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Date of Request: October 20th 2017

NCCN Guidelines Panel: NHL, B-Cell Lymphomas

On behalf of Kite, I respectfully request the NCCN *B-Cell Lymphomas* Guideline Panel review the enclosed information and consider the inclusion of YESCARTA™ (axicabtagene ciloleucel) for the treatment of patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

Specific Changes

Please consider the addition of axicabtagene ciloleucel as a treatment option for second-line and subsequent therapy for diffuse large B-cell lymphoma (intention to proceed to, and non-candidates for, high-dose therapy), primary mediastinal large B-cell lymphoma, double hit lymphoma/high grade B-cell lymphoma, and follicular lymphoma histologic transformation to DLBCL following multiple prior therapies.

FDA Clearance

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma[1]

Rationale

A recent, large, retrospective study of patients with DLBCL refractory to chemotherapy, or who had relapsed within 12 months of ASCT, demonstrated an objective response rate of 26% and a complete response rate of 7% to their subsequent line of treatment. The median overall survival was 6.3 months.[2] These data underscore the unmet need for effective therapies in the treatment of refractory large B-cell lymphoma.

A single-arm, open-label, multicenter trial evaluated the safety and efficacy of a single infusion of axicabtagene ciloleucel in adult patients with relapsed or refractory aggressive B-cell NHL. Of the patients treated, most (76%) had DLBCL, 16% had transformed follicular lymphoma, and 8% had primary mediastinal large B-cell lymphoma. The median number of prior therapies was 3 (range: 1 to 10), 77% had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT. Following a three-day lymphodepleting chemotherapy regimen (cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2), patients received a single intravenous infusion of axicabtagene ciloleucel at a

target dose of 2 x 10^6 CAR-positive T cells/kg. The primary endpoint was objective response rate by investigator's assessment. Secondary analyses included duration of response, overall survival, and safety. Of 111 patients who underwent leukapheresis, axicabtagene ciloleucel was successfully manufactured for 110 (99%) and administered to 101 (91%).[3-5]

As stated in the USPI, efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR) as determined by an independent review committee. The objective response rate was 72% (73/101) with a CR rate of 51% (52/101). With a median follow-up of 7.9 months, DOR for patients who achieved CR was not reached (range 0.4 to 14.4+ months). The median time to response was 0.9 months (range: 0.8 to 6.2 months). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or partial response (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).[1]

The safety dataset (N=108) reflect exposure to axicabtagene ciloleucel including 7 patients from the phase 1 portion of the ZUMA-1 study.[6] The median duration of follow up was 8.7 months. Grade 3 or higher CRS occurred in 13% (14/108) of patients. Grade 3 or higher neurologic toxicities occurred in 31% of patients. The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (> 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia.[1]

Sincerely,

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References:

1. YESCARTA™ [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.
2. Crump M, Neelapu SS, Faroog U, *et al.* (2017) Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood.* 130 (16) 1800-1808.
3. Locke FL, Neelapu SS, Bartlett NL, *et al.* Primary Results from ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma (NHL). Oral presented at: American Association for Cancer Research; April 2, 2017; Washington DC. Presentation CT019.
4. Locke FL, Neelapu SS, Bartlett NL, *et al.* Clinical and Biologic Covariates of Outcomes in ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma (r-NHL). Poster presented at: American Society of Clinical Oncology; June 5 2017; Chicago, IL. Poster discussion: 7512.
5. Neelapu SS, Locke FL, Bartlett NL, *et al.* Axicabtagene Ciloleucel (axi-cel; KTE-C19) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma (NHL): Primary Results of the Pivotal Trial ZUMA-1. Oral presentation at: International Conference on Malignant Lymphoma (ICML); June 13, 2017; Lugano, Switzerland. Abstract 8.
6. Locke FL, Neelapu SS, Bartlett NL, *et al.* (2017) Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Molecular Therapy*. 25(1) 285-295.