NICE National Institute for Health and Care Excellence

NICE guidance

# Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy

Technology appraisal guidance
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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

# Contents

# 1 Recommendations

1.1 Axicabtagene ciloleucel is recommended for use within the Cancer Drugs Fund as an option for treating diffuse large B-cell lymphoma in adults when an autologous stem cell transplant is suitable if it:

- has relapsed within 12 months after first-line chemoimmunotherapy or
- is refractory to first-line chemoimmunotherapy.

It is recommended only if the conditions in the managed access agreement for axicabtagene ciloleucel are followed.

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**

Standard care for relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy is chemotherapy followed by high-dose chemotherapy and an autologous stem cell transplant. Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy. It uses the person's own immune system cells (T-cells) that have been modified to attach to and kill cancer cells. It would be used as an alternative to standard care.

Clinical trial evidence suggests that, when an autologous stem cell transplant is suitable, axicabtagene ciloleucel increases how long people live compared with standard care. But it is uncertain by how much because the trial is still ongoing. Some people in the trial who had standard care went on to have a CAR T-cell therapy. This is not standard care in the NHS, so adjusting the data to reflect this also adds uncertainty. Also, another treatment that is used during CAR T-cell therapy in the NHS was not used in the trial. This adds uncertainty because it is not clear if the results from the trial fully reflect what would happen when using axicabtagene ciloleucel in the NHS.

Axicabtagene ciloleucel meets NICE's criteria to be considered a life-extending treatment at the end of life. The cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources for end of life treatments. But, because of the uncertainty, an acceptable cost-effectiveness estimate would need to be at the lower end of the range. The cost-effectiveness estimate for axicabtagene ciloleucel is above the lower end of the range, so it cannot be recommended for routine use in the NHS.

Axicabtagene ciloleucel has the potential to be cost effective, but more evidence is needed to reduce the uncertainties. Evidence from the trial and from NHS practice could help address these. So, axicabtagene ciloleucel is 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 diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy'.

## 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).

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.

## Clinical need and treatment pathway

### Disease burden

3.1 Diffuse large B-cell lymphoma (DLBCL) is an aggressive type of cancer of the lymphatic system. People with DLBCL can experience swollen lymph nodes, bone pain, night sweats, fever, weight loss and itching. Patient experts commented that in addition to physical symptoms, many people also experience significant mental health challenges. They explained that disease relapse can be particularly difficult both physically and emotionally. Patient experts also commented that relapsed or refractory DLBCL has a large impact on daily life. They explained that people with DLBCL may spend several weeks in hospital, which impacts their ability to work and spend time with friends and family. They also commented that many people need a carer, which is often a family member, in the weeks after they have axicabtagene ciloleucel. If people do not have a carer, they may stay in hospital for the first 28 days after they have axicabtagene ciloleucel. The committee recognised that relapsed or refractory DLBCL after first-line chemoimmunotherapy has a large disease burden.

### Treatment options

3.2 Clinical experts said that in current practice, people with DLBCL are usually offered rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) as initial treatment. For DLBCL that is relapsed or refractory to R-CHOP, clinicians offer salvage chemotherapy. If the disease responds, clinicians then offer high-dose chemotherapy and an autologous stem cell transplant, for those who are able to have one. Transplant suitability is based on

the person's tolerance of intensive treatment and is usually only offered to people aged under 70. Patient experts commented on the side effects of intensive chemotherapy, including sickness, diarrhoea, hair loss and neutropenia. Patient and clinical experts also said that there is a need for treatments that could improve survival for people with relapsed or refractory DLBCL. The committee concluded that people with DLBCL and clinicians would welcome a new treatment option.

## Proposed positioning

3.3 The company proposed axicabtagene ciloleucel for a narrower population than its marketing authorisation. It focused on adults with DLBCL that is primary refractory or early relapsed within 12 months of treatment, and who are intended for an autologous stem cell transplant. This narrowed the population to those who would have been considered for an autologous stem cell transplant. This was to align with the key clinical trial, ZUMA-7 (see section 3.5). Clinical experts commented that people who cannot have an autologous stem cell transplant have worse outcomes than those who can have one. They explained that it would be beneficial to have an additional treatment option for these people. They also added that there were effectively 3 groups of people: those who could tolerate either an autologous stem cell transplant or axicabtagene ciloleucel, those who could not tolerate transplant but could tolerate axicabtagene ciloleucel and those who could not tolerate either. They were mindful that people who were not well enough to have an autologous stem cell transplant but who could tolerate axicabtagene ciloleucel would not be offered treatment based on the company's proposed positioning. But the clinical experts also highlighted that there was no evidence for axicabtagene ciloleucel in this population because they were not included in ZUMA-7. So the committee agreed that it was appropriate to position axicabtagene ciloleucel for the narrower population.

## Comparator

3.4 The committee recalled that relapsed or refractory DLBCL after first-line chemoimmunotherapy is usually treated with salvage chemotherapy, high-dose chemotherapy and an autologous stem cell transplant (from now, called standard

care). The company used clinical expert opinion to estimate the chemotherapy regimens in standard care as 50% R-ICE (rituximab, ifosfamide, carboplatin and etoposide) and 50% R-GDP (rituximab, gemcitabine, dexamethasone and cisplatin). The committee concluded that standard care including salvage chemotherapy, high-dose chemotherapy and an autologous stem cell transplant was the relevant comparator.

# Clinical evidence

## ZUMA-7 trial

3.5 The company provided evidence for axicabtagene ciloleucel compared with standard care from ZUMA-7, which is ongoing. This is a phase 3, randomised, open-label trial in adults with primary refractory or early relapse (within 12 months of first-line treatment) DLBCL after chemoimmunotherapy who are intended for transplant. Standard care was defined as platinum-based chemoimmunotherapy, and if the condition responded, then high-dose chemotherapy and an autologous stem cell transplantation. The primary endpoint was event-free survival defined as time from randomisation to the earliest date of disease progression, start of new lymphoma treatment, death, or best disease response of stable disease. Best disease response of stable disease is the best response for DLBCL that is not growing or shrinking. One clinical expert commented that event-free survival was not an appropriate primary endpoint for a trial investigating second-line treatment. They said that people who went on to have third-line axicabtagene ciloleucel would not be captured in event-free survival. But the company confirmed that starting a new lymphoma treatment included off-protocol subsequent chimeric antigen receptor (CAR) T-cell therapy, so it was a component of event-free survival. Another clinical expert noted that event-free survival is increasingly used as a primary endpoint because it effectively measures the impact of the intervention. ZUMA-7 had 1 to 1 randomisation and included a total of 359 people. The median age of people in the trial was 59 and in the overall trial group 66% were men. About three quarters of people in the trial (74%) had primary refractory disease and about one quarter (26%) had disease relapse within 12 months of first-line treatment at study entry. Crossover between treatment arms was not included in the trial. But if a person's

disease did not respond to standard care, then they could have subsequent CAR T-cell therapy off protocol. In the standard care arm, 56% of people had subsequent CAR T-cell therapy. The committee acknowledged the experts' concerns but concluded that ZUMA-7 provided the best available evidence for axicabtagene ciloleucel compared with standard care.

## Chemotherapy bridging

3.6 At the first committee meeting, the clinical experts noted that chemotherapy bridging, which is chemotherapy offered between T-cell collection and reinfusion, was not included in ZUMA-7 but is commonly used in NHS practice. They commented that this might have made clinicians less likely to offer enrolment to people with fast-progressing disease in the trial. They explained that it was difficult to estimate the impact this would have on the comparative effectiveness. At the second committee meeting, the NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) commented that in NHS clinical practice 75% of people have bridging therapy. Clinicians believe that this has resulted in a reduced incidence of grade 3 or more cytokine release syndrome (CRS) and neurotoxicity. The Cancer Drugs Fund lead noted that recent evidence has shown that people who experience CRS and neurotoxicity have a higher median metabolic tumour volume. This has been shown to correlate with clinical outcomes in third-line CAR T-cell treatment. In a recent clinical trial for another CAR T-cell therapy, used in the same position as axicabtagene ciloleucel in the treatment pathway, 63% of people who had CAR T-cell therapy also had bridging chemotherapy. They explained that because bridging chemotherapy was not included in ZUMA-7 but would be commonly used with axicabtagene ciloleucel in NHS practice, the generalisability of the results from ZUMA-7 to NHS practice was very uncertain. But, this uncertainty could be reduced with Cancer Drug Fund data collection. The committee acknowledged the issues of generalisability to NHS practice, and that this increases uncertainty in the clinical and cost-effectiveness results. It concluded that collecting data on treatment that reflects NHS clinical practice could reduce the uncertainty.

## Adverse events

3.7 Clinical and patient experts explained that current standard care can be associated with adverse events, but the types of adverse events and how they are treated is different for axicabtagene ciloleucel. Two of the key adverse events associated with axicabtagene ciloleucel are CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). In ZUMA-7, 92% of people who had axicabtagene ciloleucel had CRS of any grade and 6% had CRS of grade 3 or higher. Also in the trial, more people who had axicabtagene ciloleucel had a serious neurological event compared with those who had standard care. The patient expert said that during their treatment with axicabtagene ciloleucel they experienced severely reduced mental abilities. The nursing expert also commented that neurological adverse events can develop within minutes. They explained that this is much faster than typical adverse events associated with standard care. They added that because of the risk of rapid deterioration, people who have had CAR T-cell therapy need more monitoring, and potentially 1 to 1 nursing even if they are not in intensive care. The committee understood the potential adverse events associated with axicabtagene ciloleucel and considered the implications for the cost of managing these in the NHS (see section 3.12).

# Economic model

## Model structure

3.8 The company provided a partitioned survival model to compare the cost effectiveness of axicabtagene ciloleucel with standard care. The model had 3 health states: event free, post event and death. Health state occupancy was determined by mixture cure models fitted to ZUMA-7 overall survival, event-free survival and time to next treatment curves. The model structure was similar to those used in previous CAR T-cell NICE appraisals. The company justified using event-free survival, instead of progression-free survival, because it was the primary endpoint in ZUMA-7 and it is clinically relevant given the curative intent of treatment. The model assumed that people who were alive and event free at 5 years in both the axicabtagene ciloleucel and standard care arms had a quality of life equal to the general population because they were considered effectively

cured. The ERG commented that, on balance, it was satisfied that the modelling approach was appropriate but that the model had a limited capacity to consider more than 1 post-event round of treatment. The committee concluded the model was appropriate for decision making.

## Axicabtagene ciloleucel overall survival extrapolation

3.9 The company used the most recent data cut from ZUMA-7 to inform axicabtagene ciloleucel overall survival. This provided data for approximately 2 years of follow up that the company then fitted a range of mixture cure models to. Its preferred model was the generalised gamma distribution because it had good statistical fit and was validated by clinical experts. The ERG noted that all curves fit relatively well to the trial data, but the log-logistic curve had marginally better statistical fit. Because the trial data is immature and the long-term survival for axicabtagene ciloleucel is uncertain, the ERG preferred the log-logistic curve. This provided slightly more conservative overall survival extrapolations. In its response to consultation, the company said that they were concerned with the clinical plausibility of the survival estimates produced by the log-logistic extrapolation. It provided a naive unadjusted comparison of 5-year overall survival, comparing the observed results from ZUMA-1 (a single-arm study of axicabtagene ciloleucel for treating relapsed or refractory DLBCL at third line or later) and the estimates from the log-logistic and generalised gamma extrapolations. The company explained that people having treatment at second line would be expected to be more well and have better outcomes than those having treatment at third line or later. The company considered that the log-logistic extrapolation gave a smaller difference in overall survival than would be expected at 5 years when compared with the observed overall survival difference between ZUMA-1 and ZUMA-7 at 2 years. The ERG noted that the follow-up data from ZUMA-7 was still relatively immature, which increased uncertainty around long-term survival extrapolations. It commented that any models predicting overall survival greater than the ZUMA-1 observed values were clinically plausible considering the overall uncertainty. The ERG maintained its preference for the log-logistic model. The committee concluded that both the generalised gamma and log-logistic curves appeared plausible and agreed that the log-logistic model was appropriate given the uncertainty.

## Standard care overall survival

3.10 At the time of the second committee meeting, axicabtagene ciloleucel after 2 or more systemic therapies had only been provisionally recommended for routine commissioning and the recommendation was still subject to appeal (see NICE's technology appraisal guidance on axicabtagene ciloleucel). Axicabtagene ciloleucel after 2 or more systemic therapies is not considered to be established practice until after the final guidance is published, so for the purpose of this appraisal it was not considered a relevant subsequent treatment. In ZUMA-7, 56% of people in the standard care group had third-line CAR T-cell therapy (see section 3.5). The company explored adjusting the standard care overall survival to remove the benefit of subsequent CAR T-cell therapy, which the committee agreed was necessary. Its base case treatment-switching adjustment method was the rank preserving structural failure time (RPSFT) model with full re-censoring of data for all people having standard care. This analysis gave a hazard ratio, which the company applied to the axicabtagene ciloleucel overall survival curve. The company also explored RPSFT models with different types of censoring and the inverse probability of censoring weighting method. During technical engagement, the company updated the survival analysis to recategorise 4 people in the standard care arm whose data was originally censored as lost to follow up but were confirmed to have died during the study period. This reanalysis was originally requested by the US Food and Drug Administration. The updated overall survival hazard ratio for using the RPSFT model with full re-censoring was 0.42. At the second committee meeting the Cancer Drugs Fund lead noted the results from a clinical trial for another CAR T-cell therapy in the same position in the treatment pathway as axicabtagene ciloleucel. The trial also included treatment switching and chemotherapy bridging and showed that survival benefit for people having CAR T-cell therapy was lower in longer-term follow up compared with earlier results. They advised this increased uncertainty around the long-term survival benefit of other CAR T-cell therapies such as axicabtagene ciloleucel. The committee agreed that the RPSFT model with full re-censoring was suitable. But, it added uncertainty that cannot be resolved until there is longer-term overall survival data collection.

## Crossover analysis clinical plausibility

3.11 The company compared the updated survival estimates from the different treatment-switching adjustment methods with those from SCHOLAR-1 and the comparator arm of the ORCHARRD study. SCHOLAR-1 was a retrospective evaluation of outcomes in people with refractory DLBCL and included both observational and randomised controlled trial data. ORCHARRD was a study of ofatumumab compared with rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) salvage treatment, followed by an autologous stem cell transplant. Clinical experts advised the company that overall survival for people having standard care would likely be above the SCHOLAR-1 estimates but below the ORCHARRD estimates. The company noted that the only adjustment method that met the clinician's expectations, was the RPSFT model with full re-censoring. The ERG agreed that the company's preferred adjustment was the most appropriate method but cautioned that there was remaining uncertainty about standard care overall survival. The committee questioned whether it was appropriate to apply a hazard ratio to the axicabtagene ciloleucel overall survival mixture cure model. It was concerned that standard care overall survival was disadvantaged after 5 years. Clinical expectation is that if people are alive and event free at 5 years, regardless of the treatment they had, they are effectively cured. But, applying a hazard ratio implies that the standard care survival would be proportional to axicabtagene ciloleucel even after the cure point, which may not reflect clinical expectation. The committee concluded that the company's standard care overall survival extrapolation was acceptable, but that there was remaining uncertainty in long-term survival, which could be favourable to axicabtagene ciloleucel.

## CAR T-cell therapy delivery costs

3.12 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:

- hospital administration
- leukapheresis
- conditioning chemotherapy

- bridging therapy
- 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 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. 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. 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 and intravenous immunoglobulin (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 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.

## Autologous stem cell transplant costs

3.13 As part of current standard care for relapsed or refractory DLBCL, people are offered an autologous stem cell transplant. The company included a cost of £37,736 for this procedure. This was the value used in NICE's guideline on non-Hodgkin's lymphoma: diagnosis and management inflated to 2020 to 2021 values. The ERG noted that this cost was not transparent and preferred to use the HRG for 'Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over' inflated to £17,181. The company was concerned that the ERG's approach did not include follow-up costs. It cited a study by Wang et al. (2016) of people with DLBCL in the Haematological Malignancy Research Network, which reported the cost of autologous stem cell transplants to be about £42,000. The Cancer Drugs Fund lead commented that the company's estimate appeared more consistent with the cost of the procedure in the NHS than the ERG's. The committee concluded that there was some uncertainty about the true cost of autologous stem cell transplants in the NHS, but that the company's estimate was more appropriate.

## Retreatment costs

3.14 The company noted that a small proportion of people in ZUMA-7 had retreatment with axicabtagene ciloleucel (the company considers the value to be confidential, so it cannot be reported here). It explained that retreatment was not part of the marketing authorisation and would not occur in clinical practice, so it did not include those costs. It also added that the clinical benefit for people who had retreatment was small and unlikely to impact the cost-effectiveness estimates. The ERG was concerned that excluding retreatment costs would mean that modelled treatment benefit and modelled costs were not aligned. It preferred to

include retreatment costs because there is no robust way of removing treatment benefit. The committee noted the benefit of retreatment was uncertain. NHS England confirmed that it would not commission retreatment. The committee agreed with the ERG that it was important to align modelled costs and benefits. So it concluded that it was appropriate to include axicabtagene ciloleucel retreatment costs.

# End of life

## Life-extending treatment criteria

3.15 The committee considered the advice about life-extending treatments for people with a short life expectancy in section 6 of NICE's guide to the methods of technology appraisal 2013. 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 noted that using its preferred RPSFT model with full re-censoring adjustment, the mean life years for the standard care arm was more than 24 months, but the median overall survival was less than 24 months (the company considers the exact values to be confidential, so they cannot be reported here). The model also predicted that less than one third of people in the standard care arm would be alive at 24 months (the company considers the exact value to be confidential, so it cannot be reported here). The clinical experts agreed that they would expect 20% to 30% of people in this population to be alive at 24 months with current standard care. The committee recalled that CAR T-cell therapy is not considered established practice so could not be considered part of standard care (see section 3.10). The committee agreed that although there was some uncertainty, the short life expectancy criterion was met. It then considered if axicabtagene ciloleucel was associated with a gain in overall survival of at least 3 months. When using its preferred assumptions, the model predicted axicabtagene ciloleucel would extend life by more than 3 months (the company considers the exact value to be confidential, so it cannot be reported here). The committee concluded that axicabtagene ciloleucel met both of NICE's criteria to be considered a life-extending treatment at the end of life.

# Cost-effectiveness estimate

## Preferred ICER

3.16 The committee considered the deterministic incremental cost-effectiveness ratios (ICERs) for axicabtagene ciloleucel compared with standard care. Because of confidential commercial arrangements for comparator treatments, the exact cost-effectiveness results cannot be reported here. The committee's preferred cost-effectiveness estimate included:

- a log-logistic mixture cure model for axicabtagene ciloleucel overall survival (see section 3.9)
- CAR T-cell delivery costs of £41,101 (see section 3.12)
- autologous stem cell transplant costs from NICE's guideline on non-Hodgkin's lymphoma: diagnosis and management (see section 3.13)
- retreatment costs for axicabtagene ciloleucel (see section 3.14)
- post-event treatment distributions from ZUMA-7
- post-event utility values from ZUMA-1 (a single-arm study of axicabtagene ciloleucel for relapsed or refractory DLBCL at third line or later; pre-progression values) rather than JULIET (a single-arm study of tisagenlecleucel for relapsed or refractory DLBCL)
- the cost of an additional consultation for neurological adverse events.

## Uncertainty

3.17 Section 6 of NICE's guide to the methods of technology appraisal 2013 notes that above a most plausible 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 will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty, specifically:

- long-term overall survival in people having treatment with axicabtagene ciloleucel and standard care, including:
  - immature trial data and the distribution used to extrapolate overall survival for people having treatment with axicabtagene ciloleucel in ZUMA-7 (see section 3.9)
  - the crossover adjustment needed to adjust for the use of third-line CAR T-cell therapy in ZUMA-7 (see section 3.11)
- generalisability of the results from ZUMA-7 to NHS practice because chemotherapy bridging was not used in the trial (see section 3.6).

The committee agreed that the end of life criteria applies to axicabtagene ciloleucel. This can allow it to consider ICERs of up to £50,000 per QALY gained, when the full weighting is applied to the upper end of the usual cost-effectiveness range (£30,000 per QALY gained). But, because of the uncertainty in this appraisal, the committee expected a maximum acceptable ICER to be around £20,000 per QALY gained. So, when the end-of-life weighting is applied, the maximum acceptable ICER is substantially less than £50,000 per QALY gained. The committee highlighted that the lower value for an acceptable ICER in this appraisal is based on the substantial levels of uncertainty associated with the evidence from ZUMA-7. When confidential commercial arrangements were included, the committee's most plausible ICER was less than £50,000 per QALY gained (the exact ICER cannot be reported because of the confidential comparator discounts). But the ICER was above what the committee considered to be their maximum acceptable ICER with the high level of uncertainty. So, the committee concluded that it could not recommend axicabtagene ciloleucel for routine use in the NHS.

# Cancer Drugs Fund

## Criteria for Cancer Drugs Fund

3.18 Having concluded that axicabtagene ciloleucel could not be recommended for routine use, the committee then considered if it could be recommended for

treating DLBCL after first-line chemoimmunotherapy within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum) (see NICE's managed access page). At the first committee meeting, the company acknowledged that there is uncertainty in the clinical evidence for using axicabtagene ciloleucel in this position, and that it could be a candidate for the Cancer Drugs Fund. The committee noted that ZUMA-7 is ongoing and further follow up may resolve some uncertainty around long-term survival for people who have axicabtagene ciloleucel and people who have standard care. During the second committee meeting, the Cancer Drugs Fund lead also commented that if axicabtagene ciloleucel was available in the Cancer Drugs Fund it would also help reduce uncertainty around the generalisability of the evidence from ZUMA-7 because of the absence of chemotherapy bridging (see section 3.6). This is because Systemic Anti-Cancer Therapy (SACT) data would be collected from people having treatment in the NHS. The committee agreed that reducing the uncertainty by having a longer period of data collection in the NHS would support the case for axicabtagene ciloleucel to be recommended for routine commissioning. The committee also considered that axicabtagene ciloleucel has the plausible potential to be cost-effective, if further data collection validates the current cost-effectiveness estimates. The committee concluded that axicabtagene ciloleucel met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as an option for treating DLBCL that has relapsed within 12 months after first-line chemoimmunotherapy, or is refractory to first-line chemoimmunotherapy, in adults when an autologous stem cell transplant is suitable.

# Other factors

## Innovation

3.19 The company commented that axicabtagene ciloleucel is a personalised, transformative and innovative treatment. It also noted that there may be potential benefits of axicabtagene ciloleucel treatment that were not fully captured in the QALY calculations. It stated that the true benefit of cure was likely

underestimated. It also stated that there may be benefits associated with axicabtagene ciloleucel because it is a single infusion, compared with multiple cycles of chemotherapy followed by high-dose treatment and an autologous stem cell transplant. The committee recognised that there may be these benefits to people but concluded that it had not seen evidence of these benefits over those already included in the QALY calculations.

## Equality

3.20 The committee recalled that current standard care includes an autologous stem cell transplant. The company and clinical experts explained that people 70 years and older are not usually offered stem cell transplant. The company explained that because axicabtagene ciloleucel would not have an age restriction, it could help reduce the age inequality. Age is a protected characteristic under the Equality Act 2010. The committee was aware that NICE makes recommendations for technologies within their marketing authorisations. However, the committee recalled that the company positioned axicabtagene ciloleucel only for people for whom an autologous stem cell transplant is suitable, which is usually people aged under 70. The committee considered the evidence that had been submitted. It noted that it had not seen evidence for axicabtagene ciloleucel for treating relapsed or refractory DLBCL in people for whom autologous stem cell transplant is not suitable, who are usually older and less well. The committee was aware of the need for new treatments in this population and was disappointed the company chose to position axicabtagene ciloleucel for the transplant eligible population only. A research organisation also commented that there is a geographic inequality because CAR T-cell therapy is only provided at 10 designated centres. The clinical experts explained that there are plans to deliver CAR T-cell therapy at more centres in more locations, which may mitigate this issue. The committee noted these concerns but concluded that its recommendation for axicabtagene ciloleucel would not adversely affect people protected by the equality legislation.

# 4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has relapsed or refractory diffuse large B-cell lymphoma after 1 previous chemoimmunotherapy and autologous stem cell transplant is suitable, 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 and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

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 use in the Cancer Drugs Fund, 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. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. 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 the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

# 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.

**Catie Parker and George Millington**
Technical leads

**Alex Filby**
Technical adviser

**Louise Jafferally**
Project manager

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# Accreditation