# Yescarta® (axicabtagene ciloleucel) Alternative Therapies to Tocilizumab

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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**

## Alternative Therapies to Tocilizumab

As stated in the YESCARTA US Prescribing Information (USPI), cytokine release syndrome (CRS) and neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA.[1] Please refer to the YESCARTA US Prescribing Information (Section 2.3) for the management of CRS and neurologic events (NE) with tocilizumab and corticosteroids in patients receiving YESCARTA.[1] Hospitals and their associated clinics must ensure that a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours of infusion).[1,2] The most up-to-date information on the YESCARTA and TECARTUS REMS program can be found at https://www.yescartatecartusrems.com.[2]

Kite, a Gilead Company, is committed to ensuring all providers have the resources they need to safely treat patients with chimeric antigen receptor (CAR) T-cell therapy [CAR T], including YESCARTA. Certified healthcare facilities should follow their institutional guidelines regarding CAR T standard of care and inventory management of supportive care products.

Per the YESCARTA USPI on managing CRS and NE, alternate therapies could be considered if no improvement is seen for patients with Grade 4 CRS, or Grade 4 NE with or without concurrent CRS.[1] Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, intravenous immunoglobulin (IVIG) and anti-thymocyte globulin (ATG).[1]

The use and selection of alternate therapies is at the discretion of the treating physician.

### Use of Tocilizumab Biosimilars

The Yescarta USPI refers to use and availability of "tocilizumab" for treatment of severe or life-threatening Cytokine Release Syndrome (CRS) for patients receiving Yescarta. The USPI is agnostic of a specific brand name for tocilizumab, however it should be noted that currently only ACTEMRA® (tocilizumab) has an approved indication for the treatment of CAR T-cell induced CRS, while other recently approved tocilizumab biosimilars do not.[3]

TYENNE® (tocilizumab-aazg) and TOFIDENCE® (tocilizumab-bavi) are US Food and Drug Administration (FDA) approved biosimilars to the reference product ACTEMRA® (tocilizumab), and the US FDA considers both biosimilars to be highly similar to and have no clinically meaningful differences, in terms of safety or effectiveness, from the existing approved reference product. This means that health care professionals can prescribe either product instead of the original biologic.[3]

Of note, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 1.2025 – Management of CAR T-Cell-Related Toxicities states, "an FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines."[4] Use of tocilizumab biosimilars for the treatment of CAR T-cell induced CRS should be at the discretion of the treating physician.

## Clinical Studies

In the pivotal ZUMA-1 study, alternative agents such as anti-interleukin-6 (IL-6) monoclonal antibody siltuximab or interleukin-1 (IL-1) receptor antagonist anakinra could be considered, in consultation with the Kite Medical Monitor, for cases in which tocilizumab and corticosteroids did not effectively control YESCARTA-related cytokine-mediated toxicity.[5] However, no alternative IL-6 antagonists were administered to patients enrolled in ZUMA-1. One patient in ZUMA-1 received anakinra for grade 4 CRS associated with hemophagocytic lymphohistiocytosis (HLH) that further progressed to a grade 5 event.[6] Additional data from ZUMA-1 or ZUMA-5 on the use of alternative IL-6 antagonists such as siltuximab for CRS or NE management are not available.

## Real World Evidence

A literature search was conducted to identify primary evidence describing outcomes with alternate therapies to manage CRS and NE. A case series of three patients that received siltuximab due to continued CRS symptoms after treatment with tocilizumab.[7] In the study, three patients received siltuximab after prior treatment with tocilizumab due to continued signs and symptoms of CRS.[7] Outcomes from this case series study should be interpreted with caution and with consideration to study type and sample size.

Strati et al. have described a retrospective, single-center experience with the use of anakinra to mitigate CAR T-cell therapy associated toxicity in large B-cell lymphoma in 8 patients (6 diffuse LBCL, 2 transformed follicular lymphoma) patients treated with YESCARTA.[8] CRS and immune effector cell–associated neurotoxicity syndrome (ICANS) were prospectively graded according to the CAR toxicity (CARTOX) grading system. Among the eight patients treated with anakinra, two patients received anakinra for hemophagocytic lymphohistiocytosis (HLH) and six patients received anakinra for high-grade ICANS. Of the six patients treated with anakinra for ICANS, four patients experienced a clinical benefit of mitigated CAR T-cell therapy-associated toxicities, mainly ICANS. All four patients received anakinra 100 mg SC daily for 7 days. Of the four patients who experienced mitigated toxicities, three had received prior tocilizumab. Although none of the patients continued to receive tocilizumab after initiation of anakinra, all continued to receive corticosteroids.

Additionally, a Phase II study by Oliai and colleagues have reported preliminary outcomes data from their early experience in evaluating anakinra for the prevention of severe ICANS.[9] The trial included adults eligible for YESCARTA with large B-cell lymphoma after ≥2 lines of intensive chemoimmunotherapy. The primary objective of the study was to estimate the efficacy of anakinra in preventing severe ICANS (grade ≥3) according to ASTCT 2018 consensus grading. Anakinra was initiated at the occurrence of any grade ICANS or

grade ≥3 CRS in the absence of ICANS. A protocol modification, made after the first 3 participants were treated, changed the threshold for initiation of anakinra to grade ≥2 CRS. Patients received anakinra 100 mg SC every 6 hours for 12-36 doses until ICANS returned to grade ≤1. As of the time of reporting these results, 13 patients had been enrolled, and 7 met criteria to initiate anakinra and received the first dose prior to severe ICANS. Of the 7 patients that received anakinra prior to severe ICANS, one (14%) patient developed grade 3 ICANS. Once the protocol was amended to initiate anakinra for grade ≥2 CRS (n=4), zero patients developed severe ICANS, and one patient met the institutional standard to receive corticosteroids.

The literature search also identified real-world studies where alternate therapies for toxicity management were identified as being utilized. Please refer to the following publications for additional details:

- Jacobson C, Locke FL, Ma, L, et al. Real World Evidence of Axicabtagene Ciloleucel (Axi-cel) for the Treatment of Large B Cell Lymphoma in the United States. *Transplant. Cell. Ther*. 2022, 28, 581.e1-581.e8. DOI: 10.1016/j.jtct.2022.05.026
- Gutierrez C, Brown A.R., Herr M., et al. The chimeric antigen receptor-intensive care unit (CAR-ICU) initiative: Surveying intensive care unit practices in the management of CAR T-cell associated toxicities *J Crit Care*. 2020 August; 58: 58–64. DOI: 10.1016/j.jcrc.2020.04.008
- Jacobson C.A., Hunter B.D., Redd R., et al Axicabtagene ciloleucel in the non-trial setting: Outcomes and correlates of response, resistance, and toxicity. *J. Clin. Oncol.* 2020;38(27):3095-3106. DOI: 10.1200/JCO.19.02103
- Pasquini MC, Locke FL, Herrera AF, et al. Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, Axicabtagene Ciloleucel (Axi-Cel), for the Treatment of Large B Cell Lymphoma (LBCL) in the United States (US). *Blood*. 2019;134;(Suppl. 1):764. DOI: 10.1182/blood-2019-124750

Note that this is not a comprehensive list, and you are encouraged to search the published medical literature for additional citations on this topic. Please refer to the US Prescribing Information for alternate therapies identified and/or contact the respective manufacturers for additional information on these products.

Beyond the guidance included in the YESCARTA USPI, the treatment of choice and sequence of use among the suggested alternate therapies is at the discretion of the treating physician.

# References


1. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc. 2024
2. YESCARTA and TECARTUS Risk Evaluation and Mitigation Strategy (REMS) Program. https://www.yescartatecartusrems.com/. Kite Pharma, Inc. 2024. Accessed October 18, 2024.
3. Data on File. Kite Pharma.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities, Version 1.2025 – December, 20, 2024.
5. 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 Dec 28;377(26):2531-2544. DOI: 10.1056/nejmoa1707447.
6. Data on File. Kite Pharma.

7. Siglin J, Bukhari A, Lutfi F, et al. C-reactive protein: not always a reliable marker of ongoing cytokine release syndrome in CAR-T therapy following IL-6 blockade. *Leuk Lymphoma*. 2020;61(9):2280-2282. DOI: 10.1080/10428194.2020.1757667.
8. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. *Blood Adv*. 2020;4(13):3123-3127. DOI: 10.1182/bloodadvances.2020002328.
9. Oliai C, Crosetti A, De Vos S, et al. IL-1 receptor antagonist for prevention of severe immune effector cell-associated neurotoxicity syndrome. *Journal of Clinical Oncology*. 2021;39:15_suppl, 7566-7566. DOI: 10.1200/JCO.2021.39.15_suppl.7566.

## 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.

## Follow Up

For any additional questions, please contact Kite Medical Information at:

☎1-844-454-KITE (1-844-454-5483) or ✉ medinfo@kitepharma.com

## Adverse Event Reporting

Please report all adverse events to:

Kite ☎ 1-844-454-KITE (1-844-454-5483)

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉ MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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