

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies**

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 for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies 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?

**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 for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies 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: 18 September 2018

Second appraisal committee meeting: 27 September 2018

Details of membership of the appraisal committee are given in section 5.

## 1 Recommendations

- 1.1 Axicabtagene ciloleucel is not recommended, within its anticipated marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies.
- 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 standard treatment for relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Best supportive care is used and usually includes salvage chemotherapy.

Evidence from a small, single-arm study suggests that people having axicabtagene ciloleucel have good response rates, overall survival and progression-free survival. But, there are no direct data comparing axicabtagene ciloleucel with salvage chemotherapy (referred to as best supportive care by the company). This means that the exact size of the benefit of axicabtagene ciloleucel compared with salvage chemotherapy is unknown.

Axicabtagene ciloleucel meets NICE's criteria to be considered a life-extending treatment at the end of life. However, all the cost-effectiveness estimates are above the range normally considered to be a cost-effective use of NHS resources. Axicabtagene ciloleucel does not meet the criteria

for inclusion in the Cancer Drugs Fund. Because of this, axicabtagene ciloleucel is not recommended.

## 2 Information about axicabtagene ciloleucel

<b>Anticipated marketing authorisation</b>	On 29 June 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for axicabtagene ciloleucel. It is intended for 'the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more lines of systemic therapy.'
<b>Dosage in the marketing authorisation</b>	Based on the company's submission, axicabtagene ciloleucel will be available as a single infusion product for autologous and intravenous use only.  Each single infusion bag of axicabtagene ciloleucel contains a suspension of anti-CD19 CAR T cells in about 68 mL, for a target dose of $2 \times 10^6$ anti-CD19 CAR T cells per kg body weight (range: $1 \times 10^6$ to $2.4 \times 10^6$ cells per kg), with at most $2 \times 10^8$ anti-CD19 CAR T cells.
<b>Price</b>	The price was submitted as commercial in confidence. The company has a proposed commercial arrangement which would apply if the technology had been recommended.

## 3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Kite Pharma and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

### ***Potential new treatment option***

#### **There is an unmet need for more effective treatment options**

- 3.1 Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma are aggressive subtypes of non-Hodgkin lymphoma. Outcomes for people with refractory or relapsed disease are poor. The disease has low levels of response to treatment, and limited survival. A patient expert explained that there are limited curative options; people with the disease

often have multiple courses of chemotherapy, which may cause sickness, diarrhoea and mouth ulcers. The cycle of remission and relapse when having successive treatments has a substantial psychological and physical effect on people with the disease. The committee concluded that there is an unmet need in this population, and both patients and healthcare professionals would welcome potential new treatments that improve the chance of survival.

### ***Treatment pathway and comparators***

#### **The company propose axicabtagene ciloleucel may have 4 possible positions in the treatment pathway**

3.2 The company proposed 4 potential positions for axicabtagene ciloleucel in the treatment pathway. It proposed that it could be used specifically for people:

- whose disease was refractory after 1 systemic therapy, or
- whose disease has relapsed after 1 systemic therapy, but who cannot have an autologous stem cell transplant, or
- whose disease has relapsed after 1 systemic therapy, and who have had chemotherapy and an autologous stem cell transplant but whose disease has then relapsed again, or
- whose disease has relapsed after 1 systemic therapy, and who would be able to have an autologous stem cell transplant as part of a second treatment, but whose disease does not respond to salvage chemotherapy.

The committee acknowledged the companies 4 proposed positions for axicabtagene ciloleucel in the treatment pathway and agreed to consider these further.

**Axicabtagene ciloleucel cannot be considered for people whose disease has relapsed after 1 systemic therapy**

3.3 A clinical expert explained that the clinical evidence for axicabtagene ciloleucel (ZUMA-1 study) included patients whose disease did not respond after 1 systemic therapy (primary refractory): these people are likely to have a poor prognosis with existing treatments, and so may particularly benefit from axicabtagene ciloleucel. The committee was aware that the Committee for Medicinal Products for Human Use (CHMP) positive opinion for axicabtagene ciloleucel specifies its use after 2 or more systemic therapies (see section 2), so agreed it could not consider axicabtagene ciloleucel at this position in the pathway in its decision-making.

**Axicabtagene ciloleucel cannot be considered as an alternative to autologous stem cell transplant for people who have had 1 systemic therapy followed by chemotherapy**

3.4 The committee was aware that if their disease has relapsed after 1 systemic therapy, people will usually have salvage chemotherapy with the aim of bridging to autologous stem cell transplant. NHS England's clinical lead for the Cancer Drugs Fund explained that if an autologous stem cell transplant was planned as part of the treatment after relapse with the first systemic therapy, and the disease responds well enough to chemotherapy (second systemic therapy), then patients should proceed to autologous stem cell transplant and not to axicabtagene ciloleucel. Axicabtagene ciloleucel would only be offered if their disease relapsed within 12 months of the autologous stem cell transplant. The committee understood that for patients for whom autologous stem cell transplant is inappropriate, the only current treatment options are either platinum- and gemcitabine-based regimens, or to be entered into a clinical trial. The committee noted that people having axicabtagene ciloleucel would need to have good performance status to tolerate the toxicity of the treatment

(see section 3.8). It also noted that there is considerable overlap between the fitness criteria for autologous stem cell transplant and axicabtagene ciloleucel and it is unlikely that these people would be well enough to fulfil the eligibility criteria for axicabtagene ciloleucel. The committee agreed that it could not consider axicabtagene ciloleucel for people whose disease has not responded after 1 systemic therapy but who were unable to have autologous stem cell transplants as this is not in line with its anticipated marketing authorisation (that is, after 2 or more systemic therapies). Axicabtagene ciloleucel would also not be used as an alternative to autologous stem cell transplant as this would be part of their second systemic treatment.

### **Axicabtagene ciloleucel will not be used as a bridge to allogeneic stem cell transplant**

3.5 A patient expert noted that a patient has had axicabtagene ciloleucel as a bridge to allogeneic stem cell transplant. The clinical experts explained that in clinical practice, only a small number of patients would have allogeneic stem cell transplants after 2 or more systemic therapies. This was reflected in the very small proportion of people in the ZUMA-1 study who had axicabtagene ciloleucel followed by an allogeneic transplant. The clinical experts noted that most people in the study only needed treatment with axicabtagene ciloleucel, and therefore it should not be considered a bridging therapy. The committee agreed that axicabtagene ciloleucel would not be used as a bridge to allogeneic stem cell transplant in clinical practice.

### **Axicabtagene ciloleucel could be used in 3 possible positions in the treatment pathway**

3.6 The committee concluded that axicabtagene ciloleucel would be positioned as a treatment option for people:

- whose disease did not respond after 2 systemic therapies, or

- whose disease relapsed after 1 systemic therapy, and who would be able to have an autologous stem cell transplant as a part of a second treatment, but whose disease does not respond to salvage chemotherapy, or
- whose disease has relapsed after the first systemic therapy, and who have had chemotherapy and autologous stem cell transplant but whose disease has then relapsed again.

### **Salvage chemotherapy is the most appropriate comparator**

3.7 The committee considered the currently available treatment options for the 3 positions in the treatment pathway where axicabtagene ciloleucel would most likely be used. The committee noted that in all 3 positions, the currently available treatment option is salvage chemotherapy. The committee was aware that although there is no standard salvage chemotherapy regimen for relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma, there are several regimens which clinicians consider to be equally effective. The committee also noted that the company had excluded pixantrone as a comparator. This was despite NICE recommending pixantrone after 2 or more systemic therapies (see NICE's technology appraisal guidance on [pixantrone monotherapy](#)). The clinical experts explained that pixantrone is rarely used in clinical practice and should not be considered a comparator. The committee agreed that axicabtagene ciloleucel would be used as an alternative to salvage chemotherapy (excluding pixantrone), and concluded that salvage chemotherapy was the most appropriate comparator.



## ***Clinical evidence***

### **Axicabtagene ciloleucel is clinically effective, but the lack of comparator data means the size of the benefit compared with salvage chemotherapy is unknown**

3.8 The clinical-effectiveness evidence for axicabtagene ciloleucel came from ZUMA-1, an ongoing, phase I/II, multicentre, open-label, single-arm study. The company presented results from the study using a modified intention-to-treat analysis (only patients enrolled in the study who had axicabtagene ciloleucel infusion were included). The primary outcome measure was overall response rate, defined as complete response or partial response (based on International Working Group response criteria for malignant lymphoma). Results showed an overall response rate of 82% for patients having axicabtagene ciloleucel. At the last data cut-off, 42% of patients had disease that was still responding, including 40% with complete response. Median overall survival (a secondary end point) was not reached, with overall survival rates of 78% at 6 months (95% confidence interval [CI] 69 to 85), 59% at 12 months (95% CI, 49 to 68) and 52% at 18 months (95% CI, 41 to 62). The median duration of progression-free survival was 5.8 months (95% CI, 3.3, not reached), with progression-free survival rates of 49% (95% CI, 39 to 58) at 6 months, 44% (95% CI, 34 to 53) at 12 months, and 41% (95% CI, 31 to 50) at 15 months. The committee noted the plateau in the Kaplan–Meier curves for overall and progression-free survival, but the ERG explained that from month 12 onwards, the Kaplan–Meier plots were heavily influenced by censoring of data, with very few patients remaining at risk of mortality or disease progression. The clinical experts stated that these results were clinically meaningful, because with current treatments the condition quickly gets worse. The committee noted that there is no evidence on the effectiveness of axicabtagene ciloleucel directly compared with that of salvage chemotherapy. The committee concluded that axicabtagene ciloleucel was clinically effective, but it agreed that the lack of comparative

data made the assessment of comparative effectiveness (and any cost-effectiveness analyses) more challenging.

**The results of ZUMA-1 are generalisable to the population for which axicabtagene ciloleucel would be an option in England**

3.9 The committee was concerned about how generalisable the results of the ZUMA-1 study were to clinical practice in the NHS, given that it was not done in the UK. The study population included patients with diffuse large B-cell lymphoma (n=77), primary mediastinal B-cell lymphoma (n=6) and transformed follicular lymphoma (n=16). The committee acknowledged that the CHMP's positive opinion for axicabtagene ciloleucel does not include transformed follicular lymphoma. However, the committee understood that since ZUMA-1 began, the World Health Organization's definition of diffuse large B-cell lymphoma has evolved to include the transformed follicular lymphoma population. Although the CHMP positive opinion does not specify this population, it is included in its opinion. The clinical experts were concerned that enrolment in phase I/II clinical trials could be prone to bias, as trials generally include highly selected populations. They also noted that in the ZUMA-1 study, some patients whose disease progressed had retreatment with axicabtagene ciloleucel (that is, they had it a second time). This does not represent how axicabtagene ciloleucel would be used in clinical practice in England. The committee also understood that the trial recruited people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, corresponding to a population whose activities are relatively unrestricted by their disease. The clinical experts stated that people with relapsed or refractory disease having axicabtagene ciloleucel would need to have good performance status to tolerate the toxicity of the treatment. Both the clinical experts and NHS England's clinical lead for the Cancer Drugs Fund noted that patients in ZUMA-1 were representative of the various subgroups who would be eligible for axicabtagene ciloleucel in the NHS.

The committee concluded that the results from ZUMA-1 were generalisable to patients in the NHS.

**ZUMA-1 is a single-arm study so comparator data needs to be taken from an alternative source**

3.10 Because ZUMA-1 was a single-arm study with no direct comparator data, the company provided results from SCHOLAR-1 for the comparator (salvage chemotherapy). SCHOLAR-1 is a retrospective study with pooled data from 4 datasets. These datasets included adults with diffuse large B-cell lymphoma (n=552), primary mediastinal B-cell lymphoma (n= 14), transformed follicular lymphoma (n=27) and 'other' (n=43). Treatment options included salvage chemotherapy, rituximab maintenance therapy and observation after autologous stem cell transplant. The committee noted the ERG's concerns that comparative-effectiveness results from single-arm studies are prone to bias. However, considering the population and potential difficulties with randomisation, the committee concluded that using 2 single-arm studies was suitable and that it would consider the results of these studies in its decision-making.

**There is considerable heterogeneity between the study populations of ZUMA-1 and SCHOLAR-1**

3.11 The committee discussed the differences in the study populations of ZUMA-1 and SCHOLAR-1, and in the 4 datasets included in SCHOLAR-1 itself. The committee noted that the population in SCHOLAR-1 included patients with primary refractory disease and patients with ECOG scores of 0 to 4, but patients in ZUMA-1 had more previous treatments and were more likely to have advanced disease than those in SCHOLAR-1. The committee also noted the relatively high proportion of patients in SCHOLAR-1 who went on to have stem cell transplants. Clinical experts explained that in clinical practice, this number is likely to be very small. The committee acknowledged that patients who can have autologous stem cell transplants in clinical practice would not be able to have

axicabtagene ciloleucel (see section 3.4), and are likely to have better outcomes than those having only salvage chemotherapy. The committee concluded that people who had salvage chemotherapy in SCHOLAR-1 were likely to have a lower burden of disease than the people for whom axicabtagene ciloleucel would be an option in clinical practice in England, and that the treatment benefit for these people was therefore uncertain.

**The adjustments to the SCHOLAR-1 dataset do not adequately account for the differences between the study populations of ZUMA-1 and SCHOLAR-1**

3.12 To address the baseline imbalances between the 2 studies and reduce bias in the comparative-effectiveness results, the company presented 2 standardised analyses from SCHOLAR-1. The results from these analyses are considered academic in confidence and cannot be reported here. In its first standardised analysis (base case), the company excluded patients with an ECOG performance status of more than 1 to align with the ZUMA-1 eligibility criteria. The committee noted the ERG's concerns that missing data were a problem for all covariates, and patients with unknown ECOG status were included in the company's standardised analyses. The clinical experts expressed concern at the quality of the data from SCHOLAR-1, stating that all patients with relapsed or refractory disease should have an available ECOG performance status. In response to a request for clarification, the company provided additional standardised analyses excluding patients with an unknown ECOG status. The company noted that the improved survival for patients who had salvage chemotherapy may be because 41% of patients in this group went on to have stem cell transplants. The committee discussed the company's second standardised analysis, which excluded patients with ECOG performance statuses of 2 to 4, and patients who had a stem cell transplant after salvage chemotherapy. These analyses showed that axicabtagene ciloleucel was more effective than salvage chemotherapy for relapsed or refractory disease, but the committee agreed that none of the adjustments adequately accounts for all imbalances between the

study populations. Based on the data provided, the committee concluded that the exact size of the benefit of axicabtagene ciloleucel compared with salvage chemotherapy was unknown.

### **Alternative data sources for salvage chemotherapy would reduce uncertainty**

3.13 The committee was aware that there are no randomised trials planned for axicabtagene ciloleucel and it acknowledged the rationale behind the company's use of SCHOLAR-1 data for the comparator. However, it agreed with the clinical experts that SCHOLAR-1 was not representative of the population for which axicabtagene ciloleucel would be an option in the NHS. Having noted the company's statement that no alternative data were available, the committee discussed alternative data sources for the comparator treatment arm. The clinical experts suggested that a subpopulation of the ORCHARRD study could be used to corroborate the SCHOLAR-1 data. Alternatively, NHS or UK standard-of-care data from the Haematological Malignancy Research Network should be explored to produce plausible estimates of survival for people having salvage chemotherapy. The committee concluded that alternative comparator data were needed to better assess the clinical effectiveness of axicabtagene ciloleucel, and that the company should provide analyses that explore alternative data sources (for example, ORCHARRD subgroups and the Haematological Malignancy Research Network).

## **Adverse events**

### **Axicabtagene ciloleucel is associated with frequent adverse events**

3.14 Results from ZUMA-1 showed that all patients having axicabtagene ciloleucel had an adverse event after treatment. Events over grade 3 happened in 95% of patients. Cytokine release syndrome (CRS) is a common toxicity of cellular immunotherapy. In the ZUMA-1 study, it affected 93% of patients. The clinical experts explained that CRS is often mild and can be managed through treatment with tocilizumab, close

observation and supportive care. However, severe cases (affecting 13% of patients in ZUMA-1) need intensive care treatment and may lead to haemodynamic instability and other organ toxicity. The clinical experts also noted that the use of tocilizumab had been limited in the trial because of concerns around how it may affect the efficacy of axicabtagene ciloleucel. Tocilizumab recently received a positive opinion from the CHMP for treating CRS. The clinical experts noted that tocilizumab is likely to be used at an earlier stage of CRS (grade 2 rather than at grade 3) which may reduce the severity of the events. The committee also noted that 28% of patients in ZUMA-1 had severe neurotoxicity events. These may also need intensive care treatment and monitoring. The clinical experts explained that the rate and frequency of adverse events will likely reduce as healthcare professionals gain more experience in recognising and treating the associated toxicities. A patient expert explained that although patients may find the potential side effects worrying, they would feel prepared to deal with them because of the advice they had before starting treatment. They also commented that the inconvenience of needing to stay close to hospital for adverse-event monitoring was less important than the possibility of a positive treatment outcome. The commissioning expert from NHS England explained that healthcare professionals would need extensive training in managing and supporting patients who have axicabtagene ciloleucel and that NHS England are developing a new service specification to support this. The committee concluded that axicabtagene ciloleucel is associated with frequent adverse events and the costs associated with managing and treating those events should be reflected in the cost-effectiveness modelling (see section 3.21).

### **The need for intravenous immunoglobulins treatment after axicabtagene ciloleucel is unknown**

- 3.15 Results from ZUMA-1 showed that only a small number of patients needed intravenous immunoglobulins (IVIG) treatment for B-cell aplasia.

NHS England's clinical lead for the Cancer Drugs Fund explained that B-cell ablation is a likely consequence of successful treatment with axicabtagene ciloleucel. The loss of circulating B-cells causes a reduction in serum immunoglobulin levels. The committee was concerned that the company had underestimated the effect of this with axicabtagene ciloleucel. The clinical experts explained that the rate of infection in the study had been relatively low, suggesting that not all patients would need IVIG. However, the effects on mortality later in life because of immunological deficiencies were unknown. The committee concluded that the need for IVIG treatment remained unknown so the effect of B-cell aplasia on mortality risk was uncertain.

### ***Cost effectiveness***

#### **All cost-effectiveness analyses are based on comparisons with data from SCHOLAR-1 so results are uncertain**

3.16 The company presented cost-effectiveness analyses comparing axicabtagene ciloleucel with best supportive care, which it defined as salvage chemotherapy with or without rituximab. For best supportive care, the company modelled a blended comparator assuming equal efficacy and distribution across 4 regimens: DHAP, GDP, IVE and ICE. The company used a partitioned survival approach in which progression-free and overall survival estimates were modelled independently, with the proportion of progressed patients at each cycle calculated as the difference between the values for the overall survival and progression-free survival curves. The company modelled the cost effectiveness of axicabtagene ciloleucel using data from ZUMA-1, and the cost effectiveness of best supportive care using data from SCHOLAR-1. The committee concluded that the model was appropriate for decision-making, but it recalled its conclusion about the use of SCHOLAR-1 as the comparator data source (see sections 3.11 and 3.12). The committee accepted that without any reliable evidence on the effectiveness of the

comparator treatments, there was a high degree of uncertainty around all of the cost-effectiveness estimates presented by the company and the ERG.

**Neither the company's nor the ERG's approaches to extrapolating long-term survival for people having axicabtagene ciloleucel are appropriate**

3.17 Progression-free survival and overall survival were the main effectiveness inputs included in the company's economic model. Because median overall survival was not reached in ZUMA-1 (see section 3.8), long-term overall survival had to be extrapolated over the model time horizon. The company's model had a 44-year time horizon. This was assumed to be a lifetime horizon because at the start of the modelled analysis, patients had a mean age of 56 years, as in ZUMA-1. The committee noted that using single parametric survival curves to model overall survival for axicabtagene ciloleucel produced clinically implausible results. Many of the exploratory axicabtagene ciloleucel curves crossed the curve for best supportive care which was not reflective of ZUMA-1. The committee considered the company's preferred extrapolation of overall survival for axicabtagene ciloleucel. It noted the use of a mixture cure model with the Weibull distribution to estimate a cure fraction (that is, the proportion of patients cured). The committee was aware that the company's base-case extrapolation assumed long-term remission for 50% of patients having axicabtagene ciloleucel. The cured patients were immediately restored to the age- and gender-matched mortality of the general UK population after infusion. Uncured patients followed the parametric survival curve from the time of infusion. The committee noted that the cure fraction for overall survival was a major driver of the cost-effectiveness estimates, and that it varied between 1% and 53% in the company's exploratory analyses. The committee was aware of the company's preference to use a mixture cure model for overall survival extrapolation and a parametric curve to model progression-free survival for axicabtagene ciloleucel. It noted the company's scenario analyses using mixture cure models to extrapolate



progression-free survival for axicabtagene ciloleucel produced estimates of the cure fraction ranging from 40% to 43%. The committee considered the ERG's alternative hybrid scenario, which selected the best fitting single parametric overall survival curve for axicabtagene ciloleucel (loglogistic) and constrained it, so that patients having axicabtagene ciloleucel in the model were restored to the age and gender-matched mortality of the general UK population only after the crossing of the overall and progression-free survival curves at around 52 months. The committee discussed the ERG's approach of making the overall survival gain equal to the progression-free survival gain. Clinical experts explained that patients having axicabtagene ciloleucel would need to have high fitness criteria (see section 3.9) and that they may have salvage chemotherapy if their disease relapses after having axicabtagene ciloleucel. This means that it is clinically plausible that a small proportion of patients could have long-term survival after disease relapse with axicabtagene ciloleucel. The committee agreed that the company's extrapolation was likely to overestimate the size of the cure fraction. The committee also agreed that the ERG's approach of adjusting the overall survival curve was not appropriate, because its analysis did not consider the possibility of patients having subsequent salvage chemotherapy after disease relapse with axicabtagene ciloleucel. It considered that the use of the progression-free survival cure fraction could be a conservative extrapolation of overall survival in the axicabtagene ciloleucel treatment arm. It noted that future data-cuts are planned for ZUMA-1 which may provide more certainty in the survival extrapolation modelling, but that these would not be available during the appraisal. The committee concluded that the overall survival gain for axicabtagene ciloleucel was between the company's and ERG's estimates.

### **Including retreatment with axicabtagene ciloleucel adds uncertainty to the survival estimates**

3.18 The committee recalled that ZUMA-1 included patients who had retreatment with axicabtagene ciloleucel, but that this did not reflect its use in clinical practice (see section 3.9). The committee considered how this may affect the overall survival results. It was aware that the difference in the range of cure fractions presented as part of the company's exploration of mixture cure models for progression-free and overall survival was likely a result of the immature data, and, or being cured after progression. The committee concluded that the effect of retreatment with axicabtagene ciloleucel in the clinical evidence adds to the uncertainty around the long-term survival for people treated with axicabtagene ciloleucel.

### **People having axicabtagene ciloleucel are likely to experience higher mortality risks than the general population**

3.19 The company's model assumed that people who were alive after 2 years in the pre-progression state (both treatment arms) were functionally cured and that they reverted to age-matched general population mortality. The company explained that for people having axicabtagene ciloleucel, the cured population were immediately restored to the age- and gender-matched mortality of the general UK population (see section 3.17) but for those not considered cured, more than 99% had died by 2 years. The clinical experts noted that it was unlikely that people having axicabtagene ciloleucel after 2 or more systemic therapies would return to general population health and mortality estimates. The committee recalled its conclusion that the effect of B-cell aplasia on mortality risks for long-term survival was unknown (see section 3.14). It concluded that the company's assumption of no excess mortality risk for functionally cured patients compared with the general population was not appropriate and that a higher mortality risk than the general population was more appropriate.

**Progression-free and overall survival benefits for best supportive care are unknown**

3.20 The committee recalled that when modelling survival for the comparator, the company used data from SCHOLAR-1 but excluded patients with an ECOG performance status of more than 1. It was aware that the ERG preferred to include only patients with a known ECOG performance status of 0 or 1 in its exploratory analyses. The committee was also aware that the ERG's exploratory analyses included 41% of patients who had a stem cell transplant, which was not reflective of the population for which axicabtagene ciloleucel would be an option in the NHS. Having acknowledged that neither the company's nor the ERG's approach was appropriate (see section 3.17), the committee agreed that without an alternative data source for best supportive care (see sections 3.11 and 3.12), the estimates of overall survival for the comparator were associated with a high degree of uncertainty. The committee noted that progression-free survival was not recorded in SCHOLAR-1 and that the company's approach to modelling progression-free survival by assuming that the ratio between overall survival and progression-free survival of axicabtagene ciloleucel can be directly applied to the best supportive care data did not account for the different mechanisms of actions of the 2 treatments. The committee concluded that the progression-free and overall survival benefits for best supportive care were uncertain and it would need to consider this in its decision-making.

***Costs in the model***

**The costs of allogeneic stem cell transplants should be included in the cost-effectiveness modelling**

3.21 The company had included costs associated with axicabtagene ciloleucel, including stem cell transplants, time in intensive care because of CRS and training for healthcare professionals in the cost-effectiveness modelling. The committee noted that the company updated their base case after

clarification to include costs of tocilizumab and IVIG treatment for adverse events. The ERG considered that the cost of training and length of stay in intensive care were underestimated in the model. In its preferred analysis, the ERG increased the number of intensive care days and increased the number of healthcare professionals having training. The ERG also used a different method to calculate the administration costs for salvage chemotherapy and stem cell transplants. The committee noted that the company provided scenario analyses in response to technical engagement. It explored the costs of additional storage, ambulatory care and duration of IVIG treatment for people experiencing B-cell aplasia. The committee acknowledged that these changes had little effect on the overall cost-effectiveness results. It agreed that the ERG's approach to calculating costs was reasonable. However, the clinical experts noted the cost of autologous stem cell transplant used in the ERG's base case were not reflective of clinical practice. They explained that autologous stem cell transplants are considered a second-line therapy, so patients with relapsed or refractory disease after 2 previous systemic therapies would have more expensive allogeneic stem cell transplants at this point in the treatment pathway. The committee concluded that the company's approach to modelling costs of allogeneic rather than autologous stem cell transplants was preferred as this better reflected clinical practice at this point in the treatment pathway.

### **Including health benefits from patients who did not have axicabtagene ciloleucel has a small effect on the cost-effectiveness estimates**

3.22 The committee understood that the company's base-case analysis included costs of conditioning chemotherapies and leukopheresis for patients enrolled in the ZUMA-1 study but who were then unable to have axicabtagene ciloleucel. It noted the ERG's concern that people having axicabtagene ciloleucel could experience a delay in starting treatment compared with those who had salvage chemotherapy which was not accounted for in the cost-effectiveness modelling. The company provided

an additional scenario analysis including quality-adjusted life years (QALYs) for patients enrolled in ZUMA-1 but who had not had axicabtagene ciloleucel. The committee accepted that the company's amendment had only a small effect on the cost-effectiveness estimates.

### ***Cost-effectiveness results***

#### **The range of the cost-effectiveness estimates is wide and all are above £50,000 per QALY gained**

3.23 The company's deterministic base case showed that the incremental cost-effectiveness ratio (ICER) for axicabtagene ciloleucel compared with salvage chemotherapy was over £50,000 per QALY gained. The exact ICER is commercial in confidence and cannot be reported here. The ERG made some changes to the company's model to reflect its preferred base-case analysis, specifically:

- excluding patients with unknown ECOG performance statuses from the SCHOLAR-1 cohort (see section 3.20)
- using a hybrid approach to extrapolate overall survival with axicabtagene ciloleucel (see section 3.17)
- using alternative structural cure assumptions
- assuming that CRS is managed for 4 days in intensive care
- applying discounted long-term costs for stem cell transplants
- using a different cost of stem cell transplant (see section 3.21).

These changes resulted in an ERG exploratory base-case ICER that was over £100,000 per QALY gained. The committee noted the wide range between the company's and ERG's base-case ICERs. It agreed that there was a high degree of uncertainty associated with both the company's and ERG's estimates because of the limitations in the data for the comparator and the immature survival data for axicabtagene ciloleucel. The committee concluded that based on the data and analyses presented to it,

the cost-effectiveness estimates were all above £50,000 per QALY gained.

## ***Innovation***

### **Axicabtagene ciloleucel is innovative but there are no benefits not captured in the analysis**

3.24 The committee considered axicabtagene ciloleucel to be innovative because it represents a step-change in the treatment of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma. It noted that axicabtagene ciloleucel had been awarded Priority Medicines (PRIME) designation by the European Medicines Agency. However, the company did not present any evidence to suggest that there are additional benefits that were not captured in the QALY calculations.

## ***Discount rate***

### **A discount rate of 3.5% should be applied for costs and benefits**

3.25 The committee discussed the use of the alternative discount rate. A discount rate of 1.5% for costs and benefits may be considered by the committee where treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), and if the committee are satisfied that the introduction of the technology does not commit the NHS to substantial irrecoverable costs. The committee noted that axicabtagene ciloleucel appeared clinically effective (see section 3.8), but was aware that the evidence was immature so the duration of health benefits could not robustly show cure. The committee concluded that the reference case should use a discount rate of 3.5% for both costs and benefits.

## ***End of life***

### **Axicabtagene ciloleucel meets both criteria to be considered a life-extending treatment at the end of life**

3.26 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). The company proposed that axicabtagene ciloleucel met the criteria for life-extending treatments for people with a short life expectancy (normally less than 24 months). The committee were aware the median overall survival in SCHOLAR-1 was 6.6 months, but noted that the company's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. The committee also considered clinical expert opinion which suggested that SCHOLAR-1 was not representative of the population for which axicabtagene ciloleucel would be an option, and may have optimistic results. The committee acknowledged that axicabtagene ciloleucel did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply. The committee noted that the median overall survival for axicabtagene ciloleucel in ZUMA-1 was not reached (15.4 months median follow-up), but that both the company's and ERG's modelling suggested that axicabtagene ciloleucel was associated with a gain in overall survival of over 3 months irrespective of the choice of best supportive care data. The committee concluded that axicabtagene ciloleucel met NICE's criteria to be considered a life-extending treatment at the end of life.

## ***Equality considerations***

### **There are no equality issues relevant to the recommendations**

3.27 The company highlighted that axicabtagene ciloleucel would more likely be used for men and for older people because of the epidemiology of the disease. The clinical experts noted that there may be issues related to

accessing axicabtagene ciloleucel, because it is only available at specialist centres. Because the recommendation for axicabtagene ciloleucel is for the whole population in the anticipated marketing authorisation, the committee agreed that its recommendations do not have a different effect on people protected by the equality legislation than on the wider population. The commissioning expert from NHS England confirmed that national multidisciplinary teams would be set up to ensure equality of referral and treatment access. The committee concluded that there are no relevant equality issues.

## **Conclusion**

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

3.28 Data from the ZUMA-1 study showed that people having axicabtagene ciloleucel have good response rates, overall survival and progression-free survival. The committee acknowledged that the published evidence for comparator treatments was limited, but considered that SCHOLAR-1 did not represent UK practice. It noted that there are no direct data comparing axicabtagene ciloleucel with salvage chemotherapy. This means that the exact size of the benefit of axicabtagene ciloleucel compared with salvage chemotherapy is unknown. The uncertainty around the clinical effectiveness could potentially be addressed by additional comparative analyses using UK sources of comparator data. All the cost-effectiveness estimates were above £50,000 per QALY gained, and therefore above the range normally considered to be a cost-effective use of NHS resources. The committee concluded that axicabtagene ciloleucel was not recommended for routine use for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies.



## ***Cancer Drugs Fund***

### **Axicabtagene ciloleucel does not meet the criteria to be considered for inclusion in the Cancer Drugs Fund**

3.29 Having concluded that axicabtagene ciloleucel was not recommended for routine use, the committee then considered if it could be recommended 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 the [addendum to the NICE process and methods guides](#). It noted that the company had not made a case for axicabtagene ciloleucel to be included in the Cancer Drugs Fund, and recalled that the ICERs were above the range considered to be a cost-effective use of NHS resources. It agreed that additional data on disease progression after treatment with axicabtagene ciloleucel would help to address the uncertainties around the survival benefit, and noted that a further data cut from ZUMA-1 is expected in the near future, with an additional years' follow-up. However, based on the available evidence, the committee agreed that axicabtagene ciloleucel did not meet the criteria for inclusion in the Cancer Drugs Fund.

## **4 Proposed date for review of guidance**

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Stephen O'Brien  
Chair, appraisal committee  
August 2018

## 5 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.

#### **Lorna Dunning**

Technical Lead

#### **Nicola Hay**

Technical Adviser

#### **Stephanie Callaghan**

Project Manager

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