

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal document**

**Axicabtagene ciloleucel for treating relapsed or  
refractory follicular lymphoma**

**1 Recommendations**

- 1.1 Axicabtagene ciloleucel is not recommended, within its marketing authorisation, for treating relapsed or refractory follicular lymphoma after 3 or more systemic treatments 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 treatments. Treatment can involve trying previous treatments again. Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy. The therapy uses the person's 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 increases 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 treatments 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.

The evidence suggests that axicabtagene ciloleucel is not likely to be cost effective. So, axicabtagene ciloleucel is not recommended for use in the Cancer Drugs Fund.

## **2 Information about axicabtagene ciloleucel**

### **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'.

### **Dosage in the marketing authorisation**

2.2 The dosage schedule is available in the [summary of product characteristics for axicabtagene ciloleucel](#).

### **Price**

2.3 The list price of axicabtagene ciloleucel for a single infusion including shipping, engineering and generation of chimeric antigen receptor (CAR) T cells is £280,451 (company submission). 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 Kite, 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 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 with follicular lymphoma are concerned about relapse and that 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 not being able 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 they 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 in 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 condition 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 treatments. The only option for them is to repeat courses of previous treatments. These can have significant side effects which may affect 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 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 the 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)
- cyclophosphamide, vincristine and prednisolone (CVP)
- mitoxantrone, chlorambucil and prednisolone (MCP)
- 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 treatments. If the disease does not respond adequately or if response is lost, lenalidomide with rituximab, or obinutuzumab with bendamustine is offered. The clinical experts explained that if the disease relapses after obinutuzumab with chemotherapy it may be treated with a rituximab–chemotherapy combination. They explained that it may be treated 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 fitness level. Rechallenge or reintroduction of previously used treatments is a 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

treatments. The committee agreed with the company's positioning of axicabtagene ciloleucel after 3 or more previous treatments.

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

3.4 The company compared axicabtagene ciloleucel with various treatments based on SCHOLAR-5. This was an international external control cohort study 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 treatments. The company considered that rituximab monotherapy and best supportive care were not relevant comparators. This was because these treatments would likely be used to treat people who are not well enough to have axicabtagene ciloleucel. So, rituximab monotherapy and best supportive care were excluded from the list of comparators. 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 to 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. This 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. But they considered that the population included in ZUMA-5 would be generalisable to the people who would have treatment with axicabtagene ciloleucel in clinical practice. The committee concluded that ZUMA-5 is broadly generalisable to NHS clinical practice and is appropriate for decision making.

**Axicabtagene ciloleucel is likely to be clinically effective, but survival data is immature and the long-term treatment effect is 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 after 2 treatments because this was the predefined primary efficacy analysis set. But to align with the marketing authorisation and decision problem, efficacy data was also presented for people with follicular lymphoma after 3 or more treatments. Results showed that people with relapsed or refractory follicular lymphoma who had axicabtagene ciloleucel after 3 or more treatments, had a high objective response rate and complete response. The results, including median overall survival and median progression-free survival, are 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 had an allogeneic stem cell transplant after treatment with axicabtagene ciloleucel. The committee was aware that this may affect 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. At the first meeting, the committee concluded that axicabtagene ciloleucel is likely to be clinically effective. But the size of this benefit is uncertain. This is because of the immature survival data, the inclusion of subsequent treatments (such as allogenic stem cell transplant) in the trial, and the lack of comparator data. In response to consultation, the company presented an updated analysis of data from ZUMA-5 (referred to as the 36-month data cut). The company also presented a post-hoc analysis that explored the potential impact of allogenic stem cell transplant. The analysis censored data for people at the time of subsequent transplant and compared the 24-month overall-survival rate estimate with the main analysis. The company explained that the results indicated a plateau, and subsequent stem cell treatment does not have a positive impact on overall survival. The results are also academic in confidence and cannot be reported here. The ERG explained that the Kaplan–Meier curves of overall survival and progression-free survival from the ZUMA-5 36-month data cut were broadly aligned with the company’s extrapolation to 5 years. But the median progression-free survival was slightly underestimated in the model. The ERG noted there were also signs that the Kaplan–Meier curves were flattening from 3 years, but the data was affected by heavy censoring. The ERG also explained that 24 months is too early to determine if subsequent treatment has a positive impact on overall survival, and highlighted that longer-term



follow up is needed. The committee noted the sustained benefit shown from the 36-month data cut and the relatively short follow up of the trial. It concluded that while the data indicates that axicabtagene ciloleucel reduces the risk of disease progression in people with relapsed or refractory follicular lymphoma, its long-term treatment effect is uncertain.

### **ZUMA-5 is a single-arm study, so comparator data was taken from the SCHOLAR-5 study**

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 previously had treatment with idelalisib.

The cohorts were restricted to people with follicular lymphoma who had previous treatment after at least 3 prior treatments, 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 derived 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 treatments, the

company had used a propensity-score-weighted indirect comparison (see [section 3.8](#)). The committee concluded that using data from the SCHOLAR-5 study was acceptable to inform comparative effectiveness.

### **The company's approach to adjusting the SCHOLAR-5 data is highly complex**

3.8 Clinical inputs for the comparator arm, for treatment options after 3 or more treatments, 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 using standardised mortality ratio (SMR) weighting. The ERG commented that it was not transparent how the SMR weighting had been applied to the propensity scoring. But 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 patient data from both the ZUMA-5 and SCHOLAR-5 studies, so other methods may have been more appropriate (as documented in the [NICE Decision Support Unit \[DSU\] Technical Support Document 18](#)). The company also 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. But 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. At the first meeting, the committee concluded that the company's approach and use of the propensity-score-weighting method was highly uncertain. It would have liked to see other methods explored in more detail or the uncertainties of the unanchored indirect comparison addressed. In response to consultation, the company explained that its approach for the SCHOLAR-5 analyses was based on NICE DSU Technical Support Document 18 and more recent developments in the literature. The company said that the propensity-score-weighting methods should adjust for all treatment effect modifiers and prognostic variables which must also be balanced with the sample size. So, it had focused on the covariates strongly correlated with outcomes. The ERG highlighted that generating comparative effectiveness estimates from real-world data is challenging when sample sizes are limited and not all prognostic and effect modifying variables can be adjusted for. The ERG noted that in addition to the follicular lymphoma subtype, there were some other lower grade subtypes in SCHOLAR-5 than in ZUMA-5. It noted that failure to adjust for these may have biased in favour of current fourth line care. The committee understood that propensity-score-weighting should ideally adjust for all prognostic and effect modifiers but noted the concerns raised about small sample sizes. The committee was aware that the company had done sensitivity analyses using propensity-score matching and inverse-probability treatment weighting. It noted that the company had also explored alternative methods, including G-estimation and the E-value, which provided consistent results in line with the company's original base case. The committee concluded that the adjustment method used by the company is highly complex.

## **Economic model**

### **The company's model is appropriate for decision making**

3.9 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 it noted some uncertainties in the assumptions used in its model, for example, the long-term survivor assumption (see [section 3.11](#)). 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**

3.10 The committee was aware that the company used SCHOLAR-5 data to model survival 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 their progression. So, this cohort represented people who had previous treatment with idelalisib but who were not having idelalisib as fourth line treatment. The ERG considered

the generalised gamma, log-logistic and log-normal 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 and Wales 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 although extrapolation of progression-free survival and overall survival for standard care after 3 or more treatments is uncertain, it preferred the exponential distribution for progression-free survival and the gamma distribution for overall survival.

### **The committee considered both the company's and the ERG's approaches in its decision making**

3.11 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 treatments were estimated using time-to-event data from ZUMA-5 and SCHOLAR-5 respectively. The committee noted that both the company's and ERG's models assumed that a proportion of people who had axicabtagene ciloleucel could be considered long-term survivors from a future time point 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 year 5 onwards. The company base-case assumption was that 25% of people who had treatment with axicabtagene ciloleucel were long-term survivors, and these extrapolation assumptions were applied 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 time points for non-long-term survivors, but that this is overridden by cure assumptions in the long-term survivor group from 5 years. The company clarified that based on clinical opinion and clinical validation of survival curves, it assumed that 25% of people who had axicabtagene ciloleucel were 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 treatments. 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. At the first meeting, 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. In response to consultation, the company presented a graph of the modelled overall survival stratified by long-term survivors and non-long-term survivors to address the committee's concerns. The ERG noted that the hazard of death remained lower in non-long-term survivors compared with those having standard care after 3 or more treatments. It used a Weibull distribution to extrapolate the hazard of mortality for non-long-term survival. This was adjusted to remain 1.2 times higher than that of the general population matched for age and sex. The ERG further explored scenarios by increasing this adjustment to 1.5 times and 2 times higher than that of the general population matched for age and sex. It also presented a pessimistic scenario using the generalised

gamma distribution for extrapolation of axicabtagene ciloleucel overall survival, but without upward adjustment of the extrapolated mortality hazard for non-long-term survivors. The committee noted that this predicted a steeper overall-survival curve for non-long-term survivors, with the hazard of mortality exceeding that of the standard care arm. The committee took both the company's and the ERG's approaches into account in its decision making. It noted that the presented analyses did not resolve the issues with the company's long-term and non-long-term survivor assumptions.

### **The ERG's approach for health state utility values is more appropriate**

3.12 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. But the ERG was concerned that because most people 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 treatments. So, the ERG preferred to use utility values from Wild et al. (2006) in its base case, in which EQ-5D data was 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 their life. The ERG highlighted the limitations of the Wild et al. (2006) study but considered that it better reflected the likely quality of life of people after 3 treatments 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. (2006). 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 the uncertainty, the company also presented a scenario that assumed the health state utility value for long-term survivors after axicabtagene ciloleucel treatment to be halfway between the Wild et al. (2006) progression-free estimate and the general population. The ERG broadly agreed with the company's updated base case. But it considered it unlikely 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 survivors' utility values. The committee noted that the source of utility values had a small effect on the cost-effectiveness results. At the first meeting, the committee concluded that the ERG's approach of using a utility decrement for long-term survivors was more appropriate, and it would consider other scenarios presented in its decision making. In response to consultation, the company clarified that its assumptions were based on previous NICE technology appraisal guidance which were accepted by the committee. The clinical experts explained that they would expect a minor decrement in the utilities after chimeric antigen receptor (CAR) T-cell therapy because of the higher risk of infections and relapse. They explained that if people do not have any infections and do not relapse, they would expect health-related quality of life to be near to that of the general population. The committee recognised that there are some uncertainties with this approach. The committee concluded that the ERG's approach of using a utility decrement for long-term survivors was more appropriate. The committee also noted that the assumption of a rebound



to general-population utility for long-term survivors favoured axicabtagene ciloleucel.

### **Time on treatment and subsequent treatment costs for comparators used in the model are acceptable**

3.13 In its original model, for treatments 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 an exponential distribution in its model to estimate time on comparator treatments. For simplicity, the company assumed equal subsequent treatment 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 may continue 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 the costs of standard care in the comparator arm of the model. So, in its updated base case, the company capped time on treatment for the comparator treatments at the point of progression. The ERG explained that it was broadly satisfied with the company's updated base case. But time on comparator treatments for people with relapsed or refractory follicular lymphoma after 3 or more previous treatments remains uncertain because of limited data. The committee was aware that time on comparator treatments and subsequent treatment costs had a large impact on cost-effectiveness results. Despite the uncertainty in the estimation of time on comparator treatments, the committee concluded that it would accept the approach for decision making in the context of this appraisal.

## The infusion, monitoring and hospitalisation costs in the company's original model may not reflect NHS practice

3.14 The company explained that axicabtagene ciloleucel is given 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 hospitalisation observed after axicabtagene ciloleucel treatment in ZUMA-5. The mean duration of hospitalisation is academic in confidence and cannot be reported here. The NHS England Cancer Drugs Fund clinical lead (from now, Cancer Drugs Fund lead) explained that NHS England provides the infrastructure to CAR T-cell therapy 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 to 2023 tariff for CAR T-cell therapy delivery in people aged 19 years and over is £96,016, subject to ongoing review and period updates. The committee noted that the tariff cost was higher than the costs calculated by the company. The clinical experts also 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 but are well below the NHS tariff. The committee noted that it was not provided with full details about how the NHS tariff was derived. It noted the need for greater transparency as to what the tariff cost included, to explore potential issues of double counting or undercounting costs. At the first meeting, the committee concluded that the tariff was the best available source to inform the cost that the NHS is paying currently. In

response to consultation, the company explained that it had followed recommended NICE methods and its model included the best estimate of the cost of delivering CAR T-cell therapy. It highlighted that using the NHS tariff in decision making would be procedurally unfair and unreasonable, because of the lack of transparency in how it is derived. The ERG also agreed with the company that transparency would be beneficial to estimate the true costs. The company also presented evidence from a real-world point-in-time survey of clinicians and people with diffuse large B-cell lymphoma (DLBCL) in the UK, Germany, Spain, Italy, France and Canada in 2021 (Adelphi DLBCL Disease Specific Programme [DSP]). This survey considered the 100 days after CAR T-cell therapy which showed a similar average hospitalisation duration (measured in days) to those used in the company's model, resulting in identical CAR T-cell therapy infusion, monitoring and hospitalisation costs. The results of Adelphi DLBCL DSP are academic in confidence so cannot be reported here. During the second committee meeting, Cancer Drugs Fund lead explained that the NHS tariff may have overestimated the true cost to the NHS, but also considered that the company's approach is an underestimate of the true cost. The committee noted that NHS England and the company did urgent work to provide alternative costs to NICE after the second committee meeting.

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

3.15 Additional information and clarification on costs were provided by NHS England after the second committee meeting. Based on this new information, the company used a 'bottom-up' costing approach to calculate the cost of delivering axicabtagene ciloleucel treatment in the NHS. The company included the costs of:

- infusion, monitoring and hospitalisation
- leukapheresis

- conditioning chemotherapy
- bridging therapy.

The company considered each cost category individually and combined them to give an estimate for the cost of delivering axicabtagene ciloleucel in the NHS. The committee understood that NHS England had established a single tariff to capture these costs. The tariff was developed after NICE recommended the first CAR T-cell therapy, tisagenlecleucel, for use in the Cancer Drugs Fund in December 2018. NHS England explained that the tariff includes all costs of care from the decision for the person to have CAR T-cell therapy to 100 days after infusion. NHS England explained that there is not currently a healthcare resource group (HRG) code that adequately captures the administration of CAR T-cell therapies. It also commented that a key difference between its tariff and the company's costs is the time and number of staff needed to look after people who have had CAR T-cell therapy. The company commented that it is not appropriate to use the tariff in the modelling. This is because it is a mechanism for NHS England to fund hospitals to provide CAR T-cell therapy and is not designed for health technology evaluation. It was concerned that the evidence underlying the tariff has not been transparently shared and that it may include costs that are not relevant. The ERG was also concerned about the methods used by NHS England to derive the tariff. It was unclear how individual trusts estimated expenditure and how this corresponded to quantities of resource use. But the ERG also commented that the company's approach likely underestimated the true cost of delivering CAR T-cell therapy. After the second appraisal committee meeting the company submitted a further analysis using a CAR T-cell therapy delivery cost of £41,101, informed by an ERG scenario analysis. This accounted for the impact of increased staffing needs associated with providing CAR T-cell therapy. The updated company analysis consisted of a one-off cost of £41,101 for the first

100 days as well as the costs of conditioning chemotherapy drugs, stem cell transplantation and intravenous immunoglobulin. These 3 costs are reimbursed separately by NHS England. NHS England considered that, although the company's cost differs from the tariff for CAR T-cell therapy, it was an acceptable cost to use in the cost-effectiveness analysis. This is because the current tariff represents the high hospital costs of establishing the infrastructure of a CAR T-cell therapy service and delivering a relatively new type of treatment, but economies of scale may be expected over time. Costs may also reduce with clinical developments in care that reduce toxicity and so reduce the need for more intense monitoring and treatment. The committee noted NHS England's comments and was satisfied that the company's costs adequately captured a reasonable projection of the cost to the NHS of delivering CAR T-cell therapy.

## **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 2013](#). 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 the ERG agreed that axicabtagene ciloleucel did not meet the criteria for end of life. The company explained that axicabtagene ciloleucel would be used by

clinicians as an end of life treatment for people with relapsed or refractory follicular lymphoma who had 3 or more systemic treatments. The clinical experts highlighted that they would expect people having standard care to live between approximately 30 and 36 months. In response to consultation, a consultee highlighted that they would expect people having standard care to live for 24 months or less. This is because of a lack of data for people with relapsed or refractory follicular lymphoma after 3 or more treatments. The committee noted that the median life expectancies from the treatment comparisons from both the company's and the ERG's models were higher than 24 months. The median life expectancies are academic in confidence and cannot be reported here. The committee was aware that both the company's and the ERG's base cases supported a mean survival gain of greater than 3 months. But 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 the end of life.

## **Cost-effectiveness estimates**

### **An acceptable ICER would be within the range normally considered a cost-effective use of NHS resources**

3.17 [NICE's guide to the methods of technology appraisal 2013](#) 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 committee noted that data is immature for overall survival, and extrapolations from the model are uncertain. So, the committee agreed that an acceptable

ICER would be within the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

### **Axicabtagene ciloleucel is not recommended for routine use**

3.18 Both the company's deterministic and probabilistic base cases showed that ICERs for axicabtagene ciloleucel compared with standard care were over £40,000 per QALY gained. The committee noted the high level of uncertainty in the model, particularly about:

- immature overall-survival data from ZUMA-5 (see [section 3.6](#))
- no direct comparative efficacy data for axicabtagene ciloleucel compared with standard care (see [sections 3.7 and 3.8](#))
- long-term survivor proportion assumptions (see [section 3.11](#))
- limited available evidence to inform time on treatment for comparator treatments in the company's model for people having treatment after 3 treatments (see [section 3.13](#)).

The committee preferred the following assumptions:

- using a Weibull distribution for overall survival and generalised gamma distribution for progression-free survival in the axicabtagene ciloleucel arm (see [section 3.11](#))
- using a gamma distribution for overall survival and exponential distribution for progression-free survival in the standard care arm
- including a utility decrement for long-term survivors after axicabtagene ciloleucel treatment (see [section 3.12](#))
- a CAR T-cell therapy administration cost of £41,101 (see [section 3.15](#)).

Because of confidential commercial arrangements for axicabtagene ciloleucel and comparator treatments, the exact ICERs cannot be reported here. Taking into account all confidential discounts, the committee noted that the company's cost-effectiveness estimates for

axicabtagene ciloleucel compared with standard care were above the range NICE normally considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The committee recognised the need for new effective treatments for relapsed or refractory follicular lymphoma. The committee took into account the innovative nature of axicabtagene ciloleucel and the additional benefits not captured in the model (see [section 3.20](#)). But axicabtagene ciloleucel was not shown to be a cost-effective use of NHS resources in any of the analyses presented and the evidence was highly uncertain. So, 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 for treating relapsed or refractory follicular lymphoma after 3 or more systemic treatments 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 studies are likely to provide further evidence



on survival but may not fully resolve some of the key uncertainties affecting the cost-effectiveness results, such as:

- immature overall-survival data from ZUMA-5
- no direct comparative efficacy data for axicabtagene ciloleucel compared with standard care.

The committee also noted that the evidence suggests that axicabtagene ciloleucel is not likely to be a cost effective use of NHS resources (see [section 3.18](#)). The committee concluded that axicabtagene ciloleucel did not meet the criteria to be recommended for use in the Cancer Drugs Fund.

## Innovation

### **Axicabtagene ciloleucel is an innovative treatment and the benefits may not be fully captured in the model**

3.20 The company considered axicabtagene ciloleucel to be innovative because of its mechanism of action in which a person's 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 both the benefits offered and the innovative nature of axicabtagene ciloleucel. It concluded that there could be some additional carer benefits not fully captured in the model but noted that additional evidence had not been provided in the submission.

## Equalities

3.21 There were no equality issues identified.

Stephen O'Brien  
Chair, appraisal committee  
April 2023

## **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

ISBN: **[to be added at publication]**

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