Yescarta® (axicabtagene ciloleucel)
Use in Hepatitis B Virus (HBV) infection

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The full indication, important safety information, and boxed warnings for cytokine release syndrome, neurologic toxicities and secondary hematological malignancies are available at:
https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi

Relevant Prescribing Information[1]

Per the YESCARTA US Prescribing Information (USPI), hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with drugs directed against B cells, including YESCARTA. Perform screening for HBV, HCV, and HIV and management in accordance with clinical guidelines before collection of cells for manufacturing.

Clinical Studies

ZUMA-1, ZUMA-5, and ZUMA-7 Studies

ZUMA-1 was a phase 1/2 multicenter, single-arm, open-label study which evaluated the safety and efficacy of YESCARTA in patients with chemorefractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL).[2,3]

In the ZUMA-1 study, patients with a known history of infection with hepatitis B (HBsAg positive) were ineligible to enroll in the study.[4] Patients with a history of hepatitis B were permitted if the viral load was undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing.[4] However, in ZUMA-1, one case of Grade 1 Hepatitis B viral reactivation was reported that was deemed unrelated to YESCARTA.[5]

ZUMA-5 is a multicenter, single arm, Phase 2 study to evaluate the efficacy of YESCARTA in patients with relapsed/refractory (r/r) indolent Non-Hodgkin Lymphoma (iNHL), including Follicular Lymphoma (FL, Grades 1-3a) and Marginal Zone Lymphoma (MZL, nodal or extranodal).[6,7] In the ZUMA-5 study, patients with a known history of infection with hepatitis B (HBsAg positive) were excluded from this study. History of hepatitis B is permitted if, the viral load is undetectable per Infectious Disease Society of America (IDSA) guidelines or applicable country guidelines.[7]

The ZUMA-7 study is an international, multicenter, randomized, phase 3 trial comparing YESCARTA with standard care as second-line treatment in patients with early relapsed (≤ 12 months) or refractory large B-cell lymphoma (LBCL).[8] Patients with a known history of infection with hepatitis B (HBsAg positive) were excluded from this study. If there is a positive history of treated hepatitis B, the viral load must be undetectable per quantitative PCR and/or nucleic acid testing.[9] There was one Grade 5 adverse event of HBV reactivation that was considered to be related to YESCARTA.[8]

Therefore, there are no clinical trial data available on the use of YESCARTA in patients with detectable viral loads of HBV infection.

Real-World Evidence

Abbasi, et al. retrospectively assessed the efficacy and safety of YESCARTA in a series of 10 patients with r/r DLBCL, including 2 patients with active HBV infection receiving antiviral treatment. All patients received lymphodepleting chemotherapy as per product guidelines with fludarabine and cyclophosphamide. Eight of 10 patients achieved a complete response (CR) at data cutoff, as assessed by PET-CT, including one patient with HBV. The remaining HBV-positive patient died 4 months after treatment, due to progressive disease. The treatment was generally well tolerated with 2/10 patients experiencing Grade ≥2 cytokine release syndrome (CRS) and 3/10 patients experiencing Grade ≥3 immune effector cell-associated neurotoxicity syndrome (ICANS).[10]

Strati, et al. report a series that included 2 patients with HBV on antiviral prophylaxis, treated with YESCARTA for r/r DLBCL, after 2 or more prior lines of therapy. The 2 patients achieved CR after 1 month (ongoing at follow up) and experienced treatment complications by Grade ≥2 CRS and chimeric antigen receptor (CAR)-related encephalopathy syndrome (CRES), reversible with anti-IL-6 therapy. One of the patients with concomitant HBV experienced Grade 4 CRES, characterized by benzodiazepine-refractory tonic-clonic seizure, requiring intubation. This patient required triple antiepileptic therapy, including levetiracetam, phenytoin, and lacosamide, with resolution of encephalopathy and self-extubation after 7 days. No significant viral reactivation or increase in alanine aminotransferase (ALT)/bilirubin levels were observed, except in one HBV patient, who registered an increase in bilirubin (total bilirubin peaked to 2.2 mg/dL) 2 days after YESCARTA infusion, which normalized after 6 days. The same HBV patient experienced viral reactivation 3 months after treatment, due to self-discontinuation of antiviral prophylaxis, which was successfully treated with re-initiation. No fulminant hepatitis was observed and none of the patients had concomitant liver cirrhosis.[11] Additional information from these case series can be found using the links provided in the citation details below.

It is at the discretion of the treating physician on whether to prescribe YESCARTA in patients with active or a prior history of hepatitis B infection.

References

1. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc. 2024
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3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. DOI: 10.1056/NEJMoa1707447
4. [Redacted Protocol]. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017. DOI: 10.1056/NEJMoa1707447
5. Data on file, Kite Pharma.
6. 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(1):91-103. DOI: 10.1016/S1470-2045(21)00591-X
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8. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386(7):640-654. DOI: 10.1056/NEJMoa2116133
9. [Supplementary Appendix] Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386(7):640-654. DOI: 10.1056/NEJMoa2116133
10. Abbasi A, Peeke S, Shah N, et al. Axicabtagene ciloleucel CD19 CART cell therapy results in high rates of systemic and neurologic remissions in ten patients with refractory large B cell lymphoma including two with HIV and viral hepatitis. *J Hematol Oncol*. 2020;13(1):1. DOI: 10.1186/s13045-019-0838-y
11. Strati P, Nastoupil LJ, Fayad LE, Samaniego F, Adkins S, Neelapu SS. Safety of CAR T-Cell Therapy in Patients with B-Cell Lymphoma and Chronic Hepatitis B or C Virus Infection. *Blood*. 2019;133(26):2800-2802. DOI: 10.1182/blood.2019000888

Abbreviations

ALT=alanine aminotransferase
CAR=chimeric antigen receptor
CR=complete response
CRES=CAR-related encephalopathy syndrome
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
FL=follicular lymphoma
HBV=hepatitis B virus
HBsAg=hepatitis B surface antigen
HCV=hepatitis C virus
HIV=human immunodeficiency virus
ICANS=immune effector cell-associated neurotoxicity syndrome
IDSA=Infectious Disease Society of America
IL-6=interleukin 6
iNHL=indolent Non-Hodgkin Lymphoma
LBCL= large B-cell lymphoma
MZL=marginal zone lymphoma
PCR=polymerase chain reaction
PET-CT= Positron emission tomography-computed tomography
PMBCL=primary mediastinal B-cell lymphoma
r/r=relapsed/refractory
TFL=transformed follicular lymphoma
USPI=US Prescribing Information

Product Label

For the full indication, important safety information, and Boxed Warning(s), please refer to the YESCARTA® (axicabtagene ciloleucel) US Prescribing Information available at: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf.

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