Axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL)

General information

Drug description	Indication [1]
Axicabtagene ciloleucel (Yescarta®) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy.	Axicabtagene ciloleucel (Yescarta®) is indicated for the treatment of adult patients with relapsed or refractory FL after three or more lines of systemic therapy.

Current treatment [2]

- ❖ According to ESMO guidelines, in early relapses of asymptomatic cases in follicular lymphoma, a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP, or vice versa).
- ❖ In symptomatic cases with low tumour burden, rituximab monotherapy may be applied.

Regulatory status

EMA [1]

Approval status for this indication: On 22 April 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Yescarta®.

The CHMP adopted a new indication:

- ❖ Yescarta® is indicated for the treatment of adult patients with relapsed or refractory FL after three or more lines of systemic therapy.

Other indications:

- ❖ Yescarta® is indicated for the 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.

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

FDA [3, 4]

Approval status for this indication: On 5 March 2021, the FDA granted accelerated approval to axicabtagene ciloleucel (Yescarta®) for adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

- ✓ Indication approved under accelerated approval based on response rate
- ✓ Priority review
- ✓ Breakthrough designation
- ✓ Orphan drug designation

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

- ❖ Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- ❖ Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high grade B-cell lymphoma, and DLBCL arising from FL.
- ❖ Limitations of Use: Yescarta® is not indicated for the treatment of patients with primary central nervous system lymphoma.

Costs

For the treatment of advanced lymphoma, the manufacturer announced that the cost of axicabtagene will be $373,000 [5].

Posology [6]

- ❖ Yescarta® must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Yescarta®.
- ❖ At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

Posology

- ❖ Yescarta® is intended for autologous use only.
- ❖ A single dose of Yescarta® contains 2 x 106 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 108 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.
- ❖ 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®.

❖ Monitoring
- 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 or symptoms of CRS and/or neurologic events. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion. Patients must be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Warnings and precautions [3]

❖ **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®.

❖ Yescarta® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Yescarta® and Tecartus™ REMS Program.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ZUMA-5 NCT03105336	148[1]	single IV infusion of axicabtagene ciloleucel at	-	overall response rate[2]	**ongoing**[3], multicentre, single-arm, registrational, phase 2 trial	-	Kite, a Gilead Company	[8]

[1] 153 patients with indolent non-Hodgkin lymphoma were enrolled (83% with FL, 16% with marginal zone lymphoma, and 1% who was later determined to have diffuse large B-cell lymphoma).
[2] Complete response and partial response, assessed by an independent review committee per Lugano classification.
[3] The ZUMA-5 trial is currently ongoing; estimated study completion date is 02/2037.

		a target dose of 2 × 10^6 CAR T cells per kg						

Efficacy	Safety
Median follow-up for the **primary activity analysis**: 17.5 months (IQR 14.1–22.6) **Overall response**: 92% (95% CI 85–97), with 74% having a best response of a complete response **Patients with FL (n=84)**: 94% (95% CI 87–98) had an overall response, with 79% having a complete response **Patients with marginal zone lymphoma** (n=20): 85% had an overall response, with 55% having a complete response. **Prespecified updated analysis** with a median follow-up of 23.3 months (IQR 20.0–28.0) **Overall response**: 92% (95% CI 85–96), including 94% (95% CI 87–98) of patients with FL and 83% of patients with marginal zone lymphoma. **Complete response**: 76%, including 79% of patients with FL and 65% of patients with marginal zone lymphoma **Partial response**: 16% **Median time to initial response**: 1 month (IQR 1–1) **Median time to initial complete response**: 1 month (IQR 1–3) in patients with FL and 3 months (1–5) in patients with marginal zone lymphoma. **Response** among patients who received at **least 3 previous lines of therapy** (95% of 76 who were eligible for the activity analysis): 95% of patients with FL, 94% of patients with marginal zone lymphoma **Complete response** in 79% (80% with follicular lymphoma, 75% with marginal zone lymphoma Estimated **PFS at 18 months**: 64.8% (95% CI 54.2–73.5) **18-month OS**: 87.4% (95% CI 79.2–92.5) **Disease progression or death** (as of data cutoff for the updated analysis): in 33% (31% of patients with FL, 39% of patients with marginal zone lymphoma) **Median time to next treatment**: not reached (95% CI not estimable to not estimable) 3% of patients with FL underwent **subsequent SCT** (1 autologous; 3 allogeneic) due to disease progression. **UPDATE: 24-month analysis (all leukapheresed; n= 75)** Objective response: 91% (95% CI, 82-96) Complete response: 77% Partial response: 13% Median duration of response: 38.6 (95% CI, 24.7-NE) Ongoing response: n=42 Rate of continued remission: - 12 Month: 79.5% (95% CI, 67.2-87.6) - 18 Month: 75.5% (95% CI, 62.5-84.6) - 24 Month: 67.6% (95% CI, 52.7-78.7)	**Treatment-emergent AEs of any grade:** 147/148 (99%) **AEs grade ≥3:** 128/148 (86%) **SAEs of any grade:** 74/148 (50%) **Cytokine release syndrome grade ≥3:** 10/148 (7%) **Neurological events:** 87/148 (59%) **Infections grade ≥3:** 26/148 (18%) **Deaths among patients with FL:** 15/124 (12%) **Deaths among patients with marginal zone lymphoma:** 4/24 (17%) **Deaths within 3 months of infusion:** 2 (with 1 death related to axicabtagene ciloleucel) **Deaths after 3 months after infusion:** 17 (none of these deaths were determined to be due to treatment) **Death due to progressive disease:** 9/124 (7%) patients with FL and 1/24 (4%) with marginal zone lymphoma; 1/124 (1%) patient with FL died due to secondary malignancy, 1/124 (1%) patient with FL died of infection after partial withdraw of consent and 3 (2%) patients died of unknown causes. **Deaths due to AEs:** 4 (3%)[4]

[4] Including 1 (1%) with FL who had multisystem organ failure, which was determined to be **related** to axicabtagene ciloleucel. Grade 5 aortic dissection occurred 399 days after infusion in 1/124 (1%) of patients with FL, grade 5 coccidioidomycosis infection 327 days after infusion (in ongoing response at the time of the event) occurred in 1/24 (4%) of patients with marginal zone lymphoma, and grade 5 sepsis 139 days after infusion (best response was progressive disease) occurred in 1 (4%) patient with marginal zone lymphoma, **all considered unrelated** to treatment.

Risk of bias - study level (case series) [10]								
1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear	yes
Overall risk of bias: low								
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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CHOP=Cyclophosphamide, doxorubicin, vincristine, and prednisone, CI=confidence interval, CR=complete response, DLBCL=diffuse large B-cell lymphoma, EMA=European Medicines Agency, 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, HR=hazard ratio, I=intervention, Int.=intention, IQR=interquartile range, IV=intravenous, MG=median gain, n=number of patients, NE=not estimable, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-cell lymphoma, PR=partial response, QoL=quality of life, SAE=serious adverse event, SCT=stem cell transplantation, ST=standard treatment

References:

1. European Medicines Agency (EMA). Medicines. Yescarta. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/yescarta].
2. National Institute for Health and Research (NIHR). Axicabtagene ciloleucel for relapsed/refractory indolent non-Hodgkin lymphoma. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/14980-Axicabtagene-Ciloleucel-For-Non-Hodgkins-Lymphoma-V1.0-AUG2019-NONCONF.pdf].
3. U.S. Food and Drug Administration (FDA). Yescarta. Label Information. [Available from: https://www.fda.gov/media/108377/download].
4. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to axicabtagene ciloleucel for relapsed or refractory follicular lymphoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma].
5. National Cancer Institute. With FDA Approval for Advanced Lymphoma, Second CAR T-Cell Therapy Moves to the Clinic. [Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2017/yescarta-fda-lymphoma].
6. European Medicines Agency (EMA). Yescarta: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf].
7. Supplement to: Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2021; published online Dec 8.
8. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2022; 23: 91–103. [Available from: https://linkinghub.elsevier.com/retrieve/pii/S147020452100591X].

9. U.S. National Library of Medicine, ClinicalTrials.gov. A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5). [Available from: https://clinicaltrials.gov/ct2/show/NCT03105336].
10. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].