axicabtagene ciloleucel dispersion for infusion (Yescarta®)

Kite, a Gilead company

04 October 2024

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 orphan medicine process

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

Indication under review: for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

In a randomised, open-label, phase III study in patients with relapsed or refractory DLBCL or HGBL, axicabtagene ciloleucel significantly improved event-free survival compared with standard of care.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

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

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Axicabtagene ciloleucel is an advanced therapy medicinal product, which provides CD19-directed genetically modified autologous T-cell immunotherapy. To prepare axicabtagene ciloleucel, the patient's T cells are harvested and genetically modified ex vivo to express the anti-CD19 chimeric antigen receptor (CAR). Anti-CD19 CAR-positive viable T cells are expanded and intravenously infused back into the patient, who has received lymphodepleting chemotherapy, where they can recognise and eliminate CD19 expressing target cells. A single dose of axicabtagene ciloleucel contains a target dose of 2 x 10^6 (range: 1 × 10^6 to 2 × 10^6 cells/kg) CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above). Further information on pre-treatment with lymphodepleting chemotherapy, administration of axicabtagene ciloleucel, and monitoring is included in the Summary of Product Characteristics (SPC). [1]

1.2. Disease background

Large B-cell lymphoma (LBCL) represents a subset of aggressive Non-Hodgkin's Lymphoma (NHL) originating from B cells, which includes both the fast-growing DLBCL and HGBL. LBCL represents a predominant subtype of NHL, constituting 30% to 40% of cases and DLBCL accounts for more than 80% of LBCL cases (while HGBL accounts for up to 13% of LBCL cases). Patients have varying symptoms, which may include painless lumps, fevers, and fatigue. The prognosis of relapsed or refractory patients is extremely poor. [2-4]

1.3. Treatment pathway and relevant comparators

For patients who have primary refractory disease or disease that relapses after first-line chemo-immunotherapy, guidelines recommend second-line salvage treatment with multi-agent immunochemotherapy (such as rituximab with cisplatin, cytarabine, dexamethasone [R-DHAP], rituximab with ifosfamide, carboplatin, etoposide [R-ICE], rituximab with cisplatin, gemcitabine, dexamethasone [R-GDP]). In chemosensitive patients (that is, if there has been at least a partial response to chemotherapy), high-dose chemotherapy with autologous stem cell transplantation (auto-SCT) as remission consolidation should be considered. Consolidation with allogeneic SCT can also be considered for patients with chemosensitive disease that relapses after, or in whom stem cell harvesting is not possible. [5-8] Clinical experts consulted by SMC considered that patients not eligible for auto-SCT may receive polatuzumab in combination with bendamustine and rituximab (pola-BR) (SMC2524).

1.4. Category for decision-making process (if appropriate)

Eligibility for a PACE meeting

Axicabtagene ciloleucel meets SMC end of life and orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of axicabtagene ciloleucel in the licensed indication comes from the ZUMA-7 study (in patients intended for autologous stem cell transplant [ASCT]) and the single-arm ALYCANTE study (in older patients not intended for ASCT). Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	ZUMA-7 [4, 9]	ALYCANTE [10]
Study design	Phase III, randomised, open-label, active-controlled, international, phase III study	Phase II, single-arm, open-label study
Eligible patients	The key inclusion criteria were: • Aged ≥18 years with histologically proven LBCL including the following types defined by the WHO in 2016: DLBCL not otherwise specified (including ABC/GCB); HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement; DLBCL arising from follicular lymphoma; T-cell/histiocyte rich LBCL; DLBCL associated with chronic inflammation; Primary cutaneous DLBCL, leg type; Epstein-Barr virus-positive DLBCL • Refractory to or relapsed ≤ 12 months after first-line chemoimmunotherapy (at a minimum, anti-CD20 monoclonal antibody (unless CD20 negative) and an anthracycline-containing chemotherapy regimen) • Intended to proceed to HDCT/ASCT if there was a response to second-line therapy • Had radiographically documented disease • No known history or suspicion of central nervous system involvement by lymphoma • At least 2 weeks or 5 half-lives, whichever was shorter, had elapsed since any prior systemic cancer therapy at the time the patient provided consent • Eastern Cooperative Oncology Group performance status of 0 or 1	The key inclusion criteria were: • Aged ≥18 years with histologically proven aggressive B-cell non-Hodgkin lymphoma, diagnosed according to the 2016 WHO classification criteria as DLBCL; HGBL or follicular lymphoma grade 3B • Disease was refractory to or relapsed ≤12 months after completion of first-line chemoimmunotherapy containing a monoclonal CD20 antibody and an anthracycline-containing regimen (CHOP or CHOP-like regimen) • Patients were ineligible for HDCT/ASCT based on a physician's assessment and with at least one of the following criteria: ○ Age ≥65 years ○ HCT-CI score≥3 (as reported by investigators) ○ previous ASCT (as first-line consolidation)
Treatments	Axicabtagene ciloleucel was administered after a 3-day lymphodepleting chemotherapy regimen (consisting of fludarabine 30 mg/m^2/day and	Eligible patients underwent leukapheresis at enrolment to obtain enough peripheral blood mononuclear cells to produce

	cyclophosphamide 500 mg/m^2/day; followed by 2 rest days). A single infusion of axicabtagene ciloleucel was administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR-T cells/kg (for patients > 100 kg, maximum dose was 2 x 10^8 anti-CD19 CAR-T cells). Bridging therapy with corticosteroids was allowed prior to lymphodepleting chemotherapy at the discretion of the investigator, but chemoimmunotherapy was not allowed as bridging therapy. Standard of care consisted of protocol-defined salvage chemotherapy regimens (R-ICE, R-DHAP/R-DHAX, R-ESHAP, or R-GDP), administered every 2 to 3 weeks for 2 to 3 cycles. Responders were to proceed with HDT-auto-SCT per institutional or regional standards. Patients not responding to salvage chemotherapy could receive additional treatment off protocol.	axicabtagene ciloleucel, followed by conditioning therapy with cyclophosphamide (500mg/m^2/day) and fludarabine (30mg/m^2/day) for three consecutive days. Two to seven days later, patients received a single dose of axicabtagene ciloleucel (target dose of 2x10^6 CAR-T-cells/kg). Optional bridging therapy after leukapheresis consisted of corticosteroids and/or rituximab, gemcitabine and oxaliplatin (RGemOx).
Randomisation	Patients were randomised equally. Randomisation was stratified by response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) at screening.	N/A
Primary outcome	EFS defined as the time from randomisation to the earliest date of disease progression according to the Lugano classification, the commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomisation according to blinded central review.	Investigator-assessed complete response at 3 months from the axicabtagene ciloleucel infusion, according to the Lugano response criteria.[10, 11]
Secondary outcomes	• ORR defined as the incidence of either a complete response or a partial response by the Lugano Classification as determined by blinded central review. • OS defined as the time from randomisation to death from any cause.	Progression-free survival, OS and safety.
Statistical analysis	Hierarchical statistical testing strategy was applied for primary and key	Efficacy analyses were performed in modified full analysis set (mFAS;

	secondary efficacy outcomes (EFS, followed by ORR, then OS) with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation.	n=62), which included all patients who underwent leukapheresis (n=69, full analysis set [FAS]) and received a single infusion of axicabtagene ciloleucel.

Abbreviations: ABC, activated B-cell; ASCT, Autologous stem cell transplant; BCL2, B-cell lymphoma 2 apoptosis regulator; BCL6, B-cell lymphoma 6 transcription repressor; CAR, Chimeric antigen receptor; DLBCL, Diffuse large B-cell lymphoma; EFS, Event-free survival; GCB = germinal centre B-cell; HCT-CI, Haematopoietic cell transplantation-specific index; HDCT, High-dose chemotherapy; HGBL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; MYC, myelocytomatosis ORR, Objective response rate; OS, Overall survival; R-ICE rituximab with ifosfamide, carboplatin, etoposide; R-DHAP rituximab with cisplatin, cytarabine, dexamethasone; R-DHAX rituximab with dexamethasone, cytarabine, and oxaliplatin; R-ESHAP rituximab with etoposide. methylprednisolone cytarabine, cisplatin; R-GDP rituximab with gemcitabine, dexamethasone, cisplatin. SCT = stem cell transplant; WHO, World Health Organisation.

In ZUMA-7, axicabtagene ciloleucel significantly improved event-free survival (EFS) when compared with standard of care (SoC). Details of the primary and key secondary outcomes are presented in Table 2.2.

Table 2.2. Primary and key secondary outcomes in ZUMA-7 [4, 9, 12, 13]

	axicabtagene ciloleucel (n=180)	**SoC (n=179)**	**axicabtagene ciloleucel (n=180)**	**SoC (n=179)**
Data cut-off	**Primary EFS analysis–18 March 2021**		**Primary OS analysis–25 January 2023**	
Primary outcome: EFS by blinded central review				
Median follow-up	24.9 months.		-	
Event	108	144		
Median EFS, months, (95 % CI)	8.3 (4.5 to 15.8)	2.0 (1.6 to 2.8)		
Hazard ratio (95 % CI)	0.40 (0.31 to 0.51)			
Stratified p-value	P<0.001			
2-year EFS, %	40%	16%		
Key secondary outcome: ORR by blinded central review				
Responses, n (%)	150 (83 %)	90 (50 %)	-	
Difference (95 % CI)	33 % (23 to 42)			
Odds ratio (95 % CI)	5.31 (3.08 to 8.90)			
Stratified p-value	<.001			
Key secondary outcome: OS				
Median follow-up, months	24.7[a]	24.4[a]	47.2	
Deaths	72	85[b]	82	95
Median OS, months (95 % CI)	NR (28.3 to NE)	25.7 (17.6 to NE)[b]	NR (28.6 to NE)	31.1 (17.1 to NE)
Hazard ratio (95 % CI)	0.71 (0.52 to 0.97)[b]		0.73 (0.54 to 0.98)	
p-value	NS		P=0.03	

2-year OS, %	61%	51%[b]	60 %	51 %
4-year OS, %	-		55 %	46 %

Abbreviations CI, confidence interval; EFS, event-free survival; NE, not estimable; NR, not reached; NS, not significant; ORR, Objective response rate; OS, Overall survival; SoC, standard of care.

[a] median follow-up times for OS using the reverse Kaplan Meier method

[b] The OS data presented are from post-hoc analyses. These were updated after the EFS primary analysis data cut-off date as the company had obtained additional survival follow-up for patients discontinued from ZUMA-7 that was not initially available at the time of the EFS primary analysis but occurred before the data cut-off date.

In ZUMA-7, 30% of patients (n=109/359) were aged ≥ 65 years and the HR for EFS in this subgroup was 0.28 (95% CI: 0.16 to 0.48). Results of subgroup analyses are considered descriptive only as ZUMA-7 was not designed to test for differences between subgroups. [9]

The primary and key secondary outcomes in ALYCANTE are presented in Table 2.3.

Table 2.3 Primary and key secondary outcomes in ALYCANTE [10]

	axicabtagene ciloleucel (n=69 FAS; n=62 mFAS)
Primary outcome: investigator-assessed complete response at 3 months in mFAS (n=62)	
Median follow-up	12 months
Complete response (n, %)	44 (71%)
Key secondary outcomes	
Investigator-assessed ORR at 3 months (n, %)	47 (76%)
CRP-assessed complete response at 3 months (n, %)	41 (66%)
CRP-assessed ORR at 3 months (n, %)	43 (69%)
Median EFS from leukapheresis in FAS, months	12.3
Median PFS in mFAS, months	11.8

Abbreviations: ORR, objective response rate; CRP, central review panel; EFS, event-free survival; PFS, progression-free survival; FAS, full analysis set; mFAS, modified full analysis set.

Patients in ALYCANTE were older than those in ZUMA-7 (median age 70 years versus 59 years). A post hoc analysis that excluded two patients with grade 1 to 3A follicular lymphoma and four patients who achieved a complete response with bridging therapy showed a complete response of 68%, which is similar to the complete response reported in the mFAS.

The estimated EFS rates at 6 and 12 months were 67% and 51% respectively. The estimated PFS rates at 6 and 12 months were 68% and 49%. The study is ongoing with a planned follow-up of 3 years per patient to determine longer term efficacy and safety. [10]

2.2. Health related quality of life outcomes

In ZUMA-7, Health Related Quality of Life (HRQoL) was assessed using the Euro-QoL, 5 Dimensions, 5 Levels (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30). Patients treated with axicabtagene ciloleucel experienced a clinically meaningful improvement in quality of life compared to those receiving standard care. For the EORTC QLQ-C30 Global Health Status, the axicabtagene ciloleucel group showed a greater mean change from baseline with an estimated difference versus standard care of 18.1 by Day 100 and 9.8 by Day 150. Patients in this group reached or surpassed baseline scores by Day 100, in contrast to the standard care group, which reached this point by Month 9. Similarly,

for EORTC QLQ-C30 Physical Functioning, the axicabtagene ciloleucel group demonstrated a clinically meaningful improvement with an estimated difference versus standard care of 13.1 by Day 100, returning to or exceeding baseline scores by Day 150, whereas the standard care group achieved this by Month 12. The EQ-5D-5L VAS scores also favoured axicabtagene ciloleucel, with an estimated difference versus standard care of 13.7 by Day 100 and 11.3 by Day 150, with a return to or surpassing of baseline scores by Day 100, compared to Month 9 for the standard care group. [4]

Health Related Quality of Life data were not collected in the ALYCANTE study.

3. Summary of Safety Evidence

There are no new major safety concerns in this new population. Overall, the treatment-emergent adverse events (TEAEs) and risks were considered similar to what has been described for other CAR-T cell therapies and for axicabtagene ciloleucel in other indications, and are manageable with the current risk minimisation measures.[4] Patients must be monitored daily for the first seven days following infusion for signs and symptoms of potential cytokine release syndrome, neurologic events and other toxicities.[1]

In the ZUMA-7 study at data cut-off 25 January 2023 all patients reported treatment-emergent adverse event (AE). In the axicabtagene ciloleucel (N=170) and standard care (N=168) groups respectively, patients reporting a grade 3 or higher AE were 91% versus 83%, patients with a reported serious AE were 50% versus 46%. The most frequently reported treatment-emergent AEs of a grade 3 or higher with an incidence >10% in were: neutropenia (69% versus 41% in the axicabtagene ciloleucel group versus the standard care group), hypotension (11% versus 3%), anaemia (30% versus 39%), leukopenia (29% versus 22%), thrombocytopenia (15% versus 57%), hypophosphatemia (18% versus 13%), febrile neutropenia (3.5% versus 27%), and encephalopathy (12% versus 0).[12] Fatal AE considered treatment related by the investigators occurred in one patient treated with axicabtagene ciloleucel (hepatitis B virus reactivation) and in two patients in the standard care cohort (both events [cardiac arrest and acute respiratory distress syndrome] were considered by the investigators to be related to high-dose chemotherapy).[12]

In ALYCANTE, all patients reported at least one AE of any grade. AEs ≥ grade 3 were reported in 95% of patients (n=59/62). The most frequently reported AE of grade ≥3 were neutropenia (66%), anaemia (39%), thrombocytopenia (39%). There were six treatment related deaths, all due to infections: COVID-19 (n=2); aspergillosis (n=1); mucormycosis (n=1); sepsis (n=1); perineal infection (n=1).[10]

AEs of special interest related to CAR-T cell toxicities include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In ZUMA-7, CRS occurred in 92% of patients in the axicabtagene ciloleucel group (8% ≥ grade 3). In ALYCANTE, CRS was reported in 94% of patients (8.1% ≥grade 3) and ICANS occurred in 52% of patients, with 14% ≥grade 3. These were mainly managed with administration of tocilizumab (in 77% of patients) and/or corticosteroids (in 64% of patients). The observed toxicity observed with axicabtagene ciloleucel was similar to that observed in ZUMA-7. [10]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Results from the ZUMA-7 study suggest that axicabtagene ciloleucel exhibits superior efficacy as a second-line therapy in adult patients with refractory or relapsed DLBCL or HGBL within 12 months of first-line chemoimmunotherapy completion, when compared to SoC. This was supported by EFS, objective response rate, and overall survival (OS) data.
- The ALYCANTE study provided evidence of efficacy of axicabtagene ciloleucel in older patients who were considered ineligible for ASCT. Age ≥ 65 years was the primary reason for ineligibility for ASCT in ALYCANTE. In ZUMA-7, 30% of patients were aged ≥65 years and subgroup analyses showed efficacy in this population, although these results were descriptive only.
- Axicabtagene ciloleucel is the first CAR-T cell therapy licensed for second-line use in patients with DLBCL or HGBL.
- Clinically meaningful improvements were also observed in HRQoL outcomes for axicabtagene ciloleucel compared with SoC in ZUMA-7.
- In ZUMA-7, patients randomised to SoC were less likely to receive definitive treatment than those randomised to axicabtagene ciloleucel. In the SoC group, 36% of patients received ASCT whereas 94% of patients randomised to axicabtagene ciloleucel received this therapy.

4.2. Key uncertainties

- There are no comparative data in patients who were considered ineligible for ASCT as the ALYCANTE study was uncontrolled. The study was small and of relatively short duration for a definitive treatment.
- Patients in ALYCANTE were older that those in ZUMA-7 (median age of 70 years versus 59 years.
- The ZUMA-7 protocol did not allow use of salvage chemotherapy in the axicabtagene ciloleucel group; only glucocorticoids were allowed as bridging therapy. This contrasts with the ALYCANTE study in which most patients (82%) received bridging therapy with RGemOx. Clinical experts consulted by SMC suggested that in Scottish practice, some patients may receive salvage chemotherapy while awaiting axicabtagene ciloleucel manufacturing/delivery. The approach in ZUMA-7 might have reduced the number of patients for whom urgent treatment was indicated, potentially biasing results in favour of axicabtagene ciloleucel.
- In ZUMA-7, a high number of patients in the SoC group received subsequent cellular immunotherapy (57%). It is unclear whether this observed proportion in ZUMA-7 is significantly different from that which would be seen in Scottish practice.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that axicabtagene ciloleucel fills an unmet need in this therapeutic area due to limited treatment options and poor prognosis. They considered that it is a therapeutic advancement, with significantly improved outcomes, including overall survival, demonstrated in the ZUMA-7 study. They were supportive of use of axicabtagene in the licensed population, including in those patients who would be considered ineligible for ASCT, and noted that these patients would be eligible to receive axicabtagene ciloleucel in the third-line setting currently.

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine will have major implications for both patients and service delivery. Administration must be carried out in a hospital with appropriate facilities, specialist staff, and critical care bed capacity for managing potential adverse events. Increased hospitalisation is expected as seven days hospitalisation after the infusion are likely to be needed, and the patient must remain close to the specialist treatment centre for four weeks after receiving 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.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **axicabtagene ciloleucel**, as an **end of life and orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- DLBCL and HGBL are aggressive lymphomas causing severe symptoms like pain and lethargy, with rapid progression leading to very poor prognosis in the relapse/refractory setting, and a heavy impact on patients' daily life and mental health. These also place a substantial burden on carers and families.
- There is a significant unmet need for new therapies that would improve outcomes, including survival and quality of life, with a better side effect profile and reduced burden for patients.
- Axicabtagene ciloleucel has the potential to help address this unmet need by offering an alternative treatment option that could improve outcomes, including survival, cure rate, restoration of normal life expectancy and quality of life compared with existing standard of care with intensive second-line chemotherapy followed by autologous stem cell transplant.
- It also appears to be a gentler treatment with a more favourable side effect profile and quicker recovery compared with existing standard of care.
- The aggressive nature of the disease often prevents patients from reaching CAR T-cell therapy at third line and axicabtagene ciloleucel shift from third to second line use for relapsed/refractory patients will provide an earlier chance at a potentially curative treatment.

Additional Patient and Carer Involvement

We received patient group submissions from: Anthony Nolan, Blood Cancer UK and Lymphoma Action. All three organisations are registered charities. Anthony Nolan has received 0.01% pharmaceutical company funding in the past two years, including from the submitting company. Blood Cancer UK has received 1.6% pharmaceutical company funding in the past two years, including from the submitting company. Lymphoma Action has received 8.25% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three of the patient groups participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime time horizon defined as 50 years based on a starting age of 61 years in the model (assuming a 70:30 split between the mean-average ages of patients in ZUMA-7 and ALYCANTE studies) A cycle length of one month was used and half cycle correction was applied.
Population	Adult patients with primary refractory or early relapse (≤ 12 months from completion of first-line therapy) DLBCL. The company separated the population into two cohorts of equal size: (i) transplant intended (TI) and (ii) transplant not intended (TNI). Economic results for these cohorts were estimated separately and combined into a single result.
Comparators	The comparator considered in the economic evaluation differed depending on whether patients were considered TI or TNI. For TI patients, the comparator was salvage chemotherapy followed by HDT and ASCT in responders. The analysis considered a 'basket' of salvage chemotherapy regimens used in ZUMA-7.[9, 12, 13] For TNI patients, the comparator was chemotherapy only. Again, the analysis considered a 'basket' of different chemotherapy regimens based on feedback from clinical experts working in Scotland contacted by the company.
Model description	A *de novo* model was developed using a partitioned survival analysis framework. The model structure was comprised of five health states: three 'core' health states ('event-free', 'post-event', and 'death'), with 'event-free' and 'post-event' divided into two additional 'sub' health states each ('on treatment/on next treatment', 'off treatment/off next treatment') to account for differences in the

	costs and health effects accrued by patients whilst they are receiving active treatment for their disease. All patients start in the 'event-free' health state and can transition to any of the other 'core' health states at any point in time. After experiencing an 'event', the only transition available to patients was to the 'death' health state.
Clinical data	The key clinical data used to inform economic model, for both TI and TNI patients, was the 15th January 2023 data cut of the ZUMA-7 study.[9, 12, 13] Data from the single arm ALYCANTE study was used to validate the modelling of the TNI cohort receiving axicabtagene ciloleucel, while clinical trial and real-world data of current 2-L treatment options were used to validate the modelling of the TNI cohort receiving SoC.[10]
Extrapolation	The company primarily used a 'mixture-cure' modelling approach to extrapolate EFS, OS, and time-to-next-treatment (TTNT) data collected during ZUMA-7 to the time horizon used in the economic evaluation. A 'mixture-cure' model assumes the overall population can be 'split' into two separate groups: those who are cured of their disease (experience long-term remission) and those who are uncured of their disease (do not experience long-term remission). The 'mixture-cure' models used to extrapolate these outcomes in the company's base case analysis were selected based on a combination visual inspection of the estimated survival functions, goodness-of-fit statistics, and clinical expert feedback solicited by the company. This process selected the following functions for extrapolation for TI and TNI axicabtagene ciloleucel patients and SoC TI patients: EFS= log-logisitic, OS= generalised gamma and TTNT= log-logistic. For TNI patients receiving SoC, standard parametric log-logistic models were used to extrapolate EFS and TTNT.
Quality of life	Health benefits were estimated using a generic measure of health called a quality-adjusted life year (QALY). For the 'event-free' health state, health benefits were measured using EQ-5D-5L questionnaire data collected at specific time points during ZUMA-7.[9, 12, 13] For the 'post-event' health state, health benefits were measured using EQ-5D-5L questionnaire data collected during the ZUMA-1 study conducted in adult patients with refractory aggressive non-Hodgkin's lymphoma. Disutility associated with receiving active treatment and adverse events was also accounted for. The model assumed that patients estimated to be event-free at 5 years have HRQoL equivalent to the general population level for their age and sex.

Costs and resource use	Medication related costs for patients receiving axicabtagene ciloleucel included: leukapheresis, acquisition of bridging therapy, lymphodepleting (conditioning) chemotherapy, and axicabtagene ciloleucel, and administration for all medications received. Analogous costs for SoC included: acquisition of salvage chemotherapy regimens, HDT, and ASCT (responders only), and administration for all medications received. The specific costs included differed depending on whether a patient was considered TI or TNI. The cost of different types of subsequent therapies received by patients were also accounted for using a single 'one-off' cost. Other healthcare resource use included in the analysis constituted resources associated with ongoing monitoring for patients (e.g. general practitioner and district nurse appointments, radiographic imaging, outpatient appointments with consultants, laboratory- based tests, etc) and end of life care.
PAS	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. Under the PAS, a discount was offered on the list price. PAS discounts are in place for tisagenlecleucel, pembrolizumab, nivolumab, and polatuzumab, which were included as potential subsequent therapies received by patients. Discounts associated with these therapies were included in the results used for decision-making by using estimates of their PAS prices.

Abbreviations: HDT, high-dose therapy; EFS, event-free survival; OS, overall survival; TTNT, time-to-next-treatment; SoC, standard of care; auto-SCT, autologous stem cell transplant

6.2 Results

The base case economic results at list price for all medicines are provided in Table 6.2.

For the base case, the results indicate that treatment with axicabtagene ciloleucel is more costly but more effective than treatment with SoC, resulting in an incremental cost-effectiveness ratio (ICER) of £62,161 per QALY gained.

The results presented do not take account of the PAS for tisagenlecleucel, pembrolizumab, nivolumab, and polatuzumab or the PAS for axicabtagene ciloleucel in a third-line treatment setting, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for tisagenlecleucel, pembrolizumab, nivolumab, and polatuzumab due to commercial confidentiality and competition law issues.

Table 6.2: Base case economic results using list prices for all medicines

Technologies	**ICER (£/QALY)**
axicabtagene ciloleucel versus SoC	62,161

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Disaggregated analysis of total cost figures for axicabtagene ciloleucel and the SoC indicate that the majority of the increased costs associated with axicabtagene ciloleucel are due to its

acquisition price, the impact of which is reduced by a reduction in the cost of subsequent therapies. Comparable analysis of total life year figures for axicabtagene ciloleucel and SoC indicate that incremental life years for axicabtagene ciloleucel relative to the SoC are composed of a larger number of years in the 'event-free' health state, which is reduced by a lower number of years spent in the 'post-event' health state. Disaggregated analysis of total QALY figures for axicabtagene ciloleucel and the SoC are consistent with the life years analysis, incremental QALYs for axicabtagene ciloleucel relative to the SoC are composed of a larger number of years in the 'event-free' health state, which is reduced by a lower number of years spent in the 'post-event' health state.

6.3 Sensitivity analyses

The submitting company conducted a range of different types of sensitivity analyses, which highlighted particular areas of uncertainty regarding economic results.

A selection of these results at list price for all medicines are included in Table 6.3.

Table 6.3: Scenario analyses using list prices for all medicines

	Parameter	Base Case	Scenario	ICER (£/QALY)
	Base case			62,161
1	Time horizon	50 years	10 years	117,405
2			20 years	71,569
3	Extrapolation of EFS **(axicabtagene ciloleucel only)**	**Approach:** Mixture-cure model using log-logistic distribution	**Approach:** Mixture-cure model using generalised gamma distribution	61,557
4	Extrapolation of OS **(axicabtagene ciloleucel only)**	**Approach:** Mixture-cure model using generalised gamma distribution	**Approach:** Mixture-cure model using Weibull distribution	61,568
5			**Approach:** Mixture-cure model using log-logistic distribution	68,099
6	Extrapolation of EFS **(TNI patients, SoC only)**	**Approach:** Standard parametric log-logistic model	**Approach:** Standard parametric generalised gamma model	63,668
7	Proportion of patients fit enough to receive 3-L therapies **(TNI patient group only)**	87% of patients fit enough	67% of patients fit enough	79,233
8			98% of patient fit enough	52,685
9	Proportion of patients receiving axicabtagene ciloleucel at 3-L **(SoC only)**	60% of patients alive at 3-L stage	48% of patients alive at 3-L stage	80,948
10			72% of patients alive at 3-L stage	43,372
11	Leukapheresis costs	Include as NHS costs	Exclude as NHS costs	61,258

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EFS, event-free survival; OS, overall survival; SoC, standard of care; HRQoL, health related quality of life; 3-L, third-line

Key strengths

- The ZUMA-7 study provides clinical data comparing the efficacy of axicabtagene ciloleucel versus a comparator that appears to constitute SoC in the TI patient group within the context of NHS Scotland. The availability of such 'direct evidence' to inform the economic evaluation reduces uncertainty regarding the influence of confounding variables on relative efficacy, which are a concern when clinical data is drawn from multiple different sources ('indirect evidence').
- HRQoL data from ZUMA-7 using the EQ-5D-5L questionnaire (the preferred method for SMC submissions) was available to inform the quality of life experienced by patients in the 'event-free' health state of the economic model.

Key uncertainties

- While the submitting company indicated that data from the ALYCANTE study provides validation for the modelling for TNI patients treated with axicabtagene ciloleucel and had conservatively assumed that outcomes for the TNI patients treated with standard of care would be the same as observed in ZUMA-7 for TI patients, there are uncertainties in using data from the ZUMA-7 study to extrapolate health outcomes for TNI patients. If health outcomes for TNI patients are poorer over the long term than found in this study then the cost-effectiveness of axicabtagene ciloleucel could be overestimated.
- The follow-up period of ZUMA-7 based on the data cut provided (25 January 2023) is relatively short compared to the time horizon over which the economic evaluation is conducted (50 years). The implications of this in terms of economic results are that clinical outcomes require a significant degree of extrapolation, introducing a large degree of uncertainty in economic results. The impact of this uncertainty can be viewed in scenarios 3-6 above where alternative methods for extrapolating data from ZUMA-7 for axicabtagene ciloleucel and SoC are used.
- Cost-effectiveness results were sensitive to the assumed proportion of patients in the TNI patient group fit enough to receive third-line therapies which was based on a chart review of DLBCL patients. Note that a larger proportion of patients receiving additional therapies improves the cost-effectiveness of axicabtagene ciloleucel due to higher costs among SoC patients (see scenarios 7 and 8).
- The proportion of patients in the axicabtagene ciloleucel and SoC groups receiving different types of therapy in the 'post-event' health state was based on a combination of data from ZUMA-7 and clinical expert feedback. Sensitivity analysis around the company's base case assumption regarding the proportion of patients in the SoC group receiving CAR-T therapies at a later line of treatment shows a significant impact on economic results (see scenarios 9 and 10). Note that a larger proportion of patients in this group receiving CAR-T therapies improves the cost-effectiveness of axicabtagene ciloleucel due to the high cost of these therapies.

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

7. Conclusion

The Committee also 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 the criterion for a substantial improvement in quality of life was satisfied. In addition, as axicabtagene ciloleucel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted axicabtagene ciloleucel for use in NHSScotland.

8. Guidelines and Protocols

The European Society for Medical Oncology published in August 2015 'Recommended treatment strategies in diffuse large B-cell lymphoma >2 relapse/progress'.[6]

In 2016 the British society for haematology published guidelines for the management of diffuse large B-cell lymphoma.[7]

In 2016 the National Institute for Health and Care Excellence published guidance on Non-Hodgkin's lymphoma: diagnosis and management (NG52).[5]

The National Comprehensive Cancer Network (NCCN) published in October 2023: NCCN Clinical Practice Guidelines in Oncology - B-Cell Lymphomas, Version 6.2023.[8]

9. Additional Information

9.1. Product availability date

19 December 2022

Table 9.1 List price of medicine under review

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 dose 2 × 10^8 CAR-positive viable T cells for patients ≥100 kg**	**280,451**

Costs from Dictionary of Medicines and Devices Browser on 05 July 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 89 patients eligible for treatment with axicabtagene ciloleucel in year 1 rising to 90 in year 5, to which confidential estimates of treatment uptake were applied.

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with treatments later in the treatment pathway.

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

References

1. Gilead Sciences Ltd. Yescarta 0.4 – 2 × 10^8 cells dispersion for infusion - summary of product characteristics (SPC). Last updated: July 2023. Available at: www.medicines.org.uk.

2. Olszewski AJ, Kurt H, Evens AM. Defining and treating high-grade B-cell lymphoma, NOS. Blood. 2022;140(9):943-54. 10.1182/blood.2020008374

3. Lymphoma Action. Non-Hodgkin lymphoma. 2023. Available at: https://lymphoma-action.org.uk/types-lymphoma/non-hodgkin-lymphoma.

4. The European Medicines Agency (EMA) European Public Assessment Report. Yescarta (axicabtagene ciloleucel) variation assessment. 15 September 2022. EMA/804955/2022. Available at: http://www.ema.europa.eu.

5. National Institute for H, Care E. Non-Hodgkin's lymphoma: diagnosis and management (NG52). 2016 [cited; Available from: https://www.nice.org.uk/guidance/ng52/evidence.

6. 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. Epub 2015/09/01.

7. 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.

8. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology - B-Cell Lymphomas, Version 6.2023 published in October 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

9. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO*, et al.* Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386:640-54. Epub Dec 11. 10.1056/NEJMoa2116133

10. Houot R, Bachy, E., Cartron, G. et al. Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial. Nature medicine. 2023;29:2593-601. https://doi.org/10.1038/s41591-023-02572-5

11. Cheson BD FR, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

12. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A*, et al.* Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med. 2023. Epub 2023/06/05. 10.1056/NEJMoa2301665

13. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A*, et al.* Primary Overall Survival Analysis of the Phase 3 Randomized ZUMA-7 Study of Axicabtagene Ciloleucel Versus Standard-of-Care Therapy in Relapsed/Refractory Large B-Cell Lymphoma. ASCO Annual Meeting. Chicago, IL: US; 2023.

This assessment is based on data submitted by the applicant company up to and including 16 August 2024.

**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/about-us/policies-publications/

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.