

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Tisagenlecleucel for treating relapsed or  
refractory diffuse large B-cell lymphoma after  
2 or more systemic therapies**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tisagenlecleucel in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using tisagenlecleucel in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

**The key dates for this appraisal are:**

Closing date for comments: 10 October 2018

Second appraisal committee meeting: 23 October 2018

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

## 1 Recommendations

- 1.1 Tisagenlecleucel is not recommended, within its marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies.
- 1.2 This recommendation is not intended to affect treatment with tisagenlecleucel 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 after 2 or more systemic therapies. Salvage chemotherapy (that is, chemotherapy to control the disease) is the most common treatment option.

Evidence from a single-arm study and a small observational study suggests that people having tisagenlecleucel have good response rates, overall survival and progression-free survival. But longer follow-up is needed and there are no data comparing tisagenlecleucel with salvage chemotherapy. This means that it's not known how much benefit tisagenlecleucel offers compared with the current treatment, salvage chemotherapy.

All the cost-effectiveness estimates for tisagenlecleucel are above the range that NICE normally considers acceptable, and it is not considered to meet NICE's criteria for being a life-extending treatment at the end of life. Tisagenlecleucel also does not meet the criteria for inclusion in the Cancer Drugs Fund. Therefore, tisagenlecleucel is not recommended.

## 2 Information about tisagenlecleucel

<b>Marketing authorisation</b>	Tisagenlecleucel (Kymriah, Novartis) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after 2 or more lines of systemic therapy.
<b>Dosage in the marketing authorisation</b>	Based on the company submission, tisagenlecleucel will be available as a single infusion product for intravenous use only. Each single infusion bag of tisagenlecleucel contains a suspension of CAR-positive viable T cells at a dose of 0.6 to 6.0×10 <sup>8</sup> .
<b>Price</b>	The list price for tisagenlecleucel is £282,000. The company has a commercial arrangement, which would apply if the technology had been recommended.

## 3 Committee discussion

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

### ***New treatment option***

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

3.1 Diffuse large B-cell lymphoma is an aggressive subtype of non-Hodgkin lymphoma. Outcomes for people with refractory or relapsed disease are poor. The disease has low levels of response to treatment, and is associated with limited survival. A patient expert explained that in a survey of over 100 people with the disease, the most commonly reported side effects of treatment included fatigue, hair loss, memory loss and joint pain. The clinical experts explained that there is no standard treatment for people with relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies and there are limited curative options. The clinical experts explained that treatment after 2 or more systemic therapies may be offered with palliative intent, but CAR-T therapy (such as tisagenlecleucel) offers a potential cure. The committee concluded that

there is an unmet need in this population and tisagenlecleucel offers a potential new treatment option that may improve the chance of survival.

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

#### **Positioning tisagenlecleucel for people who cannot have stem cell transplant is not appropriate because this group cannot easily be defined**

3.2 People with relapsed or refractory disease usually have salvage chemotherapy with or without autologous stem cell transplant as a second treatment. The committee heard that current treatment options after 2 or more systemic therapies include further salvage chemotherapy that may be palliative. The company positioned tisagenlecleucel as a potential treatment for diffuse large B-cell lymphoma only in people who cannot have autologous stem cell transplant. The committee understood that this was narrower than the anticipated marketing authorisation, which does not specify treatment based on eligibility for autologous stem cell transplant. However, it was aware that the clinical evidence for tisagenlecleucel was limited to patients who could not have autologous stem cell transplant or whose disease had not responded to it (see section 3.4). The clinical experts explained that defining the population who cannot have autologous stem cell transplant using objective clinical criteria is difficult. Moreover, there is a subgroup of older patients who potentially cannot have stem cell transplant but for whom CAR-T therapy may be suitable. The experts also advised that eligibility for stem cell transplant may change over time as response to chemotherapy and fitness to tolerate treatment changes. The committee concluded that the company's positioning of tisagenlecleucel only for people who cannot have stem cell transplant was not clinically appropriate because this group cannot be easily defined. Therefore the committee considered that its recommendations should cover the full anticipated marketing authorisation.

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

3.3 The committee was aware that although there is no standard salvage chemotherapy regimen for relapsed or refractory diffuse large B-cell lymphoma, there are a number of salvage chemotherapy regimens that clinicians consider to be equally effective (including gemcitabine with oxaliplatin [Gem-Ox] and gemcitabine, cisplatin and dexamethasone [GDP] with or without rituximab). The clinical experts also advised that Gem-Ox with or without rituximab is more likely to be used with palliative intent. The committee noted that the company had included pixantrone monotherapy as a comparator for some people in the [NICE appraisal scope](#) in line with [NICE's technology appraisal guidance on pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma](#). The clinical experts explained that pixantrone is rarely used in clinical practice, has poor efficacy and should not be considered a comparator for most people in this appraisal population. The committee agreed that tisagenlecleucel would be used as an alternative to salvage chemotherapy (excluding pixantrone), and concluded that salvage chemotherapy was the most appropriate comparator.

### ***Clinical evidence***

#### **Tisagenlecleucel is effective but the benefit compared with salvage chemotherapy is uncertain because the evidence is from a single-arm study**

3.4 The clinical evidence for tisagenlecleucel came from a phase II, open-label single-arm study (JULIET) and a small observational study (Schuster 2017). The committee understood that both studies included patients who could not have autologous stem cell transplant or whose disease had not responded to it. The company presented results from 111 patients from JULIET and 14 patients from Schuster (see table 1). All patients had had a tisagenlecleucel infusion. At the December 2017 data-cut, the median follow-up in JULIET was short and the survival data were immature so there was uncertainty in the robustness of all survival data. The committee noted the plateau in the Kaplan–Meier curves for overall and progression-

free survival, but was aware that from month 20 onwards there were very few patients remaining at risk so the tails of the survival curves were highly uncertain. At the technical engagement stage, the company presented data from a more recent data-cut (May 2018) that were similar to the previous data-cut. The clinical experts stated that the results were clinically very promising: with current treatments, if relapse occurs, it usually does so in 6 to 12 months. The committee was aware that Schuster had a longer median follow-up of 28.6 months and provided longer-term data, but only included 14 patients. The committee noted that there was no evidence on the effectiveness of tisagenlecleucel directly compared with that of salvage chemotherapy. The committee concluded that tisagenlecleucel is clinically effective, but immature survival data and the lack of comparator data means the size of this benefit is uncertain.

**Table 1 Clinical effectiveness results for tisagenlecleucel**

Outcome	JULIET (December 2017 data-cut)	Schuster (2017)
Overall response rate	51.6% (95% confidence interval 41% to 62%)	50% (23% to 77%)
Complete response	39.8% (not reported)	43% (18% to 71%)
Median overall survival	11.7 months (6.6 to not reached)	22.2 months (not reached)
Median progression-free survival	Results are confidential and cannot be reported here	3.2 months (0.9 to not estimable)

**Both tisagenlecleucel studies are generalisable to the population for whom it would be an option in England**

3.5 The committee considered whether the tisagenlecleucel studies were relevant to clinical practice in the NHS because they were not done in the UK. It understood that JULIET recruited people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, which means that their activities are relatively unrestricted by their disease. Also, all patients in JULIET had previously had rituximab. The clinical experts stated that people with relapsed or refractory disease having

tisagenlecleucel 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 JULIET and Schuster were representative of the patients who would be eligible for tisagenlecleucel in England in the anticipated marketing authorisation. The committee concluded that the results from JULIET and Schuster were generalisable to patients in England.

### **It is reasonable to use unadjusted pooled survival data from both studies**

3.6 The company reported unadjusted pooled data from JULIET and Schuster for overall and progression-free survival. The committee understood that median follow-up for overall survival was much longer in Schuster than in JULIET (see section 3.4). It noted that there were some differences between the JULIET and Schuster studies, for example in the regimens used to deplete lymphocytes and the proportion of patients having bridging chemotherapy. It agreed that it was reasonable to pool the survival results given that the baseline data were similar across the 2 studies. The unadjusted pooled results for overall and progression-free survival were similar to those reported in JULIET (exact results are confidential and cannot be reported here). The committee concluded that it was reasonable to use unadjusted pooled survival data from JULIET and Schuster in its decision-making.

### **Using PIX301 or Eyre as comparator data has serious limitations**

3.7 The company's preferred comparator data for both pixantrone monotherapy and salvage chemotherapy came from a retrospective observational study of 90 people with relapsed or refractory diffuse large B-cell lymphoma who had pixantrone monotherapy (Eyre 2016). The committee understood that in both JULIET (tisagenlecleucel) and Eyre (pixantrone monotherapy), most people had previous rituximab. However, it noted that pixantrone is rarely used in clinical practice (section 3.3) and that there were several imbalances in important prognostic factors at baseline in Eyre compared with JULIET. In particular, 54% of patients in



Eyre had an ECOG performance status of 2 to 4 whereas JULIET only included patients with ECOG status of 0 or 1. Also, in Eyre a higher proportion of patients had over 2 risk factors from the International Prognostic Index, so patients may not have been well enough for CAR-T therapy. The committee was aware that the ERG used comparator data from a subgroup of PIX301, a randomised, controlled, open-label phase III trial that compared pixantrone monotherapy with the physician's choice of single-agent chemotherapy. It also noted that the comparator arm in PIX301 was limited to single-agent chemotherapy and that the clinical experts said that some patients in the trial would not have been well enough to have CAR-T therapy. The committee concluded that there were serious limitations using either PIX301 or Eyre as sources of comparator data.

**The CORAL extension study is the most appropriate comparator data for salvage chemotherapy**

3.8 The CORAL trial compared 2 salvage chemotherapy regimens with or without rituximab (ifosfamide, cisplatin/carboplatin and etoposide [ICE] or cisplatin, cytarabine and dexamethasone [DHAP]) followed by autologous stem cell transplant in patients aged 18 to 65 years. The first CORAL extension study comprised 203 patients who did not have stem cell transplant because of treatment failure and the second extension study comprised 75 patients whose disease had relapsed after having stem cell transplant in CORAL. The ERG considered that although there were limited baseline data for the subgroup after 2 systemic treatments (International Prognostic Index 0 or 1, median age 55 years and prior rituximab), these were more balanced than JULIET and were in line with the full anticipated marketing authorisation. The committee noted that the first extension study provided separate survival data for patients having subsequent stem cell transplant and for those who did not have stem cell transplant. The committee also considered SCHOLAR-1, a retrospective study with pooled data from 4 datasets, and understood that it included patients with primary refractory disease and patients with ECOG status of

0 to 4. The committee agreed that the population in SCHOLAR-1 was not representative of the population covered by the anticipated marketing authorisation in clinical practice in England. The committee was aware of 2 other possible comparator data sources: a subpopulation of ORCHARRD and the Haematological Malignancy Research Network, which were not included in the company or ERG analyses. The committee recognised the limitations of all the potential data sources for the comparator arm (see section 3.7) and noted the lack of alternative data. It concluded that the CORAL extension studies were most appropriate.

**An unadjusted naive indirect comparison is acceptable but increases uncertainty about how much benefit there is with tisagenlecleucel**

3.9 At the clarification stage, the company submitted a matched adjusted indirect comparison between JULIET and Eyre that aimed to control for baseline imbalances in important prognostic variables. The company reported a small improvement in overall survival with tisagenlecleucel after adjustment. However, the ERG was concerned that insufficient information had been reported about the matching analysis and the sample size used from JULIET. The committee noted that the results seemed implausible because there was improved survival in a population with worse prognostic factors. It concluded that considering the lack of available data in this disease area, an unadjusted naive indirect comparison of tisagenlecleucel (using data from JULIET and Schuster) compared with salvage chemotherapy (using data from the first CORAL extension study) was most appropriate but increased uncertainty about the size of the benefit with tisagenlecleucel.

**Tisagenlecleucel is associated with frequent adverse events**

3.10 Results from JULIET showed that all patients having tisagenlecleucel had an adverse event after treatment. Most patients had severe adverse events (over grade 3). Cytokine release syndrome is a common toxicity of cellular immunotherapy and it affected similar proportions of patients in both Schuster and JULIET. The clinical experts explained that cytokine

release syndrome is often mild and can be managed by tocilizumab treatment, close observation and supportive care. However, severely affected patients need time in intensive care and may have unstable blood pressure and circulation and other organ toxicity. The committee also noted that more patients in Schuster had neurotoxicity than in JULIET. Neurotoxicity may also need intensive care treatment and monitoring. A patient expert explained that although patients may find the potential side effects worrying, they would feel prepared to deal with them. The patient experts also commented that the inconvenience of needing to stay close to hospital for adverse event monitoring was insignificant compared with 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 CAR-T therapies and that NHS England are developing a new service specification to support this. The committee concluded that tisagenlecleucel is associated with frequent adverse events and the costs associated with managing and treating those events should be reflected in the cost-effectiveness modelling (see section 3.15).

## ***Cost effectiveness***

### **The company's model is acceptable for decision-making**

3.11 The company submitted a partitioned survival model with 3 health states (progression-free, progressed disease and death) that also included a decision tree element for the tisagenlecleucel arm. The company presented separate cost-effectiveness analyses comparing tisagenlecleucel with Gem-Ox, GDP and pixantrone monotherapy, which it defined as salvage chemotherapy with or without rituximab. 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 tisagenlecleucel for patients who could not have autologous stem cell transplant or whose disease had not

responded to it using data from JULIET and Schuster, and salvage chemotherapy using data from Eyre. This was a narrower population than covered by the marketing authorisation and the committee recalled its earlier conclusion that its recommendations should cover the full population (see section 3.2). The committee was aware that the ERG only reported cost-effectiveness analyses comparing tisagenlecleucel with GDP because it better reflected treatment after 2 or more systemic therapies in clinical practice (see section 3.3). The committee concluded that the model was acceptable for decision-making.

### ***Survival extrapolations***

#### **The company's hybrid survival model with a cure point between 2 and 5 years is most clinically plausible for tisagenlecleucel**

3.12 In its base case, the company modelled survival in the tisagenlecleucel arm using a lognormal mixture cure model and an exponential model for salvage chemotherapy. The company used a mixture cure model to reflect what it considered a survival plateau in the observed data (see section 3.4). The company also reported a scenario analysis using a 'hybrid' model that applied a 1-knot spline curve followed by general population mortality (using a standardised mortality ratio of 1.09) after 2 years. The committee understood that this was based on the company's clinical feedback and evidence from Maurer et al. (2014). This approach assumed patients alive after 2 years were functionally cured and had mortality rates similar to those of the general population. The committee agreed that the company's base case and scenario analyses were clinically possible but considered 2 years too short to switch to general population mortality because there were limited follow-up data and some studies showed excess mortality that persisted for up to 5 years (Howlader et al. 2017). The committee understood that both the Maurer et al. and Howlader et al. studies reported data based on time since diagnosis and did not specifically include patients having treatment after 2 or more systemic therapies, the relevant population in this appraisal.

The clinical experts explained that patients with diffuse large B-cell lymphoma whose disease had not relapsed after 2 years were often considered to be cured and did not usually need further clinical follow-up. The ERG's preferred analyses used either the company's mixture cure model or the company's scenario analysis but switched to general population mortality and a standardised mortality ratio of 1.0 at 5 years. The committee understood that survival outcomes in the ERG's preferred analyses were less favourable than both the company's base case and scenario model. The committee recalled that the observed survival data were immature (see section 3.4). It understood that the choice of survival model and comparator data had a large effect on the cost-effectiveness results, with the company's hybrid model providing the most optimistic survival data. The committee preferred the hybrid model, noting that it was easier to validate clinically and allowed clinical experts to specify a time point at which patients were assumed to be cured. The committee considered a 2-year cure point to be optimistic and 5 years to be pessimistic. It therefore concluded that the company's hybrid survival model and a cure point between 2 and 5 years was the most clinically plausible, and that it would like to have a hybrid model using cure points between 2 and 5 years to reduce uncertainty in decision-making.

**It is appropriate to model the comparator arm using the first CORAL extension study and assume that 12.5% of people have subsequent stem cell transplant**

3.13 The committee recalled that the CORAL extension studies were an appropriate data source for the comparator arm (see section 3.7) but understood that the subsequent stem cell transplant rate in the CORAL trial was over 30%. NHS England's clinical lead for the Cancer Drugs Fund explained that in England, rates of subsequent stem cell transplant are around 10% to 15%. The committee noted that the ERG's preferred analyses assumed that 12.5% of patients in the CORAL extension studies had subsequent stem cell transplant after tisagenlecleucel, because this was the mid-point between the ERG's and company's predicted rates.

The ERG clarified that the cost-effectiveness modelling only included data

from the first CORAL extension study and excluded data from the second extension study of 75 patients with relapse after stem cell transplant. The committee noted it had not seen any analyses that included this potentially relevant data. It concluded that there was uncertainty around the use of stem cell transplant in clinical practice but using data from the first CORAL extension study and assuming that 12.5% of patients have subsequent stem cell transplant was appropriate to model the salvage chemotherapy comparator arm.

### **Weighted parametric survival models are appropriate to model salvage chemotherapy**

3.14 Both the ERG and company modelled overall and progression-free survival for salvage chemotherapy using a single parametric curve. The committee understood that for its preferred comparator data from the first CORAL extension study, the ERG 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. The ERG then weighted these parametric curves to combine data from all patients in the first CORAL extension study and assumed that 12.5% of patients had a subsequent stem cell transplant. It also understood that because progression-free survival was not reported in the CORAL extension study, the ERG assumed a proportional relationship between overall survival and progression-free survival. The committee concluded that a single parametric survival model applying a Gompertz curve to overall survival data from the first CORAL extension study is appropriate to model salvage chemotherapy.

### ***Resource use and costs***

#### **The ERG's changes to resource use and costs are appropriate**

3.15 In its base case, the company included resource use and costs based on JULIET. However, the committee noted that in the company's model, only patients with grade 3 or 4 cytokine release syndrome were assumed to be

admitted to intensive care. There was also uncertainty around the frequency and duration of B-cell aplasia and how much replacement intravenous immunoglobulin would be used in routine NHS practice. Not all patients in the full analysis set of JULIET would have had a response assessment after subsequent stem cell transplant. Also, the costs of a subsequent stem cell transplant were not discounted in the second year. The committee understood that the ERG's preferred analyses addressed these concerns by including:

- a higher rate of admission to intensive care to treat cytokine release syndrome
- B-cell aplasia that persists for 3 years
- administration of tisagenlecleucel in an inpatient setting only
- rates of subsequent stem cell transplant from the efficacy analysis set in JULIET and discounted long-term follow-up costs.

The committee understood that the ERG's changes did not have a large effect on the cost-effectiveness results. Nevertheless, the committee concluded that it was appropriate to include these changes in the modelling.

### ***Health-related quality of life***

#### **The use of progression-free utility values and costs should be consistent with the assumed cure point**

3.16 The company's model assumed that patients who were still alive after 2 years in either treatment group would have the same health-related quality of life as those in the progression-free health state. The committee recalled that the clinical experts considered patients having current treatment who had not relapsed after 2 years to be cured (see section 3.12). The committee agreed that in the hybrid survival model, the time at which utility values and costs revert to the progression-free health state should be the same as the time at which patients are assumed to be

functionally cured to produce clinically plausible results. It also agreed with the ERG's preferred analyses including an age-adjusted utility decrement for patients in the progression-free and progressed health states, but understood that this did not have a large effect on the cost-effectiveness results. The committee concluded that the use of progression-free utility values and costs should be consistent with the assumed cure point.

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

#### **The most plausible ICER is above the range normally considered to be a cost-effective use of NHS resources**

3.17 The company's deterministic base case showed that the incremental cost-effectiveness ratios (ICERs) were £47,684 per quality-adjusted life year (QALY) gained for tisagenlecleucel compared with Gem-Ox and £47,526 per QALY gained for tisagenlecleucel compared with GDP (with or without rituximab). All analyses included the patient access scheme for tisagenlecleucel. The committee noted that the probabilistic ICERs were higher than the deterministic ICERs; £50,793 per QALY gained for tisagenlecleucel compared with GDP and £50,963 per QALY gained for tisagenlecleucel compared with Gem-Ox. The ERG made some changes to the company's model to reflect its preferred exploratory analysis. Specifically, it used:

- alternative cost assumptions (see section 3.15)
- an age-adjusted utility decrement (see section 3.16)
- a 12.5% subsequent stem cell transplant rate when using the first CORAL extension study (see section 3.13)
- the same health state costs and utility values as the progression-free state for all treatments after 5 years (see section 3.16).

The ERG used 2 survival models (the lognormal mixture cure model and the hybrid 1-knot spline model; see section 3.12) and 2 alternative



comparator data sources (the PIX301 subgroup and the first CORAL extension study) for salvage chemotherapy in its preferred base-case analyses. The deterministic ICER ranged from £49,964 to £93,862 per QALY gained in the ERG's analyses.

The committee noted that it had not seen ICERs using all of its preferred assumptions, specifically it did not see:

- a hybrid survival model that assumed general population mortality between 2 and 5 years (see section 3.12)
- the use of progression-free utility values and costs consistent with the assumed cure point (see section 3.16)
- CORAL data to model the comparator arm assuming that 12.5% of patients had a subsequent stem cell transplant (see section 3.13).

It noted that the ICER for a company scenario was around £54,000 per QALY gained, but this assumed a cure point after 2 years and no subsequent stem cell transplant in the comparator arm. The committee understood that the ICER was likely to be much higher after taking into account subsequent stem cell transplant and a later cure point and using probabilistic analyses. It concluded that the most plausible ICER was above the range normally considered to be a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).

## ***Innovation***

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

3.18 The committee considered tisagenlecleucel to be innovative because it represents a step change in the treatment of relapsed or refractory diffuse large B-cell lymphoma. It noted that tisagenlecleucel had been designated as a priority medicine (PRIME) by the European Medicines Agency. The company did not present any evidence to suggest that there were additional benefits that were not captured in the QALY calculations. The

committee concluded that there were no benefits not captured in the analysis.

## ***End of life***

### **Tisagenlecleucel does not meet both criteria to be considered a life-extending treatment at the end of life**

3.19 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 tisagenlecleucel met the criteria for life-extending treatments for people with a short life expectancy (normally less than 24 months). It noted that the company's modelling predicted a mean overall survival for salvage chemotherapy of less than 24 months. However, the committee recalled the limitations with the company's comparator data and its preferred data source for the comparator arm was the first CORAL extension study and the assumption that 12.5% of patients had a subsequent stem cell transplant (see section 3.13). It understood that the mean overall survival estimated from this model was much more than 24 months for salvage chemotherapy (data are confidential and cannot be reported here). It noted that in a draft appraisal consultation document in the same patient population, the committee considered that the end-of-life criteria had been met (see NICE's technology appraisal guidance on [axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma](#)). However, in the axicabtagene ciloleucel appraisal, the committee had not been presented with any reliable comparator data that was representative of the population, therefore, it made a judgement that it was plausible that the criterion for short life expectancy could apply. The committee was mindful of the inconsistency across the two appraisals but acknowledged that the survival modelling approach and data sources for salvage chemotherapy were very different. The committee concluded that, when using the most appropriate data source for the comparator (the first CORAL extension study), the modelled overall survival estimates that

it had been presented with suggested that tisagenlecleucel did not meet the end-of-life criterion for short life expectancy. The committee noted the short median overall survival follow-up for tisagenlecleucel in JULIET, but understood that both the company's and ERG's modelling suggested that tisagenlecleucel was associated with a gain in overall survival of over 3 months irrespective of the choice of survival modelling and data source for the comparator (exact data are confidential and cannot be reported here). Based on the evidence presented to it, the committee agreed that tisagenlecleucel could not be considered to meet NICE's criteria to be considered a life-extending treatment at the end of life.

### ***Equality considerations***

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

3.20 The company highlighted that diffuse large B-cell lymphoma is more common in men and older people because of the epidemiology of the disease. The committee noted that the first CORAL extension study excluded patients aged over 65 years and agreed there was a lack of data for this age group. The clinical experts also noted that there may be issues related to accessing tisagenlecleucel, because it is only available at specialist centres. However, because the recommendations for tisagenlecleucel apply to 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 established to ensure equality of referral and treatment access. The committee concluded that there were no relevant equality issues.

## ***Conclusion***

### **Tisagenlecleucel is not recommended for routine use**

3.21 Data from JULIET and Schuster suggested that people having tisagenlecleucel have good response rates, overall survival and progression-free survival. The committee acknowledged that the published evidence for the relevant comparator treatments was limited, but considered that the CORAL extension studies best represent clinical practice in England. However, it noted that there are no direct data comparing tisagenlecleucel with salvage chemotherapy, so the exact size of tisagenlecleucel's benefit compared with salvage chemotherapy is unknown. All the cost-effectiveness estimates were above £40,000 per QALY gained and the most plausible ICER was likely to be much more than £54,000 per QALY gained after taking into account subsequent stem cell transplant, a later cure point and using probabilistic analyses (see section 3.17). This is above the range normally considered to be a cost-effective use of NHS resources. Therefore, the committee concluded that it could not recommend tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies for routine use in the NHS.

## ***Cancer Drugs Fund***

### **Tisagenlecleucel does not meet the criteria to be included in the Cancer Drugs Fund**

3.22 Having concluded that tisagenlecleucel was not recommended for routine use, the committee then considered if it could be recommended for use within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's [Cancer Drugs Fund methods guide \(addendum\)](#). It noted that the company had not made a case for tisagenlecleucel to be included in the Cancer Drugs Fund, and recalled that the ICERs were above the range considered to be a cost-effective

use of NHS resources. The committee noted that it had not seen ICERs using all of its preferred assumptions (see section 3.17). However, the committee recalled that the most plausible ICER was likely to be much higher than £54,000 per QALY gained after taking into account subsequent stem cell transplant, a later cure point and using probabilistic analyses (see section 3.17). Based on this, tisagenlecleucel did not have plausible potential to be cost effective. It agreed that long-term data on disease progression after treatment with tisagenlecleucel would help to address the uncertainties around the survival benefit. The committee noted that a further data-cut from JULIET is expected soon, but recalled that a more recent data-cut from May 2018 showed similar results to the December 2017 data-cut (see section 3.4). Based on the available evidence, the committee agreed that tisagenlecleucel did not meet the criteria for inclusion in the Cancer Drugs Fund.

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

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

Professor Stephen O'Brien  
Chair, appraisal committee  
September 2018

## 5 Appraisal committee members and NICE project team

### ***Appraisal committee members***

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### ***NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

#### **Abitha Senthinathan**

Technical Lead

#### **Alex Filby**

Technical Adviser

#### **Stephanie Callaghan**

Project Manager

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