Axicabtagene ciloleucel (Yescarta®) for the treatment of patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL)

General information

Drug description [1]	Indication [2]
Axicabtagene ciloleucel (Yescarta®, axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy.	Axicabtagene ciloleucel (Yescarta®) is indicated for the treatment of adult patients with DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Current treatment [3]

- Currently, there are no NICE guidelines regarding relapsed or refractory disease after failure of first-line chemoimmunotherapy.
- In the UK, the most widely used treatment for DLBCL presently is the combination known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The R-CHOP regimen is usually given in 21-day cycles (once every 21 days) for an average of 6 cycles. However, the length and number of cycles given can vary based on the patient's individual disease and health status. In certain cases 14-day cycles may be used, and for limited stage disease (Stage I or II) 3-4 cycles may be used followed by radiation therapy.

Regulatory status

EMA [2]

Approval status for this indication: On 15 September 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Yescarta®. As Yescarta® is an advanced therapy medicinal product, the CHMP positive opinion is based on an assessment by the Committee for Advanced Therapies.

The CHMP adopted an extension to the existing indication:

- Yescarta® is indicated for the treatment of adult patients with DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Other indications: Yescarta® is indicated for the treatment of:

- adult patients with relapsed or refractory (r/r) DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.
- adult patients with r/r follicular lymphoma (FL) after three or more lines of systemic therapy.

✓ **Orphan status**
✓ **Medicine under additional monitoring**

FDA [4-6]

Approval status for this indication: not approved

Other indications:

- On 1 April 2022, the FDA approved axicabtagene ciloleucel (Yescarta®) for adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy. It is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.
- On 18 October 2017, the FDA granted regular approval to axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, HGBL, and DLBCL arising from FL.
- Yescarta® is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate.

Costs

Currently, there is no cost information available for the treatment of patients with DLBCL and HGBL. For comparison, the manufacturer announced that the cost of axicabtagene for the treatment of advanced lymphoma will be $373,000 per infusion [7].

Posology [8]

- Yescarta® is intended for autologous use only.
- Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one infusion bag. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (within a range of $1 \times 10^6 – 2 \times 10^6$ cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above.
- The availability of Yescarta® must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² IV and fludarabine 30 mg/m² IV must be administered prior to infusing Yescarta®. The recommended days are on the 5th, 4th, and 3rd day before infusion of Yescarta®.

Pre-medication

- Paracetamol 500-1 000 mg given orally and diphenhydramine 12.5 to 25 mg IV or oral (or equivalent) approximately 1 hour before Yescarta® infusion is recommended.
- Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of Yescarta®.

Warnings and precautions [6, 8]

- **Cytokine release syndrome (CRS)**
  - CRS, including fatal or life-threatening reactions, occurred in patients receiving Yescarta®.
  - Do not administer Yescarta® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- **Neurologic toxicities**
  - Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving Yescarta®, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with Yescarta®. Provide supportive care and/or corticosteroids, as needed.
- **Hypersensitivity reactions**
  - Monitor for hypersensitivity reactions during infusion.
- **Serious infections**
  - Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged cytopenias**
  - Patients may exhibit Grade 3 or higher cytopenias for several weeks following Yescarta® infusion.
  - Monitor complete blood counts.
- **Hypogammaglobulinemia**
  - Monitor and provide replacement therapy.
- **Secondary malignancies**
  - In the event that a secondary malignancy occurs after treatment with Yescarta®, contact the manufacturer.
- **Effects on ability to drive and use machines**
  - Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving Yescarta®.
- **FDA**: Yescarta® is available only through a restricted program under a **Risk Evaluation and Mitigation Strategy (REMS**) called the Yescarta® and TECARTUS REMS Program.
- **HBV reactivation**
  - HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B-cells. Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta®.
- **Tumour lysis syndrome (TLS)**
  - TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Yescarta® infusion.
  - Signs and symptoms of TLS must be monitored and events managed according to standard guidelines.
- **CD19-negative disease**
  - There is limited experience with Yescarta® in patients exposed to prior CD19-directed therapy. Yescarta® is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.
  - There are limited data available on CD19-negative patients treated with Yescarta® and it is possible that CD19-negative patients may have less benefit compared with CD19-positive patients. Patients with CD19-negative status by immunohistochemistry may still express CD19 and have been shown to benefit from treatment with Yescarta®. The potential risks and benefits associated with treatment of CD19-negative patients with Yescarta® should be considered.
- **Long-term follow-up**
  - Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Yescarta®.
- **Excipients (sodium)**
  - This medicinal product contains 300 mg sodium per infusion bag, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult
- **Traceability**

- The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the product.

❖ **Autologous use**
- Yescarta® is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Yescarta® infusion bag and cassette. Yescarta® must not be administered if the information on the patient-specific infusion bag and cassette label does not match the patient's identity.

❖ **Monitoring after infusion**
- Patients must be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient is to be monitored at the physician's discretion.
- Patients are to be counselled to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Vital signs and organ function must be monitored depending on the severity of the reaction.

❖ **Reasons to delay treatment**
- Due to the risks associated with Yescarta® treatment, infusion must be delayed if a patient has any of the following conditions:
  - Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
  - Active uncontrolled infection.
  - Active graft-versus-host disease.

❖ **Serological testing**
- Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta®.

❖ **Blood, organ, tissue and cell donation**
- Patients treated with Yescarta® must not donate blood, organs, tissues, or cells for transplantation.

❖ **Concomitant disease**
- Patients with active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

❖ **Primary CNS lymphoma**
- There is no experience of use of Yescarta® in patients with primary CNS lymphoma. Therefore, the risk/benefit of Yescarta® has not been established in this population.

Study characteristics [1, 9-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ZUMA-7 NCT03391466	359 (1:1)	leukapheresis, followed by conditioning chemotherapy[1] before a single infusion of axi-cel (target dose, 2×10^6 CAR T cells per kilogram of body weight)	2 or 3 cycles of protocol-defined, investigator-selected, platinum-based chemoimmunotherapy	event-free survival according to blinded central review	**ongoing**[2], international, open-label, randomised, phase 3 trial	-	Kite	[1]
Efficacy (I vs. C); primary and key secondary analyses data							**Safety** (I vs. C); primary and key secondary analyses data	

[1] With cyclophosphamide (at a dose of 500 mg per m² of body-surface area per day) and fludarabine (30 mg per square meter per day) at −5, −4, and −3 days before receiving axi-cel. Optional bridging therapy was limited to glucocorticoids only.

[2] The ZUMA-7 trial is currently ongoing; estimated study completion date is 01/2035.

Median event-free survival: 8.3 months (95% CI, 4.5-15.8) vs. 2.0 months (95% CI, 1.6-2.8)
Estimated event-free survival at 24 months: 41% (95% CI, 33-48) vs. 16% (95% CI,11-22)
HR for event or death: 0.40 (95% CI, 0.31-0.51; p<0.001)
Patients with a response: 83% vs. 50% (difference, 33 percentage points; p<0.001)
Complete response: 65% vs. 32%
Median OS (evaluated as an interim analysis): NR vs. 35.1 months; HR for death 0.73 (95% CI, 0.53-1.01; p=0.054; statistical significance NR)
Estimated OS at 2 years (in the interim analysis): 61% vs. 52%
Patients who died from any cause: 40% and 45%
Patients who died from progressive disease: 29% vs. 36%
Patients in group C who received subsequent cellular immunotherapy: 56%
Median PFS: 14.7 months (95% CI, 5.4-could not be estimated) vs. 3.7 months (95% CI, 2.9-5.3); HR for progression or death 0.49; 95% CI, 0.37-0.65)
Estimated PFS at 24 months: 46% (95% CI, 38-53) vs. 27% (95% CI, 20-35)

- Patients who had a complete or partial response proceeded to high-dose chemotherapy with autologous stem-cell transplantation.
- Although crossover between the treatment groups was not planned, patients who did not have a response to standard care could receive cellular immunotherapy outside the protocol (**treatment switching**).

CAR T-Cell Levels

- The median time to peak CAR T-cell levels was 7 days (range, 2-233) after the axi-cel infusion.
- The median peak CAR T-cell level was 25.84 cells per cubic millimeter with CAR T-cells remaining detectable in 12 of 30 patients (40%) who could be evaluated by 24 months. The CAR T-cell peak and area under the curve within the first 28 days after treatment correlated with response (data not shown), findings that were consistent with those observed in the ZUMA-1 study.
- No occurrences of anti–axi-cel antibodies were confirmed.

AEs of grade ≥3: n=155/170 (91%) vs. n=140/168 (83%)
Serious AEs of any grade: 50% vs. 46%
Various infections of any grade: 41% vs. 30%
Infections of grade ≥3: 14% vs. 11%
Prolonged cytopenias of grade ≥3 that were present at or after 30 days after the initiation of definitive therapy: 29% vs. 19%
Fatal adverse events: 4%[3] vs. 1%[4]
CRS in patients who received axi-cel: 92% (with an event of grade ≥3 or higher in 6%)
Neurologic events of grade ≥3: 21%

Patient-reported outcomes [12]

- 296 patients (165 vs. 131) met criteria for the QoL analysis set, which required a baseline PRO plus at least 1 follow-up measure.
- **EORTC QLQ-C30 physical functioning, EORTC global health status/QoL, and EQ-5D-5L VAS**
  - For patients in the QoL analysis set, impairment in both arms compared with baseline was observed at day 50.
  - At day 100, there was a **statistically significant and clinically meaningful difference** in mean change of scores from baseline in favour of axi-cel for the prespecified hypothesis endpoints of EORTC QLQ-C30 global health status/QoL (estimated difference, 18.1; 95% CI, 12.3-23.9; adjusted p< .0001), EORTC QLQ-C30 physical functioning (13.1; 95% CI, 8.0-18.2; adjusted p< .0001), and EQ-5D-5L VAS (13.7; 95% CI, 8.5-18.8; adjusted p< .0001).
  - Sensitivity analyses showed similar results with retained significance at day 100.
  - Furthermore, scores significantly favoured axi-cel over SOC for global health status/QoL (estimated difference 9.8; 95% CI, 2.6-17.0; adjusted p= .0124) and EQ-5D-5L VAS (11.3; 95% CI, 5.4-17.1; adjusted p= .0004) at day 150; this difference was clinically meaningful for EQ-5D-5L VAS.
  - For the prespecified endpoints, the mean estimated scores for the axi-cel arm had numerically returned to or exceeded scores at baseline by day 150 vs. month 9 or later for the SOC arm.
- **Exploratory PRO analyses**
  - Additional exploratory analyses of PRO endpoints also showed improvements with axi-cel over SOC.
  - The differences in change from baseline were all in favour of axi-cel for nausea and vomiting, diarrhoea, insomnia, and appetite loss measures at day 100; role functioning at day 100 and day 150; and social functioning, fatigue, and dyspnoea measures at day 100, day 150, and month 9.

[3] Of which one event (hepatitis B virus reactivation) was considered by the investigators to be related to axi-cel.
[4] Both events (cardiac arrest and acute respiratory distress syndrome) were considered by the investigators to be related to high-dose chemotherapy.

- The differences in change from baseline for the EQ-5D-5L index (United States value set) was in favour of axi-cel at day 100 (estimated difference, 0.081; 95% CI, 0.024-0.138; adjusted p= .0112).
- Patients treated with axi-cel had significantly lower mean absenteeism and lower mean activities impairment at day 100 than those treated with SOC. Results were similar when models were adjusted for patterns of missingness and other covariates.
- Within exploratory TUDI analyses, for the EORTC QLQ-C30 global health status/QoL, there was no significant difference demonstrated in TUDI (HR, 1.24; 95% CI, 0.7-2.21), though a numerically greater proportion of patients experienced improvement in the axi-cel arm compared with patients in the SOC arm.
- This was similar for EORTC QLQ-C30 physical functioning (HR, 1.89; 95% CI, 0.79-4.53) and the EQ-5D-5L VAS (HR, 1.52; 95% CI, 0.94-2.45).
  For EORTC QLQ-C30 dyspnoea, the difference in TUDI was statistically significant in favour of axi-cel (HR, 2.59; 95% CI, 1.27-5.29; p=.0060).

ESMO-MCBS version 1.1 [13]

Disclaimer: Though not finally validated, but feasibility tested in [14], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, the original ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original		2b	≤6 months	EFS:+6.3 months	0.40 (0.31-0.51)	HR ≤0.65 AND gain ≥1.5months	3	-	QoL improvement	+1	4

Risk of bias (RCT) [15]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	no, open-label	unclear[5]	yes[6]	high

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CRS=cytokine release syndrome, DLBCL=diffuse large B-cell lymphoma, EMA=European Medicines Agency, EORTC=European Organization for Research and Treatment of Cancer, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FL=follicular lymphoma, FM=final magnitude of clinical benefit grade, HBV=hepatitis B virus, HCV=hepatitis C virus, HGBL=high-grade B-cell lymphoma, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, Int.=intention, LBCL=large B-cell lymphoma, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, NR=not reached, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-cell lymphoma, PRO=patient-reported outcome, QLQ-C30=Quality of Life Questionnaire Core 30, QoL=quality of life, r/r=relapsed or refractory, SAE=serious adverse event, SOC=standard-of-care, ST=standard treatment, TLS=tumour lysis syndrome, TUDI=time until definitive improvement, VAS=visual analogue scale, WHO=World Health Organization

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[5] Primary and key secondary analyses data available; the ZUMA-7 trial is ongoing until 01/2035.
[6] The trial sponsor and the authors collaborated on the trial design and the data collection, analysis, and interpretation. The first draft was written by the first and last authors, with medical writing assistance funded by the sponsor, and high crossover.

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