www.scottishmedicines.org.uk

SMC2189

axicabtagene ciloleucel 0.4 – 2 x 10^8 cells dispersion for infusion dispersion for infusion (Yescarta®)

Kite Pharma, a Gilead Company

06 September 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 assessed under the end of life and ultra-orphan process

axicabtagene ciloleucel (Yescarta®) is accepted for use within NHSScotland.

Indication under review: Treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Axicabtagene ciloleucel was associated with an objective response rate of 82% in a single-arm, open-label, phase I/II study in patients with refractory DLBCL.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of axicabtagene ciloleucel. This advice is contingent upon the continuing availability of the PAS in NHSScotland 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

Treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy.[1]

Dosing Information

Axicabtagene ciloleucel is intended for autologous use only.

A single dose of axicabtagene ciloleucel contains 2 x 10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100kg and above) in approximately 68mL dispersion in an infusion bag. Axicabtagene ciloleucel is to be administered via intravenous infusion.

The availability of axicabtagene ciloleucel must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy):
A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500mg/m^2 intravenous and fludarabine 30mg/m^2 intravenous should be administered on the fifth, fourth, and third day before infusion of axicabtagene ciloleucel.

Pre-medication:
Paracetamol 500mg to 1,000mg given orally and diphenhydramine 12.5mg intravenous or oral (or equivalent) approximately one hour before axicabtagene ciloleucel infusion is recommended.

Axicabtagene ciloleucel must be administered in a qualified clinical setting.
Axicabtagene ciloleucel 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 axicabtagene ciloleucel. 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.

See Summary of Product Characteristics (SPC) for further information.[1]

Product availability date

December 2018

The European Medicines Agency (EMA) has designated axicabtagene ciloleucel as an orphan medicine for the treatment of diffuse large B-cell lymphoma and the treatment of primary mediastinal large B-cell lymphoma. It also meets SMC end of life and ultra-orphan criteria.

Background

Axicabtagene ciloleucel is an advanced therapy medicinal product (ATMP) which provides CD19-directed genetically modified autologous T-cell immunotherapy. To prepare axicabtagene ciloleucel, patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction to express the anti-CD19 chimeric antigen receptor (CAR). Anti-CD19 CAR-positive viable T cells are expanded and infused back into the patient, where they can recognise and eliminate CD19 expressing target cells.[1-3]

Axicabtagene ciloleucel for use in diffuse large B cell lymphoma (DLBCL) has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

DLBCL is an aggressive form of non-Hodgkin's lymphoma (NHL) and represents 30% and 58% of NHL cases.[4] Most DLBCLs begin in lymph nodes but up to 40% may originate in extranodal sites. Approximately 10% of all DLBCLs are primary mediastinal large B-cell lymphoma (PMBCL).[5] Primary refractory disease occurs in about 10% to 15% of patients with DLBCL and a further 20% to 30% relapse.[6] Recurrence of PMBCL after successful initial treatment seems to be lower than for other DLBCLs.[5]

Patients with relapsed or refractory DLBCL and PMBCL are typically treated with salvage chemotherapy followed by autologous stem cell transplant (ASCT) for those who are eligible. Only half who respond to second-line therapy are able to proceed to ASCT.[9] Patients who have experienced two or more relapses may receive further salvage chemotherapy; other options would be enrolment in clinical trials with novel drugs or palliative care. A minority of patients who respond to third-line chemotherapy and are fit would proceed to allogeneic SCT.[4, 6] Treatment of relapsed or resistant PMBCL disease is similar to nodal DLBCLs.[5]

Clinical experts consulted by SMC highlighted the very limited treatment options and poor outcomes in adult patients with relapsed or refractory DLBCL and PMBCL after two or more lines of systemic therapy.

Overall survival of 6.3 months and a two-year survival rate of 20% have been reported in the SCHOLAR-1 observational study of patients with refractory DLBCL treated with salvage chemotherapy.[7] Axicabtagene ciloleucel meets SMC end of life and ultra-orphan criteria for this indication.

A patient and clinician engagement (PACE) meeting was held to consider the added value of axicabtagene ciloleucel in the context of treatments currently available in NHSScotland. At the PACE meeting, attention was drawn to the physical symptoms and significant emotional and psychological impacts of DLBCL and PMBCL. Symptoms may include fatigue, pain, swollen lymph nodes, night sweats, raised temperature and weight loss. Patients can feel isolated and depressed as well as anxious about the future due to limited treatment options and poor outcomes. They may depend on family members to help with personal care due to increasing debility. Lymphoma is also associated with significant psychological distress for family members.Impact of new technology.

Summary of evidence on comparative efficacy

Key evidence to support the use of axicabtagene ciloleucel comes from the phase I/II, single-arm, open-label study (ZUMA-1). Phase I assessed the safety of axicabtagene ciloleucel in seven patients with refractory DLBCL and phase II assessed efficacy and safety in 111 patients with refractory DLBCL, PMBCL, or transformed follicular lymphoma (TFL) (that is DLBCL arising from follicular lymphoma). Eligible patients had histologically confirmed DLBCL, PMBCL, or TFL and refractory disease, defined as progressive or stable disease as the best response to the most recent chemotherapy or disease progression / relapse ≤12 months after ASCT. Patients had received at least one prior anti-CD20 antibody therapy and an anthracycline containing regimen and had no central nervous system involvement or active infections.[1, 3, 8]

Patients' white blood cells were collected by leukapheresis and transported to the central cell processing facility. Axicabtagene ciloleucel was then manufactured through stimulation of the T-cells and transduction with a retroviral vector containing the CAR gene. Patients received fixed low-dose conditioning chemotherapy which included fludarabine 30mg/m^2 body surface area (BSA)/day and cyclophosphamide 500mg/m^2 BSA/day on the fifth, fourth and third day before the administration of a single intravenous infusion of axicabtagene ciloleucel. Patients weighing <100kg received a target dose of 2×10^6 CAR T-cells/kg and those ≥100kg received a fixed dose of 2×10^8 CAR T-cells. The minimum dose was 1×10^6 CAR T-cells/kg. Systemic bridging chemotherapy was not allowed after leukapheresis and before the administration of axicabtagene ciloleucel. Patients who had an initial response

and then had disease progression at least three months after the first dose of axicabtagene ciloleucel could be retreated.[8]

The primary outcome was the objective response rate (ORR) which included complete and partial responses assessed by investigators according to the International Working Group Response Criteria for Malignant Lymphoma. The primary analysis was performed after 92 patients had a minimum of six months follow-up. At this time, after a median follow-up of 8.7 months, an ORR was achieved by 82% (75/92) patients (95% confidence interval [CI]: 72 to 98). This was significantly higher than the pre-specified historical control ORR of 20%, p<0.001. Complete response was achieved by 52% (48/92) of patients. Including all 101 patients who received study treatment at the time of the primary analysis, the ORR was also 82% (83/101) (95% CI 73 to 89) and complete response rate was 54%. Subgroup analysis in patients refractory to second-line (or more) therapy found an ORR of 83% (65/78) (95% CI: 73 to 91) and in patients who relapsed after ASCT, an ORR of 76% (16/21) (95% CI: 53 to 92).[8]

At the time of the primary analysis, the median duration of response was 8.1 months (95% CI: 3.3 to could not be estimated). Disease progression had occurred in 52 patients, 44 patients were in remission (39 had a complete response), three patients had died from adverse events during treatment, one patient had stable disease and one patient started an alternative therapy before disease progression. Of the patients who had disease progression after initial response, nine were retreated, five had a response (two complete and three partial) and two had an on-going response.[8]

An updated analysis (August 2017), performed after 108 patients in phases I and II had a minimum of 12 months follow-up (median follow-up of 15.4 months) found an ORR of 82% and a complete response of 58%, At the data cut-off, 42% remained in response, including 40% with a complete response. The median duration of response was 11.1 months (95% CI: 3.9 to could not be estimated). Efficacy data from this analysis were used in the economic evaluation. The median duration of progression-free survival was 5.8 months (95% CI: 3.3 to could not be estimated) and the median overall survival had not been reached. The progression-free survival rate was 41% (95% CI: 31 to 50) at 15 months, the overall survival rate was 52% (95% CI: 41 to 62) at 18 months. Two patients who had a response went on to receive allogeneic stem cell transplant (SCT).[8]

Results from a further updated analysis are available for patients in the phase II part of the study who had received study treatment (n=101). At a median follow-up of 27.1 months, the investigator assessed ORR was 83% (84/101) and 58% (59/101) of patients had a complete response. The median duration of response was 11.1 months (95% CI 4.2 to could not be estimated) and the median duration of progression-free survival was 5.9 months (95% CI 3.3 to 15). Ongoing response was observed in 39% of patients including 37% with a complete

response. Median overall survival had still not been reached (95% CI 12.8 to could not be estimated) and estimated two year survival rate was 50% (95% CI 40 to 60).[9]

A retrospective analysis of data from 17 US academic centres was conducted which included 295 patients who were leukapharesed as of 31 August 2018 with an intention to manufacture axicabtagene ciloleucel. In 238 evaluable patients (median follow-up 3.9 months) the day 30 ORR was 80% (191/238) and 47% (113/238) of patients had a complete response.[10]

Summary of evidence on comparative safety

The ZUMA-1 study was single-arm and there are no comparative safety data.

At the time of the primary analysis in the mITT population of the phase II study, 95% (96/101) of those who received axicabtagene ciloleucel experienced a grade ≥3 treatment-emergent adverse event. These included neutropenia in 78% (79/101), anaemia in 43% (43/101), thrombocytopenia in 38% (38/101), febrile neutropenia in 31% (31/101), encephalopathy in 21% (21/101), decreased white cell count in 29% (29/101), pyrexia in 14% (14/101), hypotension in 14% (14/101) and hyponatraemia in 10% (10/101) of patients.[8]

Cytokine release syndrome (CRS) occurred in 93% (94/101) of patients and was classed as grade ≥3 in 13% (13/101).The most common adverse events related to cytokine release syndrome were pyrexia in 76% (77/101), hypotension in 41% (41/101), hypoxia in 22% (22/101), tachycardia in 21% (21/101) and chills in 20% (20/101) of patients. The most common grade ≥3 adverse events related to cytokine release syndrome were pyrexia (11% [11/101], hypoxia (9% [9/101]) and hypotension (9% [9/101]) and vasopressors were used in 17% of patients. The median time to resolution was eight days and all events resolved apart from one grade 5 event of haemophagocytic lymphohistiocytosis. A grade 5 cardiac arrest occurred in a patient with cytokine release syndrome.[8]

Neurological events were experienced by 64% (65/101) patients who received axicabtagene ciloleucel. The most common grade ≥3 neurological event was encephalopathy (21%), confusional state (9%), aphasia and somnolence (both 7%). Tocilizumab was given to 43% of patients and glucocorticoids to 27% for the management of the CRS or neurological events (or both).[8]

At the August 2017 updated analysis, when patients had a minimum of one year follow up, ten patients experienced serious treatment-emergent adverse events. These were infections in eight of the patients (nine grade ≥3 infections occurred). No new cytokine release syndrome or neurological events related to study treatment were reported.[8]

At the most recent updated analysis, at least two years after infusion, the safety profile was generally similar. No new cases of cytokine release syndrome or neurological adverse events were reported. Cumulatively, 31% (33/108) of patients were given intravenous immunoglobulin therapy.[9]

Three patients died in the phase II part of the study due to adverse events. Two of these were related to axicabtagene ciloleucel due to cytokine release syndrome and one due to a pulmonary embolism that was not thought to be related to study treatment.[8] One patient died due to adverse events in the phase I part of the study, although they did have a grade 4 cytokine release syndrome the investigators deemed their death unrelated to study medication.[3]

Summary of clinical effectiveness issues

Axicabtagene ciloleucel was the first CAR T-cell therapy to be available for the treatment of DLBCL.[11] A similar product, tisagenlecleucel (Kymriah®), is licensed for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy.

The primary outcome of ZUMA-1 identified an ORR of 82% with a median duration of response of 11.1 months after follow-up for at least one year. The EMA considered that this was clinically relevant.[12] Median progression-free survival was 5.8 months and median overall survival had not been reached.[8] At a median follow-up of 27.1 months, median overall survival had still not been reached and the overall survival rate at 24 months was estimated as 50%. Ongoing response was observed in 39% of patients including 37% with a complete response.[9] Longer term data are required to confirm whether axicabtagene ciloleucel is a curative treatment.

The ZUMA-1 study has a number of limitations. There are no comparative data available as this is a single-arm study. Data on patient reported quality of life outcomes are very limited to a small proportion of patients within a safety management cohort. The study was open-label and since the ORR was assessed by investigators, there is a potential for bias. A retrospective, independent central review reported a lower ORR of 71% and complete response of 51%. Efficacy outcomes were assessed in patients who received axicabtagene ciloleucel. The EMA noted that all enrolled patients should be included as the overall treatment includes leukapheresis, chemotherapy and administration of axicabtagene ciloleucel. ORR in the ITT population based on central review (at least one year follow-up) was lower at 66% and complete response 47%. The EMA did however note that this was still larger than the results from the historical control.[12]

Subgroup analysis in patients with DLBCL found an ORR of 83% (63/77) which was consistent with the overall population. There was no subgroup analysis for the PMBCL only patients but in PMBCL and TFL patients, the ORR was 83% (20/24). The ZUMA-1 study population

was heavily pre-treated with 69% of patients having received at least three prior lines of therapy. In the subgroup of patients refractory to second-line or subsequent therapy, an ORR of 83% (65/78) (95% CI 73 to 91) was achieved and in patients who relapsed after ASCT, the ORR was 76% (16/21). In the ZUMA-1 study, retreatment with axicabtagene ciloleucel was allowed in patients who had an initial response and then had disease progression at least three months after the first dose.[8] However, no recommendations on retreatment are included in the SPC so it is unclear if this would reflect future clinical practice.[1]

CRS and neurological events have been commonly reported following the use of axicabtagene ciloleucel. Specific monitoring and management of adverse events are described in the SPC. Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.[1] Longer term safety data are as yet unavailable.

The submitting company presented results of an unanchored indirect comparison of ZUMA-1 with patient level data from SCHOLAR-1, an international, multi-cohort retrospective study of patients with refractory DLBCL (including PMBCL and TFL), to compare axicabtagene ciloleucel with salvage chemotherapy.[7] The SCHOLAR-1 study was a pooled analysis of data from two subsets of two randomised controlled studies and two retrospective databases and included treatment with a range of salvage chemotherapies. Outcomes compared were response rate, complete response and overall survival. The results were standardised for refractory status (based on Last Refractory Categorisation) and subsequent ASCT. A further standardised analysis included refractory status as covariate based on Last Refractory Categorisation and ECOG performance status. The standardised estimate was achieved by stratifying these covariates then weighting the SCHOLAR-1 outcomes based on the proportion of patients in the ZUMA-1 study in those strata. The Last Refractory Categorisation subgroup of the SCHOLAR-1 study was used which more closely matched the ZUMA-1 patients. However, there were some other differences in the baseline characteristics in SCHOLAR-1 compared with ZUMA-1 that were not accounted for in the standardisation process. More patients had DLBCL in SCHOLAR-1 (88%) compared with ZUMA-1 (76%). Patients in ZUMA-1 were more heavily pre-treated than patients included in SCHOLAR-1, more patients in ZUMA-1 had received three or more lines of previous therapy. The results suggested that patients who received axicabtagene ciloleucel in ZUMA-1 were significantly more likely to achieve a response or complete response compared to patients receiving chemotherapy in SCHOLAR-1. Treatment with axicabtagene ciloleucel was also associated with a significant improvement in overall survival compared with salvage chemotherapy. The comparison is limited by the heterogeneity between the ZUMA-1 and SCHOLAR-1 populations and within the SCHOLAR-1 population itself. Due to the retrospective nature of SCHOLAR-1, not all baseline data were assessed.

Clinical experts consulted by SMC considered that axicabtagene ciloleucel is a major therapeutic advancement due to the novel mechanism of action and unprecedented rate of

durable responses. The use of cellular therapy to treat patients with resistant or refractory disease was seen as a significant development.

At the PACE meeting, it was noted that axicabtagene ciloleucel could potentially achieve a durable response and be a life-extending treatment option for some patients who might otherwise be offered treatments that can only control their disease for a short time, or palliative care. Those who respond may no longer experience lymphoma related symptoms.

Patient and clinician engagement

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

The key points expressed by the group were:

- Patients with relapsed or refractory DLBCL or PMBCL whose disease fails to respond to second-line chemotherapy / ASCT have poor outcomes. Median overall survival has previously been reported at around six months. Patients are likely to experience significant physical and psychological symptoms related to their disease and diagnosis.
- There are limited treatment options, no standard treatment and a very high level of unmet need in these patients. Current treatments, which include chemo-immunotherapy combinations, have low response rates and significant side-effects. Chemotherapy is a considerable burden to the patient and service requiring successive courses, inpatient delivery / management of toxicity and subsequent issues (such as infection) and frequent follow up hospital attendances.
- Axicabtagene ciloleucel is a new type of personalised treatment and potentially a life-extending treatment option, giving a durable response in some patients. It is a one-off treatment, which could be an advantage to patients and their families / carers.
- Those who respond may no longer experience lymphoma-related symptoms, could become self-caring, may be able to return to work, regain their independence, participate in family activities and overall have improved quality of life. This may also result in reduced caring responsibilities and less psychological distress for patients' families.
- Axicabtagene ciloleucel has the potential for severe acute toxicity, and long-term treatment effects are unknown. It has considerable service implications. Patients would require significant initial monitoring, likely as an inpatient in an appropriate clinical facility with critical care support and specialist staff. However, this treatment may offer

the chance of long-term disease control in some patients and the benefits are likely to outweigh the risks.

Additional Patient and Carer Involvement

We received patient group submissions from Lymphoma Action and Bloodwise, both organisations are registered charities. Lymphoma Action has received 8.55% pharmaceutical company funding in the past two years, including from the submitting company. Bloodwise has received 0.9% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of the submissions from both organisations have been included in the full PACE statement considered by SMC.

Value for money

The submitting company presented a cost-utility analysis comparing axicabtagene ciloleucel to best supportive care (BSC), where BSC was assumed to be a blended comparator of different treatment regimens (gemcitabine and methylprednisolone [GEM]/ gemcitabine, methylprednisolone and cisplatin [GEM-P]/ rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone [RGCVP] and rituximab, vinblastine and prednisolone [RVP]). A lifetime (44 year) horizon was used.

A three-state partitioned survival model with health states of pre-progression, post-progression and death was used. The economic analysis was based on a 'mixture cure' model for axicabtagene ciloleucel; this structural assumption implies that axicabtagene ciloleucel itself potentially offers long term curative benefits (without the need to link better outcomes through providing a bridge to potentially curative transplants). It is noted that the modelling allowed for the use of subsequent SCT in both arms of the model. In ZUMA-1, 3% of patients underwent allogeneic SCT while in response to axicabtagene ciloleucel.

For overall survival (OS) and progression-free survival (PFS) for axicabtagene ciloleucel, data from the modified ITT population from the August 2017 cut of the ZUMA-1 combined phase 1 and 2 study were used via patient-level data (n= 108, median follow up 15.4 months); data from the latest August 2018 cut were not used as the company stated that these were largely consistent with the August 2017 data. As noted above, a mixture cure model was used for the extrapolation of OS; that is, an assumption that a proportion of patients will have a long-term remission and thus experience normal age/ sex adjusted background mortality, with standard parametric modelling applied to patients who did not experience long-term remission. The implied cure fraction using a Weibull mixture cure was 0.5, meaning 50% of patients treated with axicabtagene ciloleucel were assumed to be cured. For PFS, extrapolation was carried out using the Gompertz distribution.

In the absence of any directly comparative data, for the comparator arm, a multi-cohort retrospective analysis of two randomised studies and two registry studies, SCHOLAR-1, was used to provide corresponding patient-level data. Patients were selected if they met the refractory disease definition used in ZUMA-1. Adjustments were made to the SCHOLAR-1 dataset to remove patients with an ECOG score of 2-4 or unknown ECOG score and also primary refractory patients. A further adjustment was made to the data to reflect the proportion of patients who would be expected to receive SCT in clinical practice, on the basis that the 29% SCT rate seen in SCHOLAR-1 was unlikely to be reflective of the rates in practice. This latter adjustment was achieved by constructing a weighted average OS extrapolation by obtaining relevant patient-level data from SCHOLAR-1 who underwent SCT (n=67) and for the patients who did not receive subsequent SCT (n=66), fitting parametric survival curves to the two respective Kaplan Meier OS data and then creating a weighted average OS curve based on the best fitting curves and assumed weights of 90% not having a subsequent SCT and 10% having SCT. OS was extrapolated using standard parametric methods, and the generalized gamma distribution was used. SCHOLAR-1 did not collect PFS data and thus an assumption was made to estimate BSC PFS. It was assumed that the same ratio between PFS and OS at each point in the axicabtagene ciloleucel arm applied to the BSC arm.

The utility values for the base case states of PFS and progressed disease (PD) were taken from EQ-5D data that were collected in a sub-sample of the ZUMA-1 patients. A key assumption was made that for patients who remain in the PFS state for 2 years, their utility value would revert to that of the age/ sex matched general population. Disutilities for adverse events were included using literature values, and it is noted that for patients experiencing Grade 3 or 4 CRS, a utility value of zero was assumed for the duration of the event.

Costs for axicabtagene ciloleucel included the costs of leukapheresis, the conditioning regimen prior to infusion and the acquisition costs of the treatment. A length of stay of 17.6 days was assumed for the infusion and associated monitoring. The costs were also adjusted to take account of patients who had leukapheresis and conditioning therapy but who did not proceed to receive axicabtagene ciloleucel. Re-treatment in ZUMA-1 was possible (and 10/108 patients were retreated by 12 months). In terms of the economic analysis, only the extra costs associated with the necessary conditioning chemotherapy, cell infusion and monitoring were included for patients who received a second treatment; no additional costs for the acquisition of axicabtagene ciloleucel were included. The company stated that this was because the quantity of axicabtagene ciloleucel initially manufactured is normally sufficient for the delivery of up to 2 treatments and that the second treatment would be made available to the NHS at no additional cost.

Specific adverse event costs were applied for CRS and B-cell aplasia for axicabtagene ciloleucel patients. Grade 3 or 4 CRS was assumed to result in an ICU stay and the use of tocilizumab in a proportion of all patients with any grade of CRS. For B-cell aplasia, 6% of patients were assumed to require treatment with immunoglobulins for a period of 12 months. Ongoing care costs for patients in the PFS and PD states were taken from an expert survey of 3 clinicians which was used in a NICE submission. As with the assumption above regarding utilities, it was assumed that a patient remaining in PFS for 2 years would no longer require such ongoing care costs and monitoring.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

The incremental cost-effectiveness ratio (ICER) was £49,136 per quality adjusted life year (QALY). The vast majority of the incremental cost was comprised of the costs of axicabtagene ciloleucel itself and the QALY gains were all largely from the progression-free state.

A range of sensitivity analyses were presented and the key areas of upwards uncertainty are presented in the table below:

Table 1: Results of key sensitivity analyses at PAS price

	Sensitivity analysis	**ICER with PAS**
	BASE CASE	£49,136
1	Overall survival for axicabtagene ciloleucel - Weibull model cure fraction parameter value of -0.54 (implied cure rate= 37%)	£65,091
2	PFS for axicabtagene ciloleucel using Gamma distribution	£69,365
3	BSC OS distribution using log normal distribution	£46,531
4	Assuming an additional mortality risk for PFS patients (SMR of 1.41 for long term DLBCL survivors after 2 years)	£52,508
5	Utility of patients in PFS after 2 years to be 90% of age-matched population mortality	£53,644
6	Utility values for PFS patients revert to general population values at 5 years rather than at 2 years and no further medical resource use also assumed from year 5 rather than year 2	£52,111
7	Time horizon- 10 years	£101,668

8	Time horizon- 20 years	£60,320
9	Costs of immunotherapy for B Cell aplasia continue indefinitely rather than ceasing at 12 months	£52,750
10	Costs associated with PFS and PD states +50%	£51,660
11	No further medical resource use for PFS patients after 5 years (2 years assumed in base case) and 10 years	£51,377 - £55,000
12	Combined scenario analysis: SMR for 'cured' patients (SMR 1.41) PFS utilities at 90% of normal population values Utilities and background resource costs for PFS patients revert to population norms at year 5 PFS for axicabtagene ciloleucel based on gamma distribution	£77,494
13	50% or 100% of any second infusions incur the full treatment acquisition cost of axicabtagene ciloleucel	£51,644 - £54,152
14	15% SCT in BSC weighted average survival curve (10% in base case)	£49,570

As shown, the base case ICER is relatively high, and the sensitivity analysis presented in table 1 shows that the results are associated with further upward uncertainty when key variables in the model were revised. The main areas of uncertainty are noted below:

- There is a lack of directly comparative data and thus the economic analysis uses an indirect comparison method, which has a range of weaknesses. These include differences between the two patient populations and that SCHOLAR-1 did not collect PFS data and thus an assumption was necessary to derive PFS estimates.
- The model has a long time horizon relative to the available data on axicabtagene ciloleucel, and thus there will be uncertainty associated with the extrapolations used. Extrapolation using the cure assumption for axicabtagene ciloleucel in the base case gives rise to around 50% of patients treated with axicabtagene ciloleucel becoming long term survivors. This is associated with uncertainty given the novel nature of the therapy and level of maturity of the clinical data, even with the updated data which is helpful in confirming the estimated effects in the early years of the model. Using alternative parameter estimates for the cure fraction for OS for axicabtagene ciloleucel (to give a lower implied cure rate) also considerably increased the ICER (sensitivity analysis 1). Patients in the BSC arm of the model who enter the PFS state were not modelled on a consistent 'cure' assumption and the revised economic modelling submitted did not allow estimation of the impact of the use of cure modelling in both arms of the model.
- The analysis assumed reversion to normal population mortality rates for patients experiencing 'cure' with axicabtagene ciloleucel. This was felt to be an inappropriate assumption and it would be more reasonable to assume an ongoing increased mortality rate in this population. As shown in sensitivity analysis 5, the ICER was sensitive to changes in the base case assumption.
- There is also uncertainty associated with the extrapolation of PFS with axicabtagene ciloleucel; the gamma distribution could be considered a reasonable alternative approach and its use increased the ICER (sensitivity analysis 2)
- The analysis assumed reversion to normal population utility values after 2 years for patients in PFS, which the New Drugs Committee (NDC) felt may be optimistic. This is associated with uncertainty and other models in this area have assumed that this occurred at year 5 rather than year 2. As many of the gains are accrued in the PFS state, the values (and timings) used for this health state are important. Sensitivity analysis 5 and 6 indicate the impact of making alternative assumptions regarding ongoing utility values.
- The analysis assumed only 1 year of costs for treating B-cell aplasia. The results were sensitive to the impact of assuming a continuing cost of immunoglobulin therapy (sensitivity analysis 9).
- The analysis assumed there would be no extra acquisition costs for any patients

requiring a second treatment with axicabtagene ciloleucel (modelled as per the re-treatment pattern in the clinical trial). The company stated that axicabtagene ciloleucel is a single infusion therapy and that if a second infusion bag of the required quality had been prepared during the initial manufacture, it would be made available free of charge for any retreatment that was required. Given that there is some uncertainty as to whether a second infusion would always be available if needed and what would happen in such circumstances in terms of acquisition costs for a subsequent manufacturing of cells, the company provided additional analysis on request to show the impact of assuming that 50% and 100% of patients requiring a second infusion resulted in the full acquisition cost of axicabtagene ciloleucel. The impact of this is shown as sensitivity analysis 13 above.

- Ongoing PFS and PD resource use is from a small expert survey (thus associated with uncertainty) and it is assumed that patients in PFS after 2 years do not accrue any costs, which NDC felt lacked credibility. Other models have used a time point of 5 years for this assumption. Sensitivity analysis showed some impact from assuming a later point from which no costs apply or a variation in the costs used (sensitivity analysis 11). SMC clinical experts have advised that patients treated with axicabtagene ciloleucel would likely continue with ongoing monitoring and thus assuming no further costs from year 2 may be a bias.
- The analysis uses standard costs for hospital resources and only a small additional cost of training. There are no extra costs associated with the set-up of any new services for the delivery of a novel therapy. It should also be noted that no costs are assumed in the base case for patients who may need to stay locally for monitoring post-infusion (that is within 2 hours of the treatment centre for a 4 week period) but sensitivity analysis on this aspect showed only a small increase in the ICER.

*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 with multiple chemotherapy courses, the one-off treatment and 28 day monitoring period could offer an advantage to family, carers and friends as well as patients. Responding patients would be expected to recover and have improvement in their symptoms following the treatment. They could become self-caring, may be able to return to work, regain their independence, experience less psychological distress and overall have improved quality of life. They would be able to be participate in family activities and be there as a parent or grandparent for any children. This could reduce the caring duties of family and carers, who may also benefit from being able to spend good quality time with the patient.

Axicabtagene ciloleucel is administered as a single infusion however requires daily monitoring, likely as a hospital in-patient, for ten days after the infusion and the patient must remain close to the specialist treatment centre for four weeks after receiving treatment. The introduction of this medicine potentially requires new service specifications, workforce and infrastructure change due to specialist requirements for manufacture, administration and monitoring. Specialist services and suitably trained staff would be required for collection, storage and transport of patients' lymphocytes. Administration must be carried out in a hospital with appropriate facilities, specialist staff, and critical care bed capacity for managing potential adverse events. The introduction of axicabtagene ciloleucel would require additional consultant and medical support, specialist nursing, pharmacy and laboratory staffing. In addition, the extremely high upfront acquisition cost for this single-dose treatment is also 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 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 axicabtagene ciloleucel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as axicabtagene ciloleucel is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted axicabtagene ciloleucel for use in NHSScotland.

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.[6] This guidance predates the availability of axicabtagene ciloleucel 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.[6]

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 axicabtagene ciloleucel; 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]

An ESMO clinical practice guideline for diagnosis, treatment and follow-up of extranodal DLBCL and PMBCL published in 2016 is also available. The guideline notes that recurrence of PMBCL after successful initial treatment seems to be lower than for other DLBCLs. Treatment of relapsed or resistant disease is similar to nodal DLBCLs with salvage chemotherapy and ASCT in patients who are responsive to chemotherapy.[5]

Additional information: comparators

Treatment in this patient group is very limited and may include further salvage chemotherapy (with a number of different chemotherapy regimens). Other options would be enrolment in clinical studies or palliative care. A minority of patients who respond to third-line chemotherapy and are fit would proceed to allogeneic SCT.

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

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
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**
tisagenlecleucel	Intravenous infusion of 0.6 to 6.0 x 10^8 CAR-positive viable T cells (non-weight based)	282,000

Cost per course including shipping, engineering and generation of the CAR T-cells as stated in the company submission. Costs do not take any patient access schemes into consideration.

References

1. Kite Pharma Inc. YESCARTA (axicabtagene ciloleucel), Summary of Product Characteristics. 2017.
2. The European Medicines Agency. Committee for Orphan Medicinal Products. Public summary of opinion on orphan designation. Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor for the treatment of diffuse large B-cell lymphoma. EMA/COMP/736525/2014.
3. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM*, et al.* Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Mol Ther. 2017;25(1):285-95.
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. Ann Oncol. 2015;26 Suppl 5:v116-25.
5. Vitolo U, Seymour JF, Martelli M, Illerhaus G, Illidge T, Zucca E*, et al.* Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v91-v102.
6. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K*, et al.* Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol. 2016;174(1):43-56. Epub 05/20.
7. 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.
8. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA*, et al.* Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. The New England Journal of Medicine. 2017. Epub 10 December 2017.
9. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO*, et al.* Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. The Lancet Oncology. 2018;20(1):31-42.
10. Nastoupil LJ, Jain MD, Yaakov Spiegel J, et al. Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Large B-cell Lymphoma: Real World Experience. American Society for Heamatology (ASH) 60th Annual Meeting and Exposition San Diego, California, USA. December 1-4, 2018 2018. Abstract 91.
11. The European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) tisagenlecleucel (Kymriah). Summary of opinion. EMA/CHMP/289459/2018.
12. The European Medicines Agency (EMA) European Public Assessment Report. Axicabtagene ciloleucel (Yescarta®). 22/06/2018, EMEA/H/C/004480/0000. www.ema.europa.eu.

This assessment is based on data submitted by the applicant company up to and including 14 June 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: https://www.scottishmedicines.org.uk/media/3572/20180710-release-of-company-data.pdf*

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.