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

Technology appraisal guidance
Published: 23 January 2019
www.nice.org.uk/guidance/ta559
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 are 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.

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 ...................................................................................................................................................... 4
2 Information about axicabtagene ciloleucel ........................................................................................................ 5
3 Committee discussion ........................................................................................................................................... 6
  Potential new treatment option ......................................................................................................................... 6
  Treatment pathway and comparators .................................................................................................................. 7
  Clinical evidence .................................................................................................................................................. 10
  Adverse events ................................................................................................................................................... 15
  Cost effectiveness ............................................................................................................................................... 16
  Costs in the model ............................................................................................................................................. 21
  Cost-effectiveness results ................................................................................................................................. 23
  Innovation .......................................................................................................................................................... 25
  Discount rate ..................................................................................................................................................... 25
  End of life .......................................................................................................................................................... 26
  Cancer Drugs Fund .......................................................................................................................................... 26
  Other factors ..................................................................................................................................................... 28
4 Implementation ..................................................................................................................................................... 30
5 Appraisal committee members and NICE project team .................................................................................... 31
  Appraisal committee members ........................................................................................................................ 31
  NICE project team ........................................................................................................................................... 31
1 Recommendations

1.1 Axicabtagene ciloleucel therapy is recommended for use within the Cancer Drugs Fund 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, only if the conditions in the managed access agreement are followed.

1.2 This recommendation is not intended to affect both treatment in preparation for and 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. Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy. It contains the patient’s own T cells that have been modified to attach to and kill cancer cells.

Evidence from a small, single-arm study suggests that people having axicabtagene ciloleucel have clinically meaningful overall and progression-free survival and good response rates. However, the evidence is uncertain because there is limited follow-up and no direct data comparing axicabtagene ciloleucel with salvage chemotherapy. Limitations in the available data mean that the exact size of the benefit of axicabtagene ciloleucel compared with salvage chemotherapy is unknown. There is also not enough evidence to determine the costs of treating side effects.

Axicabtagene ciloleucel meets NICE’s criteria to be considered a life-extending treatment at the end of life. The most plausible cost-effectiveness estimates for axicabtagene ciloleucel compared with salvage chemotherapy are uncertain because survival data on axicabtagene ciloleucel are immature. However, the range of cost-effectiveness estimates shows that axicabtagene ciloleucel has plausible potential to be cost effective, and collecting further data on progression-free survival, overall survival and immunoglobulin usage will reduce the uncertainty in the evidence. Therefore, axicabtagene ciloleucel is recommended for use as an option within the Cancer Drugs Fund.
# Information about axicabtagene ciloleucel

<table>
<thead>
<tr>
<th>Marketing authorisation indication</th>
<th>Axicabtagene ciloleucel (Yescarta, Kite Pharma) is indicated 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'. Axicabtagene ciloleucel is an immunocellular chimeric antigen receptor (CAR) T-cell therapy. It contains the patient's own T cells (a type of white blood cell) that have been modified genetically in the laboratory so that they make a protein called CAR. CAR can attach to another protein on the surface of cancer cells called CD19. When axicabtagene ciloleucel is given to the patient, the modified T cells attach to and kill cancer cells, thereby helping to clear the cancer from the body.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage in the marketing authorisation</td>
<td>Treatment with axicabtagene ciloleucel comprises a single-dose intravenous infusion of axicabtagene ciloleucel (anti-CD19 CAR T cells in about 68 ml). It is intended for autologous use only and at the following dosage:</td>
</tr>
<tr>
<td>• 2×10^6 anti-CD19 CAR T cells per kg body weight (range: 1×10^6 to 2.4×10^6 cells per kg), with at most 2×10^8 anti-CD19 CAR T cells.</td>
<td></td>
</tr>
<tr>
<td>Price</td>
<td>The price was submitted as commercial in confidence. The company has a commercial arrangement. This makes axicabtagene ciloleucel available to the NHS with a discount. The details of the arrangement are commercial in confidence. It is the company's responsibility to let relevant NHS organisations know the details of the commercial arrangement.</td>
</tr>
</tbody>
</table>
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 condition does not respond well to treatment, and survival is limited. A patient expert explained that there are few, if any, 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. In response to consultation, consultees emphasised that no curative treatment options are available for refractory or relapsed disease. A patient organisation stated that this puts tremendous strain on patients and carers. The committee understood that chimeric antigen receptor (CAR) T-cell therapies (such as axicabtagene ciloleucel) are advanced treatments for cancer and belong to a new generation of personalised cancer immunotherapies that are based on collecting and modifying patients' own immune cells to treat their cancer. The committee heard from the patient expert that treatment with CAR T-cell therapies can be intense, requiring several weeks' stay in hospital, and has challenging potential side effects. However, it can enable recovery within a few months. The committee concluded that there is an unmet need in this population, and both patients and healthcare professionals would welcome potential new treatments such as CAR T-cell therapies that improve the chance of survival.
Treatment pathway and comparators

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 company’s 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 marketing authorisation for axicabtagene ciloleucel specifies its use after 2 or more systemic therapies, 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 3.9). 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 are unable to have autologous stem cell transplants because 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, because this would be part of their second systemic treatment.

Axicabtagene ciloleucel should not be considered 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 ZUMA-1 who had axicabtagene ciloleucel followed by an allogeneic transplant. The clinical experts noted that most people
in the study only needed axicabtagene ciloleucel, and therefore it should not be considered a bridging therapy. The committee agreed that axicabtagene ciloleucel should 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 excluding pixantrone is the 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 that 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. In response to consultation, a patient organisation queried the suitability of salvage chemotherapy as a comparator to axicabtagene ciloleucel (that is, comparing a treatment that may have a short-term benefit with a potentially
curative therapy). The committee recalled that NICE’s guide to the methods of technology appraisal states that the committee will normally be guided by established practice in the NHS when identifying appropriate comparators. Because salvage chemotherapy is established practice in the NHS, the committee concluded that salvage chemotherapy (excluding pixantrone) was the appropriate comparator.

Clinical evidence

Axicabtagene ciloleucel is clinically effective, but the lack of comparator data makes assessing comparative effectiveness challenging

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, 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 large B-cell lymphoma (n=6) and transformed follicular lymphoma (n=16). The committee acknowledged that the marketing authorisation 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 marketing authorisation does not specify this population, it is included. The clinical experts were concerned that enrolment in phase I/II clinical trials could be prone to bias, because 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). The committee was aware that the summary of product characteristics makes no explicit reference to retreatment with axicabtagene ciloleucel. It heard from NHS England's clinical lead for the Cancer Drugs Fund that this does not represent how axicabtagene ciloleucel would be used in clinical practice in England and agreed to take this into account in its decision making. 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 need to be
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 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 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 adjusted SCHOLAR-1 dataset is appropriate for decision making

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 (original 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. The committee noted that the adjustments to the SCHOLAR-1 dataset did not adequately account for the differences between the study populations of ZUMA-1 and SCHOLAR-1. In response to consultation, the company provided an updated analysis using SCHOLAR-1 data intended to be more comparable to the ZUMA-1 population and to better reflect UK clinical practice. This analysis excluded patients with an ECOG performance status of 2 to 4, patients with an unknown ECOG status and patients with primary refractory disease. Excluding these patients from the analysis reduced the SCHOLAR-1 sample size from 562 to 133. To address the committee's concern around the high rate of stem cell transplant, the company used separate survival curves to generate a weighted survival estimate conditioned on if patients had or had not had a stem cell transplant. The company's revised base case assumed that 10% of patients had a subsequent stem cell transplant in the salvage chemotherapy arm. The committee was aware that this approach was broadly consistent with its preferred method used in the ongoing appraisal of tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. The committee recognised the...
limitations with the SCHOLAR-1 dataset given the reduced sample size. It concluded that it would consider the comparative-effectiveness results using the new adjustment to SCHOLAR-1 in its decision making.

Alternative data sources for salvage chemotherapy would reduce uncertainty but all data sources have limitations

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 (that is, the availability of patient-level data). 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. In response to consultation, the company provided data from the CORAL extension study and the Oxford audit dataset to support the approach taken to adjust the SCHOLAR-1 data. CORAL comprised 203 patients who did not have stem cell transplant because of treatment failure, and the Oxford audit dataset reported outcomes for 41 patients with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and transformed follicular lymphoma who were ineligible for autologous stem cell transplant. The company explained that it had approached the Haematological Malignancy Research Network for possible data but that this was not available within the appraisal timeline. The company also explained that it was unable to access the ORCHARRD data because it is owned by another company. The committee acknowledged that survival outcomes were very similar using the CORAL and SCHOLAR-1 cohorts. It noted the limited data in the small Oxford audit dataset and agreed not to consider it further. The committee agreed that there were limitations to all of the potential data sources for the comparator arm but that using patient-level data from the updated adjustments to the SCHOLAR-1 data was most appropriate. It concluded that axicabtagene ciloleucel was clinically effective compared with salvage chemotherapy, but immature survival data and limitations in the comparator data mean that the exact size of the benefit is
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 explained that the use of tocilizumab had been limited in the trial because of concerns around how it may affect the efficacy of axicabtagene ciloleucel. Using tocilizumab at an earlier stage of CRS (grade 2 rather than at grade 3) may reduce the severity of the events. The committee noted that treatment strategies for CRS are described in axicabtagene ciloleucel's summary of product characteristics and in the risk management plan that is part of the marketing authorisation. The committee was also aware that tocilizumab has a marketing authorisation for treating CAR T-cell-induced severe or life-threatening CRS in people aged 2 years and older. 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 is developing a new service specification to support this. The committee concluded that axicabtagene ciloleucel is associated with frequent adverse events.
events and the costs associated with managing and treating those events should be reflected in the cost-effectiveness modelling (see section 3.22).

The use of intravenous immunoglobulin treatment after axicabtagene ciloleucel is unknown

Results from ZUMA-1 showed that only a small number of patients needed intravenous immunoglobulin (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. In response to consultation, the company reiterated that only a small proportion of patients in ZUMA-1 had needed IVIG, and it did not expect prolonged use of this treatment. The committee noted that only a small number of patients have received axicabtagene ciloleucel in clinical trials and 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

The company’s model is acceptable for decision making

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 salvage chemotherapy (referred to as best supportive care by the company in the cost-effectiveness analyses) using data from SCHOLAR-1. The committee
concluded that the model was appropriate for decision making.

The company updated its model and cost-effectiveness analyses after the first appraisal committee meeting

3.17 After the first appraisal committee meeting, the company updated its economic model to address the committee's concerns. A revised base case incorporated an updated commercial arrangement and included:

- Further adjustments to the SCHOLAR-1 dataset to better reflect the eligible population in UK clinical practice (see section 3.12).

- The ERG's proposed cost inputs for its alternative base-case analysis. These were:
  - using monthly outpatient visit costs for the administration of salvage chemotherapy
  - including intensive care costs (4 days) for the management of CRS
  - using discounted costs of post-treatment stem cell transplants.

The revised base case used costs of allogeneic stem cell transplants for patients having post-treatment stem cell transplants, based on clinical expert opinion from the first committee meeting. The updated economic model also incorporated 2 scenario analyses:

- Increasing the proportion of patients having autologous post-treatment stem cell transplants in the salvage chemotherapy arm, to assume a 50:50 split of autologous and allogeneic transplants (see section 3.22).

- Using a standard mortality ratio of 1.09 for patients in both treatment arms who were alive after 60 months to address the uncertainty of excess mortality for long-term survivors (see section 3.20).

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

3.18 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 salvage chemotherapy, 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 proportion of patients who were cured were immediately restored to the age- and gender-matched mortality of the general UK population after infusion. The proportion of patients who were not cured 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 that 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%. In response to consultation, the company stated that a later data cut from the ZUMA-1 study supported its base-case model, which predicted distinct overall survival and progression-free survival curves. However, the committee agreed that without seeing these data, the uncertainty in the cure fraction remained. The committee considered the ERG's alternative hybrid scenario, which selected the best-fitting single parametric overall survival curve for axicabtagene ciloleucel (log-logistic) 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. NHS England’s clinical lead for the Cancer Drugs Fund explained that this would be a small minority of patients, and the difference in progression-free and overall survival is more likely a result of the immature data. The committee agreed that the company’s extrapolation was likely to overestimate the size of the cure fraction. The committee also agreed that the use of the progression-free survival cure fraction could be a conservative extrapolation of overall survival in the axicabtagene ciloleucel treatment arm. In its critique of the company’s response to consultation, the ERG provided an alternative analysis to its hybrid approach, which incorporated post-progression treatment data from the company’s model. This approach suggested that progression-free and overall survival would converge because there was no curative assumption of post-progression treatments. The ERG explained that no model was optimal because of the high uncertainty in the ZUMA-1 data, given its immaturity. The committee heard from the company that the progression-free and overall survival curves had not been seen to converge in the trial data, but reiterated that these data were not currently available. The committee acknowledged that future data cuts are planned for ZUMA-1 and that these may provide more certainty in the survival extrapolation modelling. However, because these would not be available during the appraisal, the committee concluded that based on the available evidence, the overall survival gain for axicabtagene ciloleucel was between the company’s and the ERG’s estimates.

Including retreatment with axicabtagene ciloleucel adds uncertainty to the survival estimates

3.19 The committee recalled that ZUMA-1 included patients who had retreatment with axicabtagene ciloleucel, and that although the summary of product characteristics did not explicitly exclude retreatment, it had heard from NHS England’s clinical lead for the Cancer Drugs Fund that retreatment would not reflect axicabtagene ciloleucel’s use in clinical practice in England (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, or patients being cured after progression, or both. In response to consultation, the company
provided updated data on the 10 patients who had retreatment with axicabtagene ciloleucel. The committee was reassured that the effect of retreatment with axicabtagene ciloleucel on overall survival was based on only 2 patients, but concluded that retreatment added to the uncertainty around the long-term survival for people who had axicabtagene ciloleucel.

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

3.20 The company's original 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 but for those not considered cured, more than 99% had died by 2 years. The committee recalled that the ERG's hybrid approach assumed patients who had axicabtagene ciloleucel reverted to age-matched general population mortality only after the crossing of the overall and progression-free survival curves at around 52 months. The committee considered a 2-year cure point to be optimistic. 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 3.15). In response to consultation, the company provided a scenario analysis increasing mortality risks for long-term survivors using a standard mortality ratio of 1.09 for patients in both arms who were alive after 60 months. The committee acknowledged that this was not included in the company's revised base case, but in the analysis presented, the change showed little effect on the overall cost-effectiveness results. It concluded that the company's cure assumption at 2 years was optimistic and the assumption of no excess mortality risk for functionally cured patients compared with the general population was not appropriate, but this had little effect on the cost-effectiveness results.

Gamma distribution should be used to extrapolate survival benefits for salvage chemotherapy

3.21 Both the company and the ERG modelled overall and progression-free survival
for salvage chemotherapy (referred to as best supportive care by the company) using a single parametric curve. The committee understood that for the adjusted SCHOLAR-1 data submitted in response to consultation, the company used a Gompertz curve to model overall survival in the 2 groups of patients who did or did not have a subsequent stem cell transplant. These parametric curves were then weighted to assume a 10% (company) or 12.5% (ERG) rate of stem cell transplant (see section 3.12). The committee recognised that the company’s choice of extrapolation was the most conservative, was consistent with the ongoing appraisal of tisagenlecleucel for diffuse large B-cell lymphoma and visually appeared to best fit the observed data. However, the committee considered the clinical plausibility of the extrapolated curve and the survival plateau for patients who had not had subsequent stem cell transplants. The committee noted that in the ERG’s exploratory analyses, considering external (the extent to which the long-term predictions align with other data sources or clinical experience) and internal (visual assessment and goodness of fit statistics) validity, a generalised gamma distribution was considered the more appropriate choice. The committee acknowledged there was a high degree of uncertainty surrounding the overall survival extrapolations for salvage chemotherapy and that the choice of function had important implications both for end-of-life considerations (see section 3.29) and the cost-effectiveness results. It also understood that because progression-free survival was not reported in SCHOLAR-1, both the company and the ERG had assumed a proportional relationship between overall and progression-free survival. The committee concluded that a single parametric survival model applying a generalised gamma distribution curve to overall survival data was the most clinically plausible extrapolation and was appropriate to model salvage chemotherapy.

Costs in the model

The exact proportion and associated costs of allogeneic or autologous stem cell transplants after salvage chemotherapy are unknown

3.22 In its original submission, the company included the costs of axicabtagene ciloleucel, post-treatment 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 its original 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 included scenario analyses to explore the effect of increased 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. In response to consultation, the company revised its base case to include: the cost of using monthly outpatient visit costs for the administration of salvage chemotherapy; intensive care costs for 4 days to manage CRS; and the ERG's method of calculating discounted costs of post-treatment stem cell transplants. To be consistent with the committee's preferred assumptions, the revised base case used costs of allogeneic stem cell transplants. However, in the second appraisal committee meeting, the committee heard from NHS England's clinical lead for the Cancer Drugs Fund that although most stem cell transplants after 2 previous lines of systemic therapy would be allogeneic, some would be autologous, as seen in the CORAL extension study provided by the company as supportive evidence (see section 3.13). The committee acknowledged that the company's revised base case included its preferred cost assumptions but the exact proportion of allogeneic or autologous stem cell transplants was uncertain and this would be considered in its decision making.

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

3.23 The committee understood that the company's base-case analysis included
The costs of conditioning chemotherapies and leukapheresis 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 company proposed axicabtagene ciloleucel for the Cancer Drugs Fund**

3.24 The company submitted a proposal for the committee to consider axicabtagene ciloleucel for the Cancer Drugs Fund rather than routine commissioning, and proposed a confidential commercial arrangement for its use within the Cancer Drugs Fund. The committee considered the incremental cost-effectiveness ratios (ICERs) based on this commercial arrangement in its decision making. The committee understood that it was not considering axicabtagene ciloleucel for routine use, and discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE’s Cancer Drugs Fund methods guide (addendum).

**There are a range of possible cost-effectiveness estimates**

3.25 At the first committee meeting, the committee noted that the company’s base-case ICER for axicabtagene ciloleucel compared with salvage chemotherapy was above £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 3.12)
- using a hybrid approach to extrapolate overall survival with axicabtagene ciloleucel (see section 3.18)
• using alternative structural cure assumptions (see section 3.20)
• 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 3.22).

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. In response to consultation, the company presented a revised base case, incorporating updated comparator data from SCHOLAR-1, the committee's preferred cost assumptions and an updated commercial arrangement. This resulted in an ICER for axicabtagene ciloleucel compared with salvage chemotherapy below £50,000 per QALY gained. The committee noted that the company's revised base case did not include its preferred extrapolation of overall survival in the salvage chemotherapy arm, but acknowledged that this was likely to decrease the ICER. The committee recalled its decision around the extrapolations of overall survival in the axicabtagene ciloleucel arm, and considered the analyses by the ERG. Using the ERG's alternative analysis and the combined costing approach (taking into account the use of higher proportion of post-treatment autologous stem cell transplants, a cure assumption at 5 rather than 2 years, IVIG use for 3 years and the use of the intention-to-treat population) with a gamma distribution for overall survival for salvage chemotherapy, the ICER was above £50,000 per QALY gained.

The most plausible ICER is between the company's and the ERG's revised base-case estimates

3.26 The committee noted that the range between the company's and the ERG's updated ICERs was narrower than that between the 2 original ICERs, because some of the uncertainty around the size of the clinical benefit with axicabtagene ciloleucel compared with salvage chemotherapy was addressed through adjustments to the comparator dataset. However, given the uncertainty around overall and progression-free survival with axicabtagene ciloleucel (see section 3.18), the correct incorporation of costs for post-treatment stem cell transplants (see section 3.22), the cure assumptions (see section 3.20) and the use of the intention-to-treat population (see section 3.23), the committee
concluded that the most plausible ICER (including the company's commercial arrangement) was between the company's and the ERG's estimates.

Innovation

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

3.27 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 was granted eligibility as a priority medicine through the European Medicines Agency's PRIME scheme. In response to consultation, NHS England and the patient organisations reiterated that axicabtagene ciloleucel is an innovative treatment and the transformative nature of treatment required further consideration by committee. The committee acknowledged that axicabtagene ciloleucel was considered a step-change and agreed to consider this in its decision making. 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**

3.28 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 when treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), and if the committee is 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, 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

3.29 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. 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 was aware that the median overall survival in SCHOLAR-1 was 6.6 months, but noted that using the company’s original comparator dataset, the modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. Using the revised base-case comparator data and its preferred extrapolation for overall survival, the committee noted a predicted mean of around 24 months (the exact value is commercial in confidence). The committee also considered clinical expert opinion and additional evidence submitted by the company in response to consultation, which suggested that most patients for whom axicabtagene ciloleucel is an option have a poor prognosis and that SCHOLAR-1 may have optimistic results. The committee agreed that axicabtagene ciloleucel met the criterion for short life expectancy. The committee then considered if axicabtagene ciloleucel was associated with a gain in overall survival of over 3 months. It 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 the ERG’s modelling suggested a gain in overall survival of over 3 months for patients who had axicabtagene ciloleucel compared with those having salvage chemotherapy. The committee concluded that axicabtagene ciloleucel met both of NICE’s criteria to be considered a life-extending treatment at the end of life.

Cancer Drugs Fund

Further data collection could address uncertainties in the clinical- and cost-effectiveness evidence

3.30 Having concluded that axicabtagene ciloleucel met the criteria to be considered a life-extending treatment at the end of life, the committee recalled that the company had proposed axicabtagene ciloleucel for use in 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). The committee recognised that axicabtagene ciloleucel is innovative and therefore considered whether the clinical uncertainty associated with its use could be addressed through collecting more data. The committee was aware that more data from ZUMA-1 are expected, with an additional year's follow-up. It agreed that:

- Further data on progression-free, post-progression and overall survival would be a valuable addition to the clinical evidence base and would likely resolve uncertainties around survival.

- With further evidence, it may be possible to gain a more complete understanding of the treatment for B-cell aplasia including the cost and use of IVIG.

- Using axicabtagene ciloleucel in the NHS would allow data to be collected using the Systemic Anti-Cancer Therapy (SACT) dataset, which would more accurately reflect the costs and benefits of its use in clinical practice.

**Axicabtagene ciloleucel meets the criteria for use in the Cancer Drugs Fund**

Data from ZUMA-1 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 that the revised adjustments made to the SCHOLAR-1 dataset after consultation were suitable for decision making. It noted that the company’s revised base-case ICER for axicabtagene ciloleucel compared with salvage chemotherapy was below £50,000 per QALY gained, and using the ERG’s combined scenario and the alternative modelling approach for overall survival of axicabtagene ciloleucel, the ICER was over £50,000 per QALY gained. The committee acknowledged that all the ICERs for axicabtagene ciloleucel compared with salvage chemotherapy were uncertain, but concluded that axicabtagene ciloleucel had the plausible potential to satisfy the criteria for routine use if this uncertainty could be reduced. The committee recognised that more long-term survival data for axicabtagene ciloleucel and further data on post-progression survival would allow for a more robust cost-effectiveness estimate. It noted that if the overall and progression-free survival curves remain distinct in future data cuts from ZUMA-1 and in clinical practice in the NHS,
then the ICERs would decrease. Data on the use of IVIG in NHS practice could also be collected. The committee agreed that axicabtagene ciloleucel met the criteria to be included in the Cancer Drugs Fund 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.

Other factors

Axicabtagene ciloleucel will need a phased implementation to the NHS

3.32 The committee was aware of statements from clinical experts and NHS England that introducing CAR T-cell therapies to the NHS needs the provision of a new service. Infrastructure for transporting and storing the treatment, accreditation to administer the treatment, training of staff and access to intensive care units to manage adverse events all need to be included. The committee also noted that NHS England and the company consider a cautious approach is needed because these technologies are associated with severe side effects such as CRS (see section 3.14). Working collaboratively, NHS England and the company aim to manage the risks associated with introducing axicabtagene ciloleucel by adopting a cautious approach to treatment planning, particularly concerning the management of adverse events (for further information, see the summary of product characteristics). NHS England and the company agreed that phased implementation to the NHS is necessary to deliver this treatment (see section 4.1). 

There are no relevant equality issues

3.33 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 recommendations for axicabtagene ciloleucel are 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.
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 and implementation arrangements in the managed access agreement (which for axicabtagene ciloleucel, will require that the necessary infrastructure and safety measures are in place for the treatment to be available). This means that, if a patient has relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma, has had 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 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 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.

Lorna Dunning
Technical Lead

Nicola Hay
Technical Adviser

Stephanie Callaghan
Project Manager

ISBN: 978-1-4731-3250-4
Accreditation

NICE accredited

www.nice.org.uk/accreditation