Submitted by:
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Dear NCCN Guidelines® B-Cell Lymphomas Panel,

On behalf of Kite, I respectfully request the *NCCN B-Cell Lymphomas Guideline Panel* to review the enclosed data for inclusion of YESCARTA® (axicabtagene ciloleucel) for the treatment of adult patients with relapsed or refractory B-cell indolent Non-Hodgkin's Lymphoma (iNHL) of Follicular Lymphoma (FL) and Marginal Zone Lymphoma (MZL) histological subtypes.

Specific Changes

Please consider the addition of axicabtagene ciloleucel under second-line and subsequent therapy for follicular lymphoma (FOLL-B 2 OF 4) and second-line or subsequent therapy for marginal zone lymphomas (MZL-A 2 OF 3).

FDA Clearance

YESCARTA® is not FDA approved for treatment of adult patients with relapsed or refractory B-cell indolent Non-Hodgkin's Lymphoma (iNHL) of Follicular Lymphoma (FL) and Marginal Zone Lymphoma (MZL) histological subtypes.[1] Kite, a Gilead company, recently submitted a supplemental biologics license application (BLA) to the U.S. Food and Drug Administration (FDA) for Yescarta® for the treatment of relapsed or refractory follicular FL and MZL after two or more prior lines of systemic therapy.[2] Yescarta was previously granted Breakthrough Therapy Designation (BTD) by the FDA for these indications.

Please see enclosed YESCARTA prescribing information for approved indications and limitations of use.[1]

Rationale

Advanced stage iNHL, including FL and MZL are considered an incurable malignancy with patients experiencing multiple relapses.[3] Patients who relapse within 2 years of initial chemoimmunotherapy have poor outcomes with a 5-year overall survival of 50%.[4] Furthermore, response duration and survival shortens after relapse in many of these patients.[5]

ZUMA-5 is a multicenter, single-arm, Phase 2 study evaluating the use of axicabtagene ciloleucel in patients with relapsed or refractory iNHL of either FL or MZL subtypes, who received at least two prior lines of systemic therapy, including an anti-CD20 monoclonal antibody combined with an alkylating agent.[6] The primary endpoint was the objective response rate (ORR) as assessed by central read. Key secondary endpoints included complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety. The findings from an interim analysis of ZUMA-5 were recently presented at American Society of Clinical Oncology (ASCO) and are briefly summarized below:

Of 148 patients enrolled and leukapheresed, 140 patients received conditioning chemotherapy and axicabtagene ciloleucel infusion.[6] Interim efficacy analysis included 96 patients (first 80 FL patients with ≥ 9 months follow-up and 16 MZL patients with ≥ 1 month follow-up) as part of the inferential analysis set who were treated with any dose of axicabtagene ciloleucel and were evaluable for efficacy. As of December 16, 2019, the median follow-up

among the patients for efficacy analysis was 15.3 months (range: 1.9-28.8) with follow-up for safety analysis being 12.8 months (range: 1.9-28.8).

Among the 96 efficacy-evaluable patients, 52% had Stage IV disease, 51% had a Follicular Lymphoma International Prognostic Index (FLIPI) score of ≥3 and 49% had high tumor bulk per GELF criteria.[6] Additionally, 54% patients had progression of disease in <24 months from treatment with first anti-CD20 monoclonal antibody. As part of the interim analysis, an ORR of 93% (95% CI: 86-97) was reported with a CR rate of 80% (95%CI: 71-88) by central read. ORR was also consistent among key subgroups. Median time to first response was 1 month (range: 0.8-3.1). The median DOR in all patients was 20.8 months (95% CI: 19.7-Not estimable) with 68% patients with FL having an ongoing response as of data cut-off. The median PFS was 23.5 months (95% CI: 22.8- Not estimable) and median OS was not reached. The estimated 12-month OS rate was 94.3% (95%CI: 86.8-97.6) for all patients.

Safety in the ZUMA-5 study was evaluated in all 140 patients treated with axicabtagene ciloleucel.[6] Of the 140 patients, 119 (85%) experienced grade≥3 adverse events (AEs) with neutropenia (34%), decreased neutrophil count (28%) and anemia (22%) being the most commonly reported grade ≥3 AEs. Any grade CRS events were experienced in 79% patients with 8% experiencing grade ≥3 CRS. Any grade neurologic events (NE) were experienced in 58% patients with 17% experiencing grade ≥3 NE. The most common adverse reactions (incidence ≥ 25%) were pyrexia, hypotension, fatigue, headache, nausea, neutropenia, anemia, sinus tachycardia, decreased neutrophil count, tremor, constipation, chills, diarrhea and decreased appetite.

Because of the risk of CRS and neurologic toxicities, YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program.[1] Additional information regarding the REMS program can be found at www.YescartaTecartusREMS.com.

We appreciate the opportunity to submit this information for consideration by the NCCN Guidelines® B-Cell Lymphomas Panel. If you have any questions or require additional information, please do not hesitate to contact us via phone 1-844-454-5483 or email medinfo@kitepharma.com

Sincerely,
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Enclosures YESCARTA® Prescribing Information[1] and referenced literature[3-6]

References

1. YESCARTA® (axicabtagene ciloleucel) Prescribing Information, Kite Pharma, Inc. Santa Monica, CA. 2019.
2. Gilead Sciences, Inc., 2020. Kite submits supplemental Biologics License Application to U.S. Food and Drug Administration for YESCARTA® in relapsed or refractory indolent Non-Hodgkin Lymphomas. Available at https://www.gilead.com/news-and-press/press-room/press-releases/2020/9/kite-submits-supplemental-biologics-license-application-to-us-food-and-drug-administration-for-yescarta-in-relapsed-or-refractory-indolent-nonhodg. Accessed September 5, 2020.
3. Wang T, Scott J, Barta S. The evolving role of targeted biological agents in the management of indolent B-cell lymphomas. Ther Adv Hematol. 2017;8(12):329-344. doi:10.1177/2040620717738740
4. Casulo C, Byrtek M, Dawson K et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *Journal of Clinical Oncology*. 2015;33(23):2516-2522. doi:10.1200/jco.2014.59.7534
5. Rivas-Delgado A, Magnano L, Moreno-Velázquez M, et al. Response duration and survival shorten after each relapse in patients with follicular lymphoma treated in the rituximab era. Br J Hematol. 2019;184(5):753-759. doi: 10.1111/bjh.15708
6. Jacobson CA, Chavez JC, Sehgal AR, et al. Interim analysis of ZUMA-5: A phase 2 study of axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory indolent non-Hodgkin lymphoma. Oral presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Chicago, IL.