

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

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

1 Recommendations

- 1.1 Tisagenlecleucel therapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory diffuse 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 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. Tisagenlecleucel is a 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 single-arm study with short follow-up and a small observational study suggests that people having tisagenlecleucel may live for longer, or have more time before their disease relapses. But longer follow-up from the study is needed and there are no data directly comparing tisagenlecleucel with salvage chemotherapy. To assess the comparative effectiveness of tisagenlecleucel and salvage chemotherapy, data from the first CORAL extension study are used. Limitations in the available data mean that the exact size of the benefit of tisagenlecleucel compared with salvage chemotherapy is difficult to establish.

Tisagenlecleucel meets NICE's criteria to be considered a life-extending treatment at the end of life. All the cost-effectiveness estimates for tisagenlecleucel compared with salvage chemotherapy are uncertain because of limitations in the data. Because some of these estimates are higher than what NICE normally considers an acceptable use of NHS resources and are associated with a high degree of uncertainty, tisagenlecleucel cannot be recommended for routine use in the NHS.

Collecting more data on progression-free survival, overall survival and immunoglobulin usage will reduce the uncertainty in the evidence.

Therefore, tisagenlecleucel is recommended for use in the Cancer Drugs Fund.

2 Information about tisagenlecleucel

Marketing authorisation	<p>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'.</p> <p>Tisagenlecleucel is an immunocellular 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 chimeric antigen receptor (CAR). CAR can attach to another protein on the surface of cancer cells called CD-19. When tisagenlecleucel is given to the patient, the modified T cells attach to and kill cancer cells, thereby helping to clear the cancer from the body.</p>
Dosage in the marketing authorisation	<p>Treatment with tisagenlecleucel comprises a single-dose intravenous infusion of tisagenlecleucel. It is intended for autologous use only and the dosage for adults with diffuse large B-cell lymphoma is 0.6 to 6.0×10^8.</p>
Price	<p>The list price for tisagenlecleucel is £282,000 per infusion (company submission).</p> <p>The company has a commercial arrangement (managed access agreement with a simple discount and rebate scheme). This makes tisagenlecleucel available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.</p>

3 Committee discussion

The appraisal committee ([section 6](#)) 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-cell therapy offers a potential cure. The committee understood that CAR T-cell therapies (such as tisagenlecleucel) are advanced therapies for cancers 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 concluded that there is an unmet need in this population and that as a CAR T-cell therapy, tisagenlecleucel offers a potential new treatment option that may improve the chance of survival.

Treatment pathway and comparators

The population in the full marketing authorisation for tisagenlecleucel is appropriate

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 originally 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 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-cell 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 noted that in its response to consultation, the company included the whole population in the marketing authorisation. The committee concluded that people who cannot have stem cell transplant cannot be easily defined, so its recommendations should cover the full marketing authorisation.

Salvage chemotherapy excluding pixantrone is the 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 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 clinically effective but immature data and the lack of direct comparative trial data means the size of this benefit is difficult to establish

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 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. 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. At the technical engagement stage and after consultation, the company presented data from JULIET using a more recent data-cut (May 2018); results were similar to the previous data-cut (exact results are confidential and cannot be reported here). The committee concluded that tisagenlecleucel is clinically effective, but immature survival data and the lack of trial data directly comparing tisagenlecleucel with salvage chemotherapy means the size of this benefit is difficult to establish.

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 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 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 comparator data from PIX301 or Eyre 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 (see [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-cell 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-cell therapy. The committee concluded that there were serious limitations using either PIX301 or Eyre as a source of comparator data.

All potential sources of comparator data have limitations but the CORAL extension study is acceptable for decision-making

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 similar to JULIET and were in line with the full 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 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 (HMRN), which were not included in the original analyses from the company or ERG. In response to consultation, the company submitted additional real-world data from patients in the HMRN having fourth- or fifth-line treatment. However, the ERG explained that it is unclear whether the HMRN population would be eligible for tisagenlecleucel because it included people with ECOG performance status 2 to 4 and the baseline characteristics were not available by line of therapy. The committee discussed the HMRN data but considered that tisagenlecleucel was most likely to be used as a third-line

treatment if it were available in clinical practice. It recognised that patients having third-line treatment were not included in the company's analyses of the HMRN data, so it did not consider them in its decision-making. The committee recognised the limitations of all the potential data sources for the comparator arm (see [section 3.7](#)), including the lack of robust long-term data, but agreed that no alternative data were available. It concluded that the first CORAL extension study was acceptable for decision-making.

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 as a CAR T-cell therapy 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. The committee was aware that tocilizumab recently received a marketing authorisation for treating cytokine release syndrome. 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-cell therapies and that NHS England has developed a new service to implement 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 3.16](#)).

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. 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. In its revised base case after consultation, the company modelled tisagenlecleucel using data from JULIET and Schuster, and salvage chemotherapy using data from HMRN and the first CORAL extension study. It also included scenarios using CORAL data alone. The committee noted this covered the whole population in the marketing

authorisation (see [section 3.2](#)). The committee was aware that the ERG reported cost-effectiveness analyses comparing tisagenlecleucel with GDP only because it better reflected treatment after 2 or more systemic therapies in clinical practice. After consultation, the company provided new evidence which compared tisagenlecleucel with GDP only. The committee concluded that the model structure was acceptable for decision-making.

Survival extrapolations

The company's hybrid survival model with a 1-knot spline extrapolation is appropriate to model overall survival for tisagenlecleucel

3.12 In its revised base case after consultation, the company modelled overall survival in the tisagenlecleucel arm using a hybrid model with a 1-knot spline extrapolation and a 3-knot spline extrapolation for progression-free survival. The committee understood that the company's scenario analysis using an alternative Gompertz curve had overestimated survival, and this had a larger effect with cure points after 2 years. It noted the more favourable cost-effectiveness estimates for tisagenlecleucel using the alternative Gompertz extrapolation. The committee accepted the hybrid model with a 1-knot spline, 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 concluded that the company's hybrid model with a 1-knot spline extrapolation was appropriate to model overall survival for tisagenlecleucel.

A cure point between 2 and 5 years with excess mortality after a cure is plausible but further long-term data are needed

3.13 The company's revised base case after consultation assumed that patients alive after 2 years were functionally cured and had mortality rates similar to those of the general population without any excess mortality risk after a cure (that is, general population mortality using a standardised mortality ratio of 1.00 was applied after 2 years). The company also

reported scenario analyses with a 3-year cure point. The company chose these cure points based on clinical feedback, evidence from Maurer et al. (2014) and clinical guidelines suggesting that regular monitoring for relapse is stopped after 3 years of remission. The committee agreed that the company's revised base case after consultation was clinically plausible but, in the absence of longer-term data, had concerns that the disease may still relapse after 2 years. It considered 2 years too short to switch to general population mortality: 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 Maurer et al. and Howlader et al. 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 whose disease had not relapsed after 2 years were often considered to be cured and did not usually need further clinical follow-up. Having recalled the uncertainty in the long-term survival data for tisagenlecleucel, the committee considered the ERG's analyses using alternative cure points of 4 and 5 years and some excess mortality after a cure (that is, a standardised mortality ratio of 1.09 was applied after a cure). It understood that survival outcomes in the ERG's exploratory and preferred analyses were less favourable than those in the company's revised base case. The committee concluded that a cure point between 2 and 5 years was plausible but the former was optimistic while the latter was pessimistic especially when including excess mortality after 5 years. The committee agreed that collecting further long-term data for tisagenlecleucel was essential to address this uncertainty.

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

3.14 The committee recalled that the first CORAL extension study was an appropriate data source for the comparator arm (see [section 3.8](#)) 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 salvage chemotherapy, 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.

Gompertz distribution is appropriate to model the survival benefit for salvage chemotherapy but other extrapolations are plausible

3.15 Both the ERG and company modelled overall and progression-free survival for salvage chemotherapy using a single parametric curve. In its revised base case after consultation, the company used data from CORAL to model overall survival in patients having third-line salvage chemotherapy and data from HMRN to model overall survival in patients having fourth- or fifth-line treatment. However, the committee recalled that the HMRN data used in the company's revised modelling was not relevant (see [section 3.8](#)). Using these data substantially lowered the cost-effectiveness estimate for tisagenlecleucel, such that the committee preferred to use comparator data from the first CORAL extension study alone. 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. The committee understood that because progression-free survival was not

reported in the CORAL extension study, the ERG assumed a proportional relationship between overall and progression-free survival. In its revised base case after consultation, the company used a 2-knot spline model to extrapolate survival in patients who did not have a subsequent stem cell transplant. The company explained this was because the Gompertz curve overestimated survival and produced a survival plateau that would not be expected in patients having treatment with palliative intent only. The committee considered the clinical plausibility of the extrapolated curve and the survival plateau for patients who had not had subsequent stem cell transplants. It noted that in the ongoing appraisal of [axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies](#), the committee had accepted an alternative generalised gamma extrapolation after considering external and internal validity. The committee acknowledged that there was a high degree of uncertainty surrounding the overall survival extrapolations for salvage chemotherapy and that the choice of function had important implications for end-of-life considerations (see [section 3.18](#)). The committee understood that the company's alternative 2-knot spline extrapolation provided more favourable cost-effectiveness results for tisagenlecleucel but that it was not robustly supported by the goodness-of-fit data. The committee concluded that a single parametric survival model applying a Gompertz curve to overall survival data for patients who did or did not have subsequent stem cell transplant was appropriate to model survival benefit for salvage chemotherapy, but that other extrapolations may also be plausible.

Resource use and costs

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

3.16 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 (IVIG) 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

3.17 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.

End of life

Tisagenlecleucel meets both criteria to be considered a life-extending treatment at the end of life

3.18 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). The committee noted that the company's revised base case after consultation (including the HMRN data) predicted a mean overall survival for salvage chemotherapy of 20.4 months and a median of 5.0 months. However, it recalled that the fourth- and fifth-line HMRN data were not directly relevant (see [section 3.8](#)). The model using the committee's preferred comparator data (from CORAL alone) predicted a mean overall survival for salvage chemotherapy of 43.0 months and a median of around 4.0 months. The committee understood that this included optimistic survival predictions using the Gompertz extrapolation; mean overall survival was less than 24 months using other distributions which may also be plausible. It noted the large difference in the median and mean values and understood that the mean overall survival predicted by the model was driven by the assumption that a small proportion of people having salvage chemotherapy would survive for a long time. The committee considered the proportion of people alive at 2 years using its preferred comparator data and noted this was small (14%). Having considered the median and mean survival data from CORAL, the uncertainty in long-term outcomes and the end-of-life decision in an

ongoing appraisal in the same population (see [axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma](#)), the committee concluded that tisagenlecleucel met 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). The committee concluded that tisagenlecleucel met both of NICE's criteria to be considered a life-extending treatment at the end of life.

Cost-effectiveness results

The ICERs are associated with uncertainty and some are higher than what NICE normally considers an acceptable use of NHS resources

3.19 The company's revised base case after consultation showed that the deterministic incremental cost-effectiveness ratio (ICER) was £46,325 per quality-adjusted life year (QALY) gained for tisagenlecleucel compared with GDP (with or without rituximab). All analyses included the patient access scheme for tisagenlecleucel but probabilistic ICERs were not reported. The company's revised base case included most of the committee's preferred assumptions, specifically:

- updated survival data from JULIET (see [section 3.4](#))
- alternative costs and utility values (see [section 3.16](#))
- an age-adjusted utility decrement (see [section 3.17](#))
- a 12.5% subsequent stem cell transplant rate in the comparator arm (see [section 3.14](#))
- a hybrid survival model using a 1-knot spline to extrapolate overall survival for tisagenlecleucel (see [section 3.12](#))
- a 3-knot spline model to extrapolate progression-free survival for tisagenlecleucel (see [section 3.12](#)).

However, the revised base case did not include the committee's preferred assumptions of a cure point between 2 and 5 years for tisagenlecleucel with some excess mortality (see [section 3.13](#)) and using CORAL data alone to model the comparator arm using the Gompertz curve for patients who did and did not have subsequent stem cell transplant (see sections [3.8](#) and [3.15](#)). The committee therefore agreed to use the ERG's analyses that included its preferred assumptions; these analyses produced ICERs of £42,991 per QALY gained with a 2-year cure point, £49,963 per QALY gained with a 3-year cure point and £55,403 per QALY gained with a 4-year cure point. The committee was aware that these were based on Gompertz extrapolations, but it recalled that other distributions may also be plausible (see [section 3.15](#)). Based on the available evidence, the committee concluded that the ICER (with the discount agreed in the commercial arrangement) ranged between £42,991 and £55,403 per QALY gained. The committee concluded that the ICER range on which it was basing its decision was associated with uncertainty which needed to be accounted for when making its judgement about the acceptability of tisagenlecleucel as an effective use of NHS resources. Considering the risk to the NHS of paying for a treatment that was not cost effective, the committee concluded tisagenlecleucel could not be recommended for routine use in the NHS.

Innovation

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

3.20 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.

Cancer Drugs Fund

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

3.21 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 the [addendum to the NICE technology appraisal methods guide](#). The committee recognised that tisagenlecleucel 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 JULIET are expected and agreed that:

- Further data from the JULIET trial on progression-free, post-progression and overall survival up to 5 years would be a valuable addition to the clinical evidence base and would likely resolve uncertainties around longer-term relapse rates and survival.
- With further evidence, it may be possible to gain a more complete understanding of the costs of IVIG treatment for B-cell aplasia.
- Using tisagenlecleucel 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. Specifically it may be possible to gain a more complete understanding of the costs of IVIG treatment for B-cell aplasia.

Tisagenlecleucel meets the criteria to be included in the Cancer Drugs Fund

3.22 Data from JULIET showed that people having tisagenlecleucel may have good response rates, overall survival and progression-free survival (see

[table 1](#)). The committee acknowledged that the published evidence for comparator treatments was limited but that the first extension study from CORAL was suitable for decision-making (see [section 3.8](#)). It noted that the company's revised base-case ICER for tisagenlecleucel compared with salvage chemotherapy was below £50,000 per QALY gained, but recognised that using its preferred assumptions the most plausible ICER ranged between £42,991 and £55,403 per QALY gained. The committee acknowledged that all the ICERs for tisagenlecleucel compared with salvage chemotherapy were uncertain, but concluded that tisagenlecleucel 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 tisagenlecleucel and further data on post-progression survival would allow for a more robust cost-effectiveness estimate and could address some of the uncertainty around the most plausible cure point. Data on the use of IVIG in NHS practice should also be collected. The committee agreed that tisagenlecleucel met the criteria to be included in the Cancer Drugs Fund for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies.

Equality considerations

There are no equality issues relevant to the recommendations

3.23 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 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.

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 tisagenlecleucel, 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 and has had 2 or more systemic therapies and the doctor responsible for their care thinks that tisagenlecleucel 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 latter.

5 Review of guidance

- 5.1 The data collection period is expected to end in February 2023 when the 5-year follow-up of the final patient in the JULIET trial will be completed. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.
- 5.2 As part of the managed access agreement, tisagenlecleucel will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in NICE's [Cancer Drugs Fund methods guide \(addendum\)](#).

Professor Stephen O'Brien
Chair, Appraisal Committee
January 2019

6 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.

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Technical Lead

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