The clinical experts explained that treatment was unlikely to continue beyond progression. At technical engagement, the company agreed with the ERG that allowing treatment beyond progression while applying subsequent treatment costs at the point of progression may overestimate costs of standard care in the comparator arm of the model. Therefore, in its updated base case, the company capped comparator time on treatment at the point of progression. The ERG explained that it was broadly satisfied with the company's updated base case. However, time on treatment with comparator therapies for people with relapsed or refractory follicular lymphoma after 3 or more previous therapies remains uncertain because of limited data. The committee was aware that time on comparator therapies and subsequent treatment costs had a large impact on cost-effectiveness results. Despite the uncertainty in the estimation of time on treatment with comparator therapies, the committee concluded that it would accept the approach for decision making in the context of this appraisal.

The infusion and monitoring costs for axicabtagene ciloleucel in the company model may not be reflective of NHS practice

3.15 The company explained that axicabtagene ciloleucel is administered as a single infusion within 30 minutes. It explained that in line with previous appraisals for CAR T-cell therapies (NICE technology appraisal guidance on axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies and autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma), people are monitored in an elective inpatient setting. To account for this, the company applied daily hospitalisation costs of £903 to the mean duration of hospitalisations

observed after axicabtagene ciloleucel treatment in ZUMA-5. The mean duration of hospitalisations is academic in confidence and cannot be reported here. The committee noted that mean hospitalisation in ZUMA-5 was longer than reported in the Hospital Episode Statistics database. The Cancer Drugs Fund clinical lead explained that NHS England provides the infrastructure to CAR-T centres for them to deliver the entire treatment, including infusion and monitoring. NHS England has established a single delivery tariff for the cost of delivering current CAR T-cell therapies. The 2022/23 tariff cost for CAR-T delivery in people aged 19 years and over is £96,016, subject to ongoing review. The clinical experts explained that they would expect intravenous immunoglobulin to be used for longer than the company's modelled time of 12 months. They also explained that in clinical practice the costs are higher than the company's estimates used in the model and well below the NHS tariff cost. The committee noted that it was not provided with the full details about how the NHS tariff cost was derived. It noted the need for greater transparency as to what the tariff cost included, in order to explore potential issues of double counting or under counting. Despite this, the committee concluded that the tariff estimate was the best available source to inform the cost that the NHS is paying currently.

End of life

Axicabtagene ciloleucel does not meet the criteria to be considered a life-extending treatment at the end of life

3.16 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. This states that a treatment can be considered as a life-extending treatment at the end of life if it is indicated for people with a short life expectancy (normally less than 24 months) and it offers an extension to life (normally a mean value of at least an additional 3 months

compared with current NHS treatment). The committee noted that both the company and ERG agreed that axicabtagene ciloleucel did not meet the criteria for end of life. The company explained that axicabtagene ciloleucel would be adopted by clinicians as an end of life therapy for people with relapsed or refractory follicular lymphoma who had 3 or more systemic therapies. The clinical experts highlighted that they would expect people having standard care to live between approximately 30 to 36 months. The median life expectancies from the treatment comparison from the model are academic in confidence and cannot be reported here. The committee considered that the short life expectancy criterion of less than 24 months was not met because the life expectancy of people who would have axicabtagene ciloleucel would normally be longer than 24 months. The committee concluded that axicabtagene ciloleucel does not meet the criteria to be considered a life-extending treatment at end of life.

Cost-effectiveness estimates

An acceptable ICER would be within the range normally considered cost effective

3.17 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (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 data is immature for overall survival and extrapolations from the model are uncertain. So, the committee agreed that an acceptable ICER would be in the within the range normally considered a cost-effective use of NHS resources (that is, between £20,000 to £30,000 per QALY gained).

The most likely cost-effectiveness estimates are higher than those normally considered an acceptable use of NHS resources

3.18 Both the company's and the ERG's deterministic base cases showed that ICERs for axicabtagene ciloleucel compared with standard care were over £50,000 per QALY gained. The committee noted the high level of uncertainty in the model, particularly concerning:

- immature progression-free survival and overall survival data from ZUMA-5 (see section 3.6)
- no direct comparative efficacy data for axicabtagene ciloleucel compared with standard care (see section 3.7 and section 3.9)
- long-term survivor proportion assumptions (see section 3.12)
- time on treatment for comparator therapies is not well informed in the company's model for people receiving treatment after 3 therapies (see section 3.14)
- source for the higher costs associated with axicabtagene ciloleucel treatment (see section 3.15)

Because of confidential commercial arrangements for axicabtagene ciloleucel and other comparators, the ICERs cannot be reported here. Taking into account all confidential discounts, the committee noted that both the company's and the ERG's cost-effectiveness estimates for axicabtagene ciloleucel compared with standard care were above what NICE considers a cost-effective use of NHS resources. Therefore, axicabtagene ciloleucel is not recommended for routine use in the NHS.

Cancer Drugs Fund

Axicabtagene ciloleucel is not recommended for use in the Cancer Drugs Fund

3.19 Having concluded that axicabtagene ciloleucel could not be recommended for routine use in the NHS, the committee then considered

if it could be recommended 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 technology appraisal process and methods guide (addendum). The committee recognised that people with relapsed or refractory follicular lymphoma have a high unmet need, and the availability of new treatments is very important. The committee was aware that the company had expressed an interest in the treatment being considered for funding through the Cancer Drugs Fund. It understood that ZUMA-5 (a single-arm, phase 2 study) is ongoing and that a further study for axicabtagene ciloleucel is also planned (ZUMA-22, a phase 3 study). The committee noted that these are likely to provide further evidence on survival. However, these studies may not resolve some of key uncertainties affecting the cost-effectiveness results, such as :

- immature progression-free survival and overall survival data from ZUMA-5.
- no direct comparative efficacy data for axicabtagene ciloleucel compared with standard care.
- source for the higher costs associated with axicabtagene ciloleucel treatment.

The committee also noted that there was also no plausible potential for axicabtagene ciloleucel to be considered a cost-effective use of NHS resources. The committee concluded that axicabtagene ciloleucel did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Innovation

Axicabtagene ciloleucel is an innovative treatment for relapsed or refractory follicular lymphoma, but all relevant benefits are reflected in the cost-effectiveness estimates

3.20 The company considered axicabtagene ciloleucel to be innovative because of its mechanism of action in which a person's own T cells are modified to target and kill cancer cells. The company explained that it was the first of the breakthrough class of CAR T-cell therapies to be licensed for use in Europe and the US. The clinical experts explained that a single infusion may benefit some people with this condition. The committee acknowledged the benefits offered by axicabtagene ciloleucel. However, it concluded that it had not been presented with evidence of any additional benefits that were not captured in the QALY.

Equalities

3.21 There were no equality issues identified.

Stephen O'Brien
Chair, appraisal committee
July 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.

Harsimran Sarpal
Technical lead

Louise Crathorne
Technical adviser

Celia Mayers
Project manager

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