www.scottishmedicines.org.uk

SMC2200

tisagenlecleucel 1.2 x 10^6 to 6 x 10^8 cells dispersion for infusion (Kymriah®)

Novartis Pharmaceuticals UK Ltd

9 August 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission under the end of life and ultra-orphan medicine process

tisagenlecleucel (Kymriah®) is accepted for use within NHSScotland.

Indication under review: for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Tisagenlecleucel was associated with an overall response rate of 53% in a single-arm, open-label, phase II study in patients with relapsed or refractory DLBCL.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tisagenleceucel. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.[1]

Dosing Information

Tisagenlecleucel is intended for autologous use only. Tisagenlecleucel is to be administered via intravenous infusion.

The recommended single dose of tisagenlecleucel for DLBCL patients is 0.6 to 6.0 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells (non-weight based).

Lymphodepleting chemotherapy is recommended to be administered before tisagenlecleucel infusion unless the white blood cell count within one week prior to infusion is ≤1,000 cells/microlitre. The recommended lymphodepleting chemotherapy regimen is fludarabine (25mg/m^2 intravenously daily for three days) and cyclophosphamide (250mg/m^2 intravenously daily for three days starting with the first dose of fludarabine). It is recommended that tisagenlecleucel is infused two to 14 days after completion of the lymphodepleting chemotherapy. The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen.

To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol and diphenhydramine (or another H1 antihistamine) approximately 30 to 60 minutes before tisagenlecleucel infusion.

Tisagenlecleucel must be administered in a qualified treatment centre, and should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with tisagenlecleucel. A minimum of four doses of tocilizumab for use in the event of cytokine release syndrome and emergency equipment must be available prior to infusion.

Please refer to the summary of product characteristics for further information.[1]

Product availability date

February 2019

The EMA designated tisagenlecleucel as an orphan medicinal product for the treatment of DLBCL. Tisagenlecleucel met the SMC ultra-orphan at the time of submission and meets the end of life criteria for this indication.

Background

Tisagenlecleucel is an advanced therapy medicinal product (ATMP). It is an engineered autologous immunocellular cancer therapy which involves reprogramming the patient's own T-cells with a chimeric antigen receptor (CAR) that binds to and eliminates CD19 expressing cells.[1, 2]

Tisagenlecleucel for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

Tisagenlecleucel is a novel CAR T-cell therapy and an advanced therapy medicinal product (ATMP). It is one of two CAR-T therapies to be approved to date by the European Medicines Agency (EMA) for this indication.[1, 2] Axicabtagene ciloleucel (Yescarta®) is currently being reviewed by SMC for DLBCL and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy. DLBCL is an aggressive form of non-Hodgkin's lymphoma.[2] Primary refractory disease occurs in about 10% to 15% of patients with DLBCL and a further 20% to 30% relapse.[3] In patients with DLBCL who have relapsed or progressed, salvage chemotherapy and autologous SCT in eligible patients who are responsive to chemotherapy is recommended. Outcomes are extremely poor in patients who have relapsed or progressed following salvage chemotherapy or autologous SCT. In patients who have experienced two or more relapses, treatment may include further salvage chemotherapy, enrolment in clinical trials with novel drugs, allogeneic SCT or palliative care.[3, 4] A median overall survival of 6.3 months and two-year survival rate of 20% has been observed in patients with refractory DLBCL.[5] Tisagenlecleucel meets the SMC end-of-life criteria for this indication and met the SMC ultra-orphan criteria at the time of submission. Clinical experts consulted by SMC considered that tisagenlecleucel fills an unmet need in this therapeutic area, as there are limited effective treatment options for patients with relapsed or refractory DLBCL who have failed two or more lines of systemic therapy.

A patient and clinician engagement (PACE) meeting was held to consider the added value of tisagenlecleucel in the context of treatments currently available in NHSScotland. At the PACE meeting, attention was drawn to the very poor prognosis of patients with relapsed or refractory disease after two or more lines of systemic therapy. This, together with the limited availability of effective treatments to control DLBCL symptoms (fatigue, pain, swollen lymph nodes, night sweats, raised temperature and weight loss) has a substantial emotional impact, causing psychological distress to patients and their families. In addition,

the burden of disease symptoms and side effects of salvage chemotherapy have a devastating impact of their quality of life.

Impact of new technology

Summary of evidence on comparative efficacy

The key evidence for the use of tisagenlecleucel in DLCBL comes from the pivotal, open-label, single-arm, phase II study (JULIET). Eligible patients were aged ≥18 years with histologically confirmed relapsed or refractory DLBCL after two or more lines of chemotherapy including rituximab and an anthracycline, and either have failed autologous stem cell transplant (SCT) or were not eligible or refused consent. Patients were required to have measurable disease, a life expectancy of at least 12 weeks and Eastern Co-operative Oncology Group (ECOG) performance status of either 0 or 1 at screening, with adequate renal, hepatic, pulmonary and cardiac functions, and adequate bone marrow reserves without transfusion.[2]

Patient's white blood cells were collected by leukapheresis, cryopreserved and transported to the manufacturing facility where tisagenlecleucel was manufactured through a process that involved enriching for and activating the T-cells, transduction with a retroviral vector containing the CAR gene construct and expanding ex vivo for approximately 10 days. The investigator decided if patients also received bridging chemotherapy. Lymphodepleting chemotherapy was administered 2 to 14 days prior to tisagenlecleucel infusion, unless their white blood cell count was ≤1,000 cells/microlitre within the previous week. The lymphodepleting regimen comprised fludarabine (25mg/m^2 intravenously daily for three doses) and cyclophosphamide (250mg/m^2 intravenously daily for three doses). Patients who had previous grade IV haemorrhagic cystitis or resistance to previous cyclophosphamide containing regimens were treated with bendamustine (90mg/m^2 intravenously for 2 days). The targeted dose of tisagenlecleucel was a single intravenous infusion of 5.0×10^8 viable tisagenlecleucel transduced cells (acceptable dose range was 1.0 to 5.0×10^8 viable tisagenlecleucel transduced cells). Patients were given premedication with paracetamol and diphenhydramine or another H1 antihistamine every six hours as needed.[2]

The primary outcome was overall response rate (ORR), defined as a best overall response of complete or partial response until progressive disease or start of new anticancer therapy. Response was assessed by central independent review committee according to the Lugano Classification Criteria. The primary analysis of the primary outcome was carried out in the efficacy analysis set (EAS) which comprised those in the full analysis set (FAS, which included all patients who received tisagenlecleucel), who had been followed up for at least three months after treatment, in the main cohort of patients, treated from the US manufacturing facility. At the time of the primary analysis (March 2017), 147 patients had been enrolled

and 99 had been treated with tisagenlecleucel, 92 of these patients from the US manufacturing facility. An ORR was achieved by 53% (43/81; 95% confidence interval [CI] 42 to 64; p<0.0001) of patients in the main cohort who received tisagenlecleucel with at least 3 months follow up (EAS). The best overall response was complete response in 40% (32/81) of patients and partial response in 14% (11/81) of patients.[2] At an updated analysis (December 2017), the ORR was 52% (48/93) including a complete response in 40% and a partial response in 12%.[2] The primary outcome results from the most recent analysis (11 December 2018) are similar to the previous analyses.

Secondary efficacy outcomes included duration of response, progression free survival (PFS) and overall survival. Median duration of response (defined as the time from achievement of complete or partial response, to relapse or death due to DLBCL) had not been reached (95% CI: 10 months to not estimable) at the time of the latest published analysis (December 2017). Median PFS (defined as the time from date of tisagenlecleucel infusion to the date of first documented disease progression or death due to any cause), assessed in the FAS, was 2.9 months (95% CI: 2.2 to 6.2) at the primary analysis (March 2017) but was not reported at the latest published analysis. Median overall survival (defined as the time from date of tisagenlecleucel infusion to the date of death due to any cause), assessed in the FAS, was 11.7 months (95% CI: 6.6 to not estimable). [2]

Quality of life was assessed at baseline and month 3 using the disease specific Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) questionnaire, and the Short Form Health Survey (SF-36 v2; acute form). Among the 34 patients with data available at 3 months, 29 patients had an ORR. The results suggest a slight increase in health-related quality of life after 3 months for patients who responded to treatment.[2]

Supporting evidence, with a longer follow up, comes from the ongoing phase II case series study, A2101J, evaluating the efficacy of tisagenlecleucel in adult patients with relapsed or refractory DLBCL. Refractory DLBCL was defined as disease progressive or stable disease for <12 months after ≥four cycles of first-line therapy or two cycles of second-line, third-line, or later therapy or as relapse <12 months after autologous SCT. All patients had previously received an anti-CD20 monoclonal antibody and an anthracycline. Eligible patients had CD19-positive DLBCL, measurable residual disease after primary and salvage therapies, had relapsed or residual disease after autologous SCT, or were not eligible for autologous or allogeneic SCT. Between March 2014 and August 2016, 14 patients received a single infusion of tisagenlecleucel 1.0 to 5.0 x 10^8 cells, 1 to 4 days after completing lymphodepleting therapy. The primary outcome was ORR at 3 months, assessed according to the International Working Group 1999 criteria. At analysis after a median of 28.6 months of follow up (cut off May 2017), 50% (7/14) of patients had an ORR. Secondary outcomes included PFS (median 3.2 months) and overall survival (median 22.2 months).[2, 8]

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The pivotal JULIET study was single-arm and there are no comparative safety data.

At the time of the latest published analysis (December 2017), 111 patients had been treated with a single intravenous tisagenlecleucel infusion and all patients had an adverse event; 86% of patients had an adverse event suspected to be related to the study drug within 8 weeks of infusion and 31% ≥8 weeks after infusion.[2] A serious adverse event was reported by 65% (72/111) of patients and these were considered to be treatment related in 47%. A grade 3 or 4 adverse events was reported by 89%.[2]

The most frequently reported non-haematological adverse reactions were cytokine release syndrome (58%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%) and fatigue (26%). The most common grade 3 and 4 non-haematological adverse reactions were infections (32%) and cytokine release syndrome (22%). The most common grade 3 or 4 haematological laboratory abnormalities were decreased lymphocyte count (95%), decreased neutrophil count (81%), decreased white blood cell count (77%), decreased haemoglobin (59%) and decreased platelet count (55%). Febrile neutropenia was reported in 16% of patients. At the primary analysis (March 2017) neurological events were experienced by 21% (21/99) patients who received tisagenlecleucel, most commonly confusional state (8.1%) and encephalopathy (6.1%).[1, 2, 6]

Three patients died within 30 days of tisagenlecleucel infusion, all due to lymphoma progression. There were another 47 deaths more than 30 days after tisagenlecleucel infusion, 42 of which were due to lymphoma progression, and three due to chronic kidney disease, pulmonary haemorrhage and sepsis, respectively.[2]

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

In the pivotal JULIET study, the ORR was 53% at the primary analysis and 52% in the updated analysis including a complete response rate of 40%. This was assessed in the EAS (Main Cohort) which included patients who were infused with tisagenlecleucel from the US facility and had ≥ 3 months follow up. At the latest published analysis, median duration of response had not been reached. In all treated patients, median PFS was 2.9 months at the primary analysis but was not reported at the latest published analysis when median overall survival was 11.7 months. The duration of response was considered remarkable by the EMA with more than 60% of responders still responding after a median follow-up of 19 months.[2]

There are a number of limitations with the JULIET study including its single-arm design with no control or comparator arm. In JULIET, patients could receive bridging therapy prior to

tisagenlecleucel infusion at the discretion of the investigator and at the analysis in December 2017, 91% (101/111) of patients had.[1] Of these patients who received bridging therapy and had two disease assessments before receiving tisagenlecleucel, response ORR was 24% in the EAS. Therefore bridging therapy may have had an impact on the treatment effect.[2] Due to a prolonged production time during JULIET, the median duration from screening and enrolment to infusion of tisagenlecleucel was 119 days (range 49 to 396) and 54 days (range 30 to 357) respectively. This was noted as a concern by the EMA since tisagenlecleucel is intended for treatment of patients with advanced disease that is expected to progress rapidly. During this time, 54/165 of enrolled patients did not go on to receive tisagenlecleucel. Baseline characteristics were generally worse in the 54 patients enrolled but not infused with tisagenlecleucel than in the EAS and FAS. Analysis in the EAS ignores the impact of waiting times and bridging therapy, leading to an enrichment of patients in the EAS population which may overestimate the treatment effect of tisagenlecleucel. Analysis of results in the enrolled (ITT) population, including patients who did not receive tisagenlecleucel, found an ORR of 34% (56/165) and a median overall survival of 8.2 months at the latest published data cut-off. The EMA considered the ITT population to be the most conservative and relevant population and the treatment effect in terms of ORR as modest but the duration of response in complete responders as substantial and therefore clinically relevant in the patient population.[1, 2] Improvements in the manufacturing process are expected to reduce the production time of tisagenlecleucel for clinical practice.

The short median duration of follow-up and high censoring rate make it difficult to draw meaningful conclusions from the time to event analyses at the reported data cut offs from the pivotal JULIET study. The study excluded patients who were eligible for autologous SCT or who had a prior allogeneic SCT.

Cytokine release syndrome was reported by 58% of patients in JULIET. The SPC specifies that at least four doses of tocilizumab and emergency equipment must be available on-site for each patient for the management of cytokine release syndrome. Longer term safety data are also awaited.

Since there are no comparative data, the submitting company performed a naïve, unadjusted, indirect comparison of overall survival for tisagenlecleucel, based on pooled data from the JULIET and Schuster 2017 studies, with salvage chemotherapy data from Haematological Malignancy Research Network (HMRN). The company did not present results of the indirect comparison but used the Kaplan-Meier curves for each data source in the economic modelling. The median overall survival was longer for tisagenlecleucel from the JULIET and Schuster 2017 studies than for third-line salvage chemotherapy from HMRN. There are differences between the JULIET and Schuster studies which may affect the appropriateness of pooling their results. HMRN is an ongoing population-based patient

cohort from Yorkshire and Humber including 3.8 million people in which patients diagnosed with haematological malignancy have details of treatments, responses and outcomes collected from medical records and electronic systems.[10] Some factors may limit the appropriateness of comparing the HMRN data with JULIET and Schuster including the age of the data (recorded between 2004 and 2015), small numbers of patients receiving later lines of therapy, range of different salvage chemotherapy and patient characteristics only being collected at initial diagnosis and not at relapsed/refractory stage.

The EMA reported some indirectly compared data between the JULIET study and external datasets; CORAL extension studies (203 patients with previously treated DLBCL who did not go on to autologous SCT and continued to third-line salvage chemotherapy) and SCHOLAR-1 (patient-level retrospective pooled analysis which included subsets from two randomised clinical studies [NCIC and CORAL] and data from two retrospective databases). There were differences between the patient populations in terms of disease, previous treatments and subsequent proportions of patients receiving subsequent SCT and the submitting company considered the CORAL and SCHOLAR-1 data less relevant to the population under review. However, the ORR, complete response rate and overall survival from JULIET compared favourably with the ORR from CORAL (39%, 27% and 4.4 months) and SCHOLAR-1 (26%, 7% and 6.3 months).[2, 11, 12]

Clinical experts consulted by SMC considered that tisagenlecleucel is a therapeutic advancement due to its different mode of action and considerable clinical benefit. Tisagenlecleucel is administered as a single infusion but daily monitoring is necessary, possibly in hospital, for 10 days following infusion. Thereafter, monitoring is at the physician's discretion but patients should remain close to a qualified clinical facility for four weeks after the infusion. Specialist services and suitably trained staff would be required for collection, storage and transport of patient's lymphocytes. Tisagenlecleucel would be manufactured in a specialist laboratory. Administration must be carried out in a hospital with appropriate facilities and specialist staff who have clinical expertise in this area including critical care bed capacity for managing potential adverse events. The introduction of tisagenlecleucel would require additional consultant and medical support, specialist nursing, pharmacy and laboratory staffing.

At the PACE meeting, it was noted that tisagenlecleucel offers the opportunity to achieve a durable complete response. After the first month following treatment, patients who respond are expected to recover quickly compared with patients receiving salvage chemotherapy. They may experience reduced B symptoms and fatigue and an improvement in performance status and their quality of life.

Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of tisagenlecleucel as an ultra-orphan in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- DLBCL is an aggressive lymphoma and patients with relapsed or refractory disease, after two or more lines of systemic therapy, have a very poor prognosis, with a median survival of approximately 6 months. This has a devastating impact on the quality of life of patients and their families.
- There is no standard treatment for these patients and treatment options are currently limited to salvage or palliative chemotherapy, stem cell transplant for a very small number of suitable patients and enrolment in a clinical trial. Therefore, there is a significant unmet need for more tolerable and effective treatments for patients with relapsed or refractory disease.
- Tisagenlecleucel is an innovative treatment and offers patients and their families the hope of a durable complete response. It is administered as a single treatment, which may be an advantage over cycles of chemotherapy to patients and their families.
- Patients who respond to tisagenlecleucel, may experience quick improvements in B symptoms, performance status and fatigue. Patients may regain independence, return to work and participate in family life. The effects on quality of life could be transformational.
- Tisagenlecleucel has the potential for severe, acute toxicity and long-term treatment effects are unknown. Patients require intense initial monitoring as an inpatients in an appropriate clinical facility with critical care support and specialist staff. Patients may be willing to risk the potentially significant side effects for the opportunity of long-term response, avoiding the need for further chemotherapy.

Additional Patient and Carer Involvement

We received patient group submissions from Bloodwise, Leukaemia CARE and Lymphoma Action. All three organisations are registered charities. Bloodwise has received 0.9% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia CARE has received 12.6% pharmaceutical company funding in the past two years, including from the submitting company. Lymphoma Action has received 8.55% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Value for money

The company submitted a cost-utility analysis which compared tisagenlecleucel against salvage chemotherapy in adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. Two salvage chemotherapy regimens were considered as comparators: gemcitabine and oxaliplatin (Gem-Ox) and gemcitabine, dexamethasone and cisplatin (GDP) and 50% of patients who received each regimen, were also assumed to receive rituximab. Therefore the comparators were also labelled Gem-Ox and GDP with or without rituximab ([R-]Gem-Ox and [R-]GDP) in the submission.

A cohort-based partitioned survival model was used to model the cost-effectiveness of tisagenlecleucel versus the comparators. In terms of model structure, the model consisted of three health states - progression-free (PF), progressed disease (PD) and death. Patients were redistributed across the three health states at each model cycle and patients could remain in a given health state or progress to a worse health state throughout the analysis. The economic analysis also included a decision tree which was applied before entry into the partitioned survival model in the tisagenlecleucel arm only. The decision tree included three outcomes which reflected different events which may occur in the early stages of treatment. The three outcomes were: successfully receive infusion with tisagenlecleucel (and proceed to the partitioned survival model for tisagenlecleucel); do not receive tisagenlecleucel due to manufacturing failure or adverse events (therefore discontinue treatment and revert to comparator therapies); and death before tisagenlecleucel infusion. For patients who withdrew from tisagenlecleucel and switched to comparator therapies in the decision tree, the model assumed these patients would receive the salvage chemotherapy ([R-]Gem-Ox or [R-]GDP) which was being used as the comparator in that particular analysis. Therefore the model assigned the costs and quality-adjusted life-years (QALYs) associated with the relevant salvage chemotherapy to the proportion of patients who did not receive tisagenlecleucel infusion due to manufacturing failure or adverse events. The time horizon used in the analysis was 46 years.

Clinical data used in the model included pooled data from the JULIET and Schuster studies discussed above which informed estimates of PFS and overall survival (OS) for tisagenlecleucel. The OS data from the JULIET study were taken from the December 2018 data cut. The HMRN was used to estimate PFS and OS for salvage chemotherapy, thus meaning that a naïve indirect comparison was used as the basis of the estimation of clinical outcomes in the economic model. The submitting company also provided additional analysis using the CORAL study as the source of data for the comparator arm. In order to extrapolate the available data for tisagenlecleucel over the duration of the time horizon, the economic analysis applied a spline model with three knots and a spline model with one knot

to the observed data for PFS and OS respectively. However, for OS, the spline function was only applied until month 36, after which patients who were still alive were assumed to switch to a risk of death slightly elevated (SMR of 1.09) from that of the general population. This approach therefore assumed that patients who were alive at 36 months were effectively cured.

PFS and OS for salvage chemotherapy were estimated by extrapolating the available data for different lines of therapy (second line, third line, fourth line and fifth and later line) using a range of standard parametric functions and spline models. The chosen functions for each line of therapy were then combined as a weighted average to determine final PFS and OS curves to use in the economic model.

It is also worth noting that a cure assumption was not explicitly included in the modelling of OS for salvage chemotherapy, ie the comparator arm did not include a switch to general population mortality estimates at a predetermined time point. In addition, the same outcome data were used for both salvage chemotherapy regimens included in the model.

Utility values were derived by mapping the SF-36 data collected in the JULIET study on to the EQ-5D. The model assumed patients still alive at 36 months were effectively cured and therefore these patients would be assigned the PF utility value irrespective of health state. A range of other utilities were also included in the analysis such as disutilities associated with adverse events, grade 3 or 4 cytokine release syndrome (CRS, ICU stay) and ICU stays not associated with CRS. The economic model also allowed patients to receive allogeneic or autologous SCT as a subsequent treatment and a disutility associated with SCT was included in the analysis.

Costs included pre-treatment costs for tisagenlecleucel (leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy), medicine acquisition costs for all comparators, and associated administration costs. Associated hospitalisation and ICU costs, adverse event, subsequent SCT, other medical and terminal care costs were included in the economic model. CRS and B-cell aplasia costs were also captured and applied to the tisagenlecleucel arm only. Specifically, the CRS cost included an ICU admission and treatment with tocilizumab while the B-cell aplasia cost reflected treatment with intravenous immunoglobulin applied to a proportion of patients for a duration 11.4 months.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The base case results are presented below.

Table 1: Base-case results – with PAS

Tisagenlecleucel versus comparator:	**Incremental cost-effectiveness ratio (ICER) (£/QALY)**
[R-]Gem-Ox	£44,330
[R-]GDP	£44,151

Selected sensitivity analysis are available in table 2.

Table 2: Selected sensitivity analyses – with PAS

Analysis	**Original base case (using HMRN as the comparator data)**		**Alternative base case using CORAL as source for comparator arm modelling**	
	[R-]Gem-Ox	**[R-]GDP**	**[R-]Gem-Ox**	**[R-]GDP**
Base case	**£44,330**	**£44,151**	**£48,116**	**£47,903**
10 year time horizon	£96,882	£96,137	£97,506	£96,733
20 year time horizon	£56,381	£56,106	£59,968	£59,652
Alternative source for health state utility values	£48,334	£48,124	£52,506	£52,257
Alternative source for PF costs	£50,049	£49,852	£53,886	£53,653
Cure point of 5 years and long term survival costs and utilities applied at 5 years	£52,347	£52,107	£56,343	£56,054
Tisagenlecleucel cost applied to all tisagenlecleucel patients (i.e. even those who do not eventually receive an infusion)	£61,493	£61,261	£67,249	£66,970
PF and PD costs for tisagenlecleucel doubled	£48,924	£48,731	£53,237	£53,006
IVIG therapy cost indefinitely	£48,901	£48,707	£53,211	£52,980
Generalized gamma for extrapolation of tisagenlecleucel OS up to 36 months	£47,205	£47,005	£51,614	£51,373
CORAL data used for comparator data (and Gompertz used for both SCT and 'no SCT' groups- NICE preferred approach)	£48,116	£47,903	Not applicable	Not applicable
JULIET study only (Gompertz function) to extrapolate OS up to 36 months	£45,621	£45,432	£49,691	£49,465
Clinical data from non-infused patients from JULIET used for patients who did not receive tisagenlecleucel infusion	£48,036	£47,828	£54,170	£53,903

In addition to the relatively high cost-effectiveness ratio, there were a number of issues noted with the analysis:

- The economic analysis is based on a naïve indirect comparison which used data from JULIET to model outcomes for tisagenlecleucel and the HMRN for salvage chemotherapy. In addition, patients in the HMRN received a range of chemotherapy agents and were not restricted to [R-]Gem-Ox and [R-]GDP, which are the two salvage chemotherapy regimens used in the base case. Therefore, the analysis used proxy data, ie assuming the HMRN is an adequate source of data to model the efficacy of [R-]Gem-Ox and [R-]GDP, and the efficacy of these treatments can be considered interchangeable. In the resubmission, the company provided additional analysis using CORAL as the data source for the comparator arm of the model. This may be considered a more acceptable source. As noted above, using CORAL increased the base case and associated sensitivity ICERs.
- The data which informed efficacy for patients who received the tisagenlecleucel infusion may have been enriched by the delay in production of tisagenlecleucel in JULIET. It may, therefore, have been the "fitter" patients who were able to overcome the delay in tisagenlecleucel production and still receive the infusion. In addition, outcomes for patients who did not receive the infusion (potentially the "less fit" patients) were based on the efficacy of comparators in the economic model, as opposed to data specific to these patients. Further to this, bridging chemotherapy may have had an impact on the treatment effect of tisagenelecleucel in the JULIET study as noted above. The company provided sensitivity analysis where OS data for patients who did not receive the tisagenlecleucel infusion in JULIET were used to model OS for patients who discontinued tisagenlecleucel in the decision tree (sensitivity analysis 12).
- Alternative and more conservative OS functions may be available to extrapolate outcomes for tisagenlecleucel. The model includes a cure assumption where tisagenlecleucel OS switches to general population estimates at 36 months which is an unknown; this is a more conservative assumption that was used in the original submission (24 months). Changing the assumed point further increases the ICER. The results of these analyses are shown as sensitivity analysis 5 in table 2 above.
- There were limitations with the modelling of OS for salvage chemotherapy in the company's base case as estimating a range of parametric functions for each line of therapy suggests variation in outcomes at each line depending on the curve chosen. In addition, "stitching" the data (i.e. parametric curves) together using weighted averages is highly uncertain. No cure assumption was used in the modelling of OS for salvage chemotherapy.

- Duration of treatment for intravenous immunoglobulin (11.4 months) may be an underestimate if this is an ongoing treatment. The company has subsequently provided a sensitivity analysis where this is treated as an ongoing cost, as shown in sensitivity analysis 8 in table 2.

*Other data were also assessed but remain confidential.**

Impact beyond direct health benefits and on specialist services

At the PACE meeting, participants noted that compared to ongoing cycles of salvage chemotherapy, the single treatment of one tisagenlecleucel infusion and initial monitoring period could offer an advantage to patients, their families and carers. Patients who respond are expected to recover quickly and may regain their independence, allowing them to return to work and participate in family life. This can substantially reduce the burden and psychological distress on families and carers, improving the quality of life of patients, families and carers.

Due to the risk of acute toxicity, particularly cytokine release syndrome and neurological toxicity, patients are required to stay in the vicinity of a major hospital with access to critical care beds for around a month. In practice, this is likely to be initially as an inpatient and then as an outpatient staying close to the treatment centre. This requirement may have a disruptive impact on the lives of the patient, their family and carers and could add an emotional and financial burden if they have to stay away for home for an extended time.

Specialist facilities and appropriately trained staff and units with access to relevant specialties and intensive care would be required for the appropriate collection of patients' lymphocyte for the manufacture of tisagenlecleucel, as well as for its administration and monitoring and support of the patient after treatment.

The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

Costs to NHS and Personal Social Services

SMC is unable to publish the with- PAS budget impact or estimated patient numbers due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

The submitting company did not estimate any costs outside the NHS.

*Other data were also assessed but remain confidential.**

Conclusion

The Committee considered the benefits of tisagenlecleucel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as tisagenlecleucel is an ultra- orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, the Committee accepted tisagenlecleucel for use in NHS Scotland.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology published Guidelines for the management of diffuse large B-cell lymphoma in 2016.[3] This guidance predates the availability of tisagenlecleucel and therefore no specific recommendations were made. The guidance makes the following relevant recommendations for patients with relapsed / refractory disease who are eligible for transplant:
Transplant-eligible patients should receive intensive salvage chemotherapy with a non-cross resistant regimen followed by ASCT consolidation in those achieving complete response. In those achieving a partial response, second line salvage chemotherapy can be given followed by ASCT if complete response is achieved, or consolidation by ASCT in partial response can be considered. Treatment options for patients who do not respond to first-line salvage chemotherapy are limited and outcomes very poor. The guidance notes that many clinicians try second-line salvage chemotherapy however clinical trials of novel agents should be considered in these patients. Outcomes are also poor for patients relapsing after ASCT but a small number may respond to salvage chemotherapy and potentially considered for allogeneic SCT.[3]

The European Society for Medical Oncology (ESMO) published diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up in 2002.

This guidance was subsequently updated in 2012 and again in 2015.[4] This guideline predates the availability of tisagenlecleucel; therefore no specific recommendations were made. In patients who have relapsed or progressed and are eligible for transplant the ESMO guidance recommends platinum based chemotherapy regimens as salvage treatment and ASCT in patients who are responsive to chemotherapy. In patients unsuitable for transplant who have experienced a first relapse or progression platinum- and / or gemcitabine-based regimens or enrolment in clinical trials with novel drugs should be considered. In patients who have experienced two or more relapses, the guideline recommends enrolment in clinical trials with novel drugs, allogeneic transplant or palliative care.[4]

Additional information: comparators

Treatment in this patient group is very limited and may include further salvage chemotherapy (with a number of different chemotherapy regimens), enrolment in clinical studies, allogeneic SCT (in a very small number of patients) or palliative care.

Another CAR-T-cell therapy, axicabtagene ciloleucel (Yescarta®) is currently undergoing SMC assessment for the treatment of DLBCL.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
tisagenlecleucel	Intravenous infusion of 0.6 to 6.0 x 10^8 CAR-positive viable T cells (non-weight based)	**282,000**
axicabtagene ciloleucel	A single intravenous dose with 1 x 10^6 to 2 x 10^6 CAR-positive viable T cells per kg of body weight; maximum of 2 × 10^8 CAR-positive viable T cells for patients ≥100 kg	280,451

Cost per course including shipping, engineering and generation of the CAR T-cells as stated in the company submission. Costs for tisagenlecleucel are from the company submission and axicabtagene ciloleucel from dm+d. Costs do not take any patient access schemes into consideration.

References

1. European Medicines Agency (EMA). Kymriah: Summary of product characteristics. Available at: https://www.ema.europa.eu/documents/product-information/kymriah-epar-product-information_en.pdf [Last accessed: 25th September 2018].
2. European Medicines Agency (EMA). Assessment Report. Tisagenlecleucel (Kymriah®). 28/06/2018, EMA/485563/2018. www.ema.europa.eu. 2018.
3. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K*, et al.* Guidelines for the management of diffuse large B-cell lymphoma. British journal of haematology. 2016;174(1):43-56.
4. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A*, et al.* Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2015;26(suppl_5):v116-v25.
5. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J*, et al.* Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.
6. *Commercial in Confidence**
7. *Commercial in Confidence**
8. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak O*, et al.* Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. The New England journal of medicine. 2017;377(26):2545-54. Epub 12/12.
9. *Commercial In Confidence**
10. Smith A, Howell D, Crouch S, Painter D, Blase D et al. Cohort Profile: The Haematological Malignancy Research Network (HMRN); a UK population-based patient cohort. International Journal of Epidemiology 2018; 47: 700-700g. .
11. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J*, et al.* Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017:blood-2017-03-769620.
12. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M*, et al.* Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone marrow transplantation. 2016;51(1):51-7.

This assessment is based on data submitted by the applicant company up to and including 12 July 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.