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 TECARTUS™ (brexucabtagene autoleucel or brexu-cel, formerly referred to as KTE-X19) for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Specific Changes

Please consider the addition of brexucabtagene autoleucel as a second line therapy for relapsed or refractory MCL (MANT-A 2 OF 4)

FDA Clearance

TECARTUS™ (brexucabtagene autoleucel) is a novel CD19-directed genetically modified autologous T-cell immunotherapy that was granted priority review designation by the FDA on February 10, 2020.[1] TECARTUS™ was approved by the FDA on July 24, 2020 for the treatment of adult patients with relapsed or refractory MCL.[2] This indication is approved under accelerated approval based on the overall response rate and durability of response with continued approval being contingent upon verification and description of clinical benefit in a confirmatory trial.

Rationale

Patients with relapsed or refractory MCL remain difficult to treat with declining complete remission (CR) rates of 45% or less with second and subsequent lines of therapy.[3,4] Based on the results from the ZUMA-2 study, brexu-cel became the first chimeric antigen receptor (CAR) T-cell therapy approved by the FDA for adult patients with relapsed or refractory MCL.[2,5] Results from this study demonstrated 87% of patients responding with 62% achieving a CR.[2] Grade ≥3 Cytokine Release Syndrome (CRS) and Neurologic Events (NE) was experienced in 18% and 37% patients respectively. Additional details from the ZUMA-2 study are described below:

ZUMA-2 is a Phase 2, single-arm, open-label, multicenter study evaluating the safety and efficacy of brexu-cel in patients with MCL who relapsed after or were refractory to 2 to 5 prior therapies.[2,5] Eligible patients underwent leukapheresis to obtain peripheral blood mononuclear cells for brexu-cel production. The manufacture of brexu-cel includes a T-cell enrichment step that may reduce the likelihood of circulating CD19-expressing tumor cells in the leukapheresis material driving the activation, expansion, and exhaustion of the anti-CD19 CAR T cells during the *ex vivo* manufacturing process.[2] Per protocol, patients were to receive lymphodepleting chemotherapy regimen consisting of 30 mg/m^2 fludarabine IV and 500 mg/m^2 cyclophosphamide IV on Days −5, −4, and −3 followed by a single IV infusion of brexu-cel at a target dose of 2 × 10^6 CAR T-cells/kg.[5] The primary endpoint was the objective response rate (ORR) as assessed by an independent radiology review committee (IRRC) per the Lugano classification.[2,5]

Of 74 patients enrolled and leukapheresed, brexu-cel was successfully manufactured for 71 (96%) and administered to 68 (92%).[2] Sixty of these patients were followed for at least 6 months after their week 4 disease assessment and were considered efficacy evaluable. For these 60 patients, the median age was 65 years (range:

38 to 79 years) with 83% having Stage IV disease and 23% having blastoid MCL. The median number of prior therapies was 3 (range: 2-5). Twenty-six (43%) patients had relapsed after or were refractory to autologous hematopoietic stem cell transplant (HSCT). Twenty-one (35%) had relapsed after their last therapy for MCL, while 36 (60%) were refractory to their last therapy for MCL. Twenty-one (35%) patients received bridging therapy post-apheresis with a BTK inhibitor and/or corticosteroids. The primary efficacy analysis, conducted on the 60 efficacy evaluable patients, demonstrated an ORR of 87% (95% CI, 75 – 94), with a 62% rate of complete remission (CR; 95% CI, 48 – 74).[2] With median follow-up of 8.6 months, the median duration of response (DOR) was not reached.

The safety of brexu-cel was evaluated in 82 patients from the ZUMA-2 study and included all patients who received a single dose of viable anti-CD19 CAR T-cells/kg (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) that was weight based.[2] Grade ≥3 CRS occurred in 18% patients and Grade ≥3 NE occurred in 37% patients. The most common adverse reactions (incidence ≥ 20%) were pyrexia, CRS, hypotension, encephalopathy, fatigue, tachycardia, arrhythmia, infection – pathogen unspecified, chills, hypoxia, cough, tremor, musculoskeletal pain, headache, nausea, edema, motor dysfunction, constipation, diarrhea, decreased appetite, dyspnea, rash, insomnia, pleural effusion, and aphasia. Serious adverse reactions occurred in 66% of patients. The most common serious adverse reactions (> 2%) were encephalopathy, pyrexia, infection – pathogen unspecified, CRS, hypoxia, aphasia, renal insufficiency, pleural effusion, respiratory failure, bacterial infections, dyspnea, fatigue, arrhythmia, tachycardia and viral infections.

Because of the risk of CRS and neurologic toxicities, TECARTUS™ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program.[2] 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

TECARTUS™ Prescribing Information[2] and referenced primary literature[3-5]

References

1. Gilead Sciences, Inc., 2020. U.S. FDA Grants Priority Review For Kite'S KTE-X19 Biologics License Application (BLA) In Relapsed Or Refractory Mantle Cell Lymphoma. Available at https://www.gilead.com/news-and-press/press-room/press-releases/2020/2/us-fda-grants-priority-review-for-kites-ktex19-biologics-license-application-bla-in-relapsed-or-refractory-mantle-cell-lymphoma. Accessed May 12, 2020.
2. TECARTUS™ (brexucabtagene autoleucel). Prescribing information. Kite Pharma, Inc; 2020.
3. Kumar A, Sha F, Toure A, et al. Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. *Blood Cancer J*. 2019;9(6):50. doi: 10.1038/s41408-019-0209-5
4. Jain P, Wang M. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. *Am J Hematol*. 2019 Jun;94(6):710-725. doi: 10.1002/ajh.25487
5. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382(14):1331-1342. doi: 10.1056/NEJMoa1914347