

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

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

1 Recommendations

- 1.1 Axicabtagene ciloleucel is recommended, within its marketing authorisation, as an option 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. It is recommended only if the company provides axicabtagene ciloleucel according to the commercial arrangement (see [section 2](#)).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for axicabtagene ciloleucel 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 (NICE technology appraisal guidance 559).

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. Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy (also called CAR-T therapy). It uses the patient's own immune cells that have been modified to attach to and kill cancer cells.

The new evidence includes data from a clinical trial and from people having axicabtagene ciloleucel in the NHS while it was available in the Cancer Drugs Fund. It suggests that people having axicabtagene ciloleucel live longer than people having salvage chemotherapy and have longer before their condition gets worse.

Axicabtagene ciloleucel meets NICE's criteria to be considered a life-extending treatment at the end of life. Taking this into account, the cost-effectiveness estimates for axicabtagene ciloleucel are within what NICE considers an acceptable use of NHS resources. So, axicabtagene ciloleucel is recommended for routine use in the NHS.

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 diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after 2 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 for axicabtagene ciloleucel is £280,451 per 68-ml single infusion bag (company submission).

2.4 The company has a commercial arrangement. This makes axicabtagene ciloleucel available to the NHS with a discount. 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.

This review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund's managed access arrangement, the company was required to collect updated efficacy data from the ZUMA-1 trial. Data was also collected on the use of axicabtagene ciloleucel in the NHS through the Cancer Drugs Fund using the Systemic Anti-Cancer Therapy (SACT) dataset.

Clinical need

Value of treatment

- 3.1 Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma are aggressive subtypes of non-Hodgkin lymphoma. The condition does not respond well to chemotherapy, and outcomes for people with refractory or relapsed disease are poor and survival is limited. Axicabtagene ciloleucel is part of a group of advanced cancer treatments called chimeric antigen receptor (CAR) T-cell therapies. CAR T-cell therapies are personalised cancer immunotherapies which involve collecting and modifying people's own immune cells to treat their cancer. Axicabtagene ciloleucel is indicated for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more lines of systemic therapy. Clinical and patient experts explained that without CAR T-cell therapy there is a lack of treatment options if the condition relapses after 2 therapies. The patient expert explained that chemotherapy treatments are intense, frequent and extremely difficult to endure. They described that chemotherapy treatments have challenging side effects and a large impact on quality of life for little clinical success. The patient and clinical

experts explained that the introduction of axicabtagene ciloleucel into the treatment pathway has revolutionised treatment and provided hope of a cure for this aggressive condition. The committee concluded that axicabtagene ciloleucel is a valuable treatment option.

Treatment pathway

3.2 In the original appraisal, the company proposed that axicabtagene ciloleucel can be used in 4 possible positions in the treatment pathway, specifically for people whose disease:

- was refractory after 1 systemic therapy, or
- has relapsed after 1 systemic therapy, but who cannot have an autologous stem cell transplant, or
- 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
- has relapsed after 1 systemic therapy, and who would have been 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 considered the company's proposed positions in the pathway. During the original appraisal, the committee concluded that it could not consider axicabtagene ciloleucel for people whose disease has not responded to 1 systemic therapy but who are unable to have an autologous stem cell transplant. It considered this position was not in line with the anticipated marketing authorisation of axicabtagene ciloleucel (that is, after 2 or more systemic therapies). Axicabtagene ciloleucel would also not be used as an alternative to autologous stem cell transplant, because this would be part of the second systemic treatment. So, the committee concluded that axicabtagene ciloleucel would be positioned as a treatment option for people whose disease:

- was refractory after 1 systemic therapy, or

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

Clinical experts explained that all 3 populations have axicabtagene ciloleucel in NHS clinical practice, and they would expect this to continue. Without axicabtagene ciloleucel, the only available treatment option for people who have had 2 previous systemic therapies is salvage chemotherapy. Salvage chemotherapy is only expected to provide short-term benefits, but axicabtagene ciloleucel has the potential to be curative. The committee concluded that considering axicabtagene ciloleucel in 3 positions of the treatment pathway is appropriate.

Clinical evidence

ZUMA-1 data

3.3 The clinical-effectiveness evidence for axicabtagene ciloleucel was from ZUMA-1, an ongoing, phase 1/2, multicentre, open-label, single-arm trial. ZUMA-1 investigated axicabtagene ciloleucel in adults with aggressive relapsed or refractory B-cell non-Hodgkin lymphoma (including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and transformed follicular lymphoma) that was refractory to treatment or had relapsed within 12 months of autologous stem cell transplant. The company presented updated overall survival results collected in ZUMA-1 which included a minimum follow-up of 5 years. The updated ZUMA-1 results showed that 64 patients (59%) had died at database lock (11 August 2021). Updated median overall survival was 23.5 months with an observed plateau of 45% at around 26.0 months. Updated median progression-free survival was 5.8 months with an observed plateau in

progression-free survival of 40% at 9.0 months. The committee heard that ZUMA-1 progression-free survival was only updated to 2 years, because there was no protocol mandate to collect data after 2 years. The company stated that any progression-free survival data collected after 2 years would not be consistent with progression-free survival data collected before 2 years. The committee would have preferred to see more mature progression-free survival data but accepted that additional overall survival data had reduced uncertainty. The committee concluded that additional axicabtagene ciloleucel data supported the predictions in the original submission of long survival times for a substantial proportion of patients.

SACT data

3.4 Further clinical evidence was collected from the SACT dataset while axicabtagene ciloleucel was available in the Cancer Drugs Fund. The SACT dataset contains UK real-world clinical-effectiveness data from the Cancer Drugs Fund population between December 2018 and October 2021. The median age of people having axicabtagene ciloleucel was 59.5 years, similar to ZUMA-1. Overall survival rates in the Cancer Drugs Fund population were comparable to ZUMA-1 over the 36 months of data collection. Median overall survival of people having axicabtagene ciloleucel was 28.5 months and 45% of people were alive after 3 years. The ERG highlighted that Eastern Cooperative Oncology Group (ECOG) performance status was not collected for a proportion of people in the SACT dataset, which made comparisons with ZUMA-1 more difficult. Clinical experts explained that they expect axicabtagene ciloleucel to perform similarly in routine NHS practice to ZUMA-1 and the SACT dataset. The committee concluded that outcomes from the SACT dataset were comparable to those from ZUMA-1 and supported the use of axicabtagene ciloleucel in routine NHS practice.

Salvage chemotherapy efficacy

3.5 Because ZUMA-1 is a single-arm trial, the primary evidence source for the comparator was the SCHOLAR-1 study. SCHOLAR-1 was a retrospective

study of pooled data from 4 datasets. These datasets included adults with diffuse large B-cell lymphoma (n=552), primary mediastinal large 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 company did a targeted literature review of studies on diffuse large B-cell lymphoma after 2 or more lines of systemic therapy. This was to respond to the Cancer Drugs Fund review terms of engagement's request for additional data to address uncertainties in comparator data. The company identified 3 studies, with only 1 study from the UK. Radford et al. (2019) investigated treatment patterns and outcomes in people with relapsed or refractory diffuse large B-cell lymphoma from a single UK centre. The company argued that SCHOLAR-1 is still the most appropriate source of data for salvage chemotherapy and stressed the approach maintained consistency with the original submission. The company also outlined that SCHOLAR-1 outcomes were similar to the third-line population in the Radford study, validating their SCHOLAR-1 approach. Clinical experts highlighted issues with SCHOLAR-1. They argued that the populations in SCHOLAR-1 were not comparable to ZUMA-1. They also noted that there are large datasets that could have been used to validate SCHOLAR-1. The ERG explained that the company's targeted literature review used only 1 database, highlighting that important sources of comparator data may have been missed. The ERG explained that both ZUMA-1 and SCHOLAR-1 were not done in the UK, so the company's argument for not selecting other studies on this basis was flawed. The ERG explained that running alternative survival extrapolation scenarios with the SCHOLAR-1 data show that results are sensitive to changes in survival estimates for salvage chemotherapy. The committee noted that it would have liked the company to have explored further sources of comparator data. It noted the limitations with SCHOLAR-1 but concluded that the dataset was appropriate for decision making.

Indirect comparison

3.6 The same approach used in the original appraisal to model salvage chemotherapy was applied. SCHOLAR-1 data was adjusted to address imbalances in baseline characteristics and ensure comparability between ZUMA-1 and SCHOLAR-1. People with an ECOG performance status of 2 to 4, an unknown ECOG status or primary refractory disease were excluded from the SCHOLAR-1 dataset. Separate survival curves were used to generate a weighted survival estimate dependent on whether people had a stem cell transplant or not. The ERG highlighted that these adjustments substantially reduced the sample size of the study, from 562 people to 133 people, increasing uncertainty. The ERG also highlighted that this reduced sample size was similar to those in the alternative comparator studies (Radford [UK], n=89; Fuji [Japan], n=189; Nakaya [Japan], n=131). The committee asked why the company didn't apply more formal adjustment methods involving matching. The company explained that it did not update the analysis because the adjustment approaches were accepted by the committee in the original appraisal. The committee would have preferred to see matching adjustments applied in the indirect comparison. Comparing ZUMA-1 and SCHOLAR-1 data, axicabtagene ciloleucel is associated with longer overall survival than salvage chemotherapy and sustained progression-free survival. The committee concluded that axicabtagene ciloleucel showed clinical benefit compared with salvage chemotherapy, however limitations in the comparator data mean that the exact size of the benefit is unknown.

Cost effectiveness

Company economic model

3.7 The company's economic model used the same approach as in the original appraisal. The model included 3 health states: pre-progression survival, post-progression survival, and death. The company used a partitioned survival modelling approach in which progression-free and overall survival estimates were modelled independently. The proportion of

people whose disease progressed at each cycle was calculated as the difference between the overall survival and progression-free survival curves. The company modelled axicabtagene ciloleucel using updated data from ZUMA-1, and salvage chemotherapy using data from SCHOLAR-1. The company analysis was largely consistent with the original appraisal. The model time horizon was 44 years with a monthly cycle length. The company updated inputs for intravenous immunoglobulin (IVIg). In the original appraisal, the proportion of people who had IVIg was informed by ZUMA-1 data and was assumed to be for 12 months. During technical engagement, the company and ERG agreed to use available SACT data to inform IVIg inputs, that is, 16% of people had IVIg treatment for 6.5 months. Health state utility values were applied using data from ZUMA-1. The committee questioned the assumption that people in remission returned to general population utility. The committee thought it would be more clinically valid for people in remission to have a utility decrement applied to account for the impact of having had diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma and intensive treatments. The company explained that it kept the analysis consistent with the original appraisal. The committee would have preferred scenarios investigating the impact of health state utility, but concluded that, as in the original appraisal, the economic model was appropriate for decision making.

Modelling overall survival

3.8 Since the original appraisal, the company collected additional 60-month axicabtagene ciloleucel overall survival data in ZUMA-1. The company used a mixture cure modelling approach containing a proportion of people whose disease responds to axicabtagene ciloleucel and a proportion whose does not. People whose disease responds were assumed to have a mortality rate identical to that of the general population. Survival of people whose disease does not respond to axicabtagene ciloleucel was modelled using a standard parametric survival model. The combined survival curves made up the overall population of people with diffuse large

B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. The company indicated that all mixture cure models fit well to ZUMA-1 overall survival data and selected a log-logistic model based on statistical fit. The ERG generally agreed with the company approach and explained that the updated 60-month ZUMA-1 data reduced uncertainty in the estimated cure fraction. However, the ERG highlighted that all extrapolations using mixture cure and spline models were higher than ZUMA-1 Kaplan–Meier data from 50 months onwards. It argued that this was potentially overestimating long-term survival. Clinical experts thought the company extrapolations fitted well with their experience of how CAR T-cell therapies perform in clinical practice. They explained that CAR T-cell therapies are expected to provide a durable response in a minority of people, and the plateau present in the extrapolations seemed reasonable. The committee concluded that the company's overall survival extrapolation modelling approach was appropriate.

Modelling progression-free survival

3.9 The company extrapolated progression-free survival using a standard Gompertz distribution. The company noted that this was the distribution used in the original appraisal and was based on the updated progression-free survival results at 2 years. The committee heard that the ERG had requested progression-free survival data beyond 2 years but the company explained this was not collected (see [section 3.3](#)). The company further explained that because overall survival data was mature and stable, further progression-free survival data was not likely to impact cost-effectiveness estimates. The NICE technical team and ERG outlined that, because of the heavy censoring in the progression-free survival curve and low numbers at risk in the tail of the curve, any plateau in progression-free survival is still uncertain. The technical team highlighted that there were overall survival events between 2 years and 4 years and these events may well feature in the progression-free survival curve. This would cause the progression-free survival curve to drop. Clinical experts explained that

people whose condition had not progressed by 2 years would likely remain progression-free. Clinical experts thought the company's axicabtagene ciloleucel progression-free survival extrapolation was plausible and stated they would be surprised to see many people progressing after 2 years. The committee noted that other plausible extrapolations increased the incremental cost-effectiveness ratio (ICER). The committee also asked why the company hadn't used mixture cure models for progression-free survival as it had for overall survival. The committee would have preferred longer-term progression data, as outlined in the terms of engagement, and flexible models considered in the base-case analysis. The committee concluded that the company analysis was acceptable but associated with uncertainty.

Modelling salvage chemotherapy

3.10 The company used SCHOLAR-1 data to extrapolate long-term overall and progression-free survival data for the comparator (salvage chemotherapy). For overall survival, the company used a standard generalised gamma parametric model fit to adjusted SCHOLAR-1 data in the base case. To extrapolate progression-free survival the company generated an estimate by applying the ratio between axicabtagene ciloleucel overall survival and progression-free survival to salvage chemotherapy overall survival. These were consistent with the methods used in the original appraisal. Overall and progression-free survival extrapolation curves show a steep drop over the first 24 months before levelling off. Clinical experts explained that these extrapolations were clinically plausible for people who had the available treatment at the time. They added that the proportion of people alive in the extrapolation using SCHOLAR-1 data and people who remain progression-free using the company's methods were broadly consistent with other studies. The committee would have preferred to see consistent methods across outcomes for the 2 treatments but acknowledged limitations of available data. The committee concluded that the company's approach to modelling

long-term survival for people having salvage chemotherapy was appropriate.

CAR T-cell therapy delivery costs

3.11 The company used a 'bottom-up' costing approach to calculate the cost of delivering axicabtagene ciloleucel in the NHS. The company included the costs of:

- hospital administration
- leukapheresis
- conditioning chemotherapy
- retreatment
- training
- stem cell transplants
- treating adverse events.

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 required 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. However, the ERG also commented that the company's approach likely underestimated the true cost of delivering CAR T-cell therapy. After the first 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 in the [ongoing technology appraisal of axicabtagene ciloleucel for treating diffuse large B-cell lymphoma after 1 systemic therapy](#). This accounted for the impact of increased staffing requirements 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 plus the costs of conditioning chemotherapy drugs, stem cell transplantation and IVIg. 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 while 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, economies of scale may be expected over time. Particularly with clinical developments in care that reduce toxicity and 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.

Cost-effectiveness estimates

Most plausible ICER

- 3.12 The company's base-case analysis was updated after technical engagement and aligned with the ERG's preferred analysis. Because there are confidential discounts for treatments included in best supportive

care, the exact ICERs cannot be reported here. The committee concluded that the most plausible probabilistic ICER, using the £41,101 CAR T-cell therapy delivery cost, was below £50,000 per quality-adjusted life year gained.

End of life

End of life criteria are met

3.13 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](#). In the original appraisal the committee concluded that axicabtagene ciloleucel met both criteria for end of life. The company updated ZUMA-1 survival data for axicabtagene ciloleucel for this review, but salvage chemotherapy data was not updated. The committee concluded that axicabtagene ciloleucel offers more than 3 months' extension to life in a population that has a life expectancy of less than 24 months. The committee concluded that axicabtagene ciloleucel continues to meet the end of life criteria.

Other factors

3.14 No equality or social value judgement issues were identified.

Conclusion

Axicabtagene ciloleucel is recommended for routine use

3.15 New evidence was considered from the ZUMA-1 trial and the Cancer Drugs Fund SACT data (see [section 3.3](#) and [section 3.4](#)). The committee recognised that there was some uncertainty in the company's, progression-free survival extrapolation and limited available data on the comparator (see [section 3.5](#) and [section 3.6](#)). The committee also acknowledged uncertainty in the true cost of providing CAR T-cell therapies in the NHS (see [section 3.11](#)). However, the cost-effectiveness estimates for axicabtagene ciloleucel compared with salvage

chemotherapy were below what NICE considers a cost-effective use of NHS resources. This is in the context of the end of life criteria being met. Axicabtagene ciloleucel is therefore recommended as an option in routine commissioning for treating diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after 2 or more systemic therapies.

4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources

for it within 2 months of the first publication of the final appraisal document.

- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after 2 or more systemic therapies and the doctor responsible for their care thinks that axicabtagene ciloleucel is the right treatment, it should be available for use, in line with NICE’s recommendations.

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.

Chair

Richard Nicholas

Chair, technology appraisal committee C

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.

Lewis Ralph

Technical lead

Vicky Kelly

Technical adviser

Louise Jafferally

Project manager

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