Submitted by
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Dear NCCN Guidelines® Acute Lymphoblastic Leukemia Panel,

In consideration of the submission request to NCCN guideline panels, we respectfully request the *NCCN Acute Lymphoblastic Leukemia Panel* review the enclosed data for inclusion of TECARTUS®(brexucabtagene autoleucel, brexu-cel or KTE-X19) for the treatment of adult patients (18 years and older) with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (B-ALL).

Specific Changes

Please consider the addition of TECARTUS® (brexucabtagene autoleucel) under the regimens for relapsed or refractory Philadelphia chromosome (Ph)-Positive B-ALL (ALL-D 3 OF 10) as well as the regimens for relapsed or refractory Ph-Negative B-ALL (ALL-D 4 OF 10)

FDA Approval

TECARTUS® has been granted a full approval on October 1, 2021 for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).[1]

TECARTUS® has received accelerated approval for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).[1]

Because of the risk of Cytokine Release Syndrome (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.[1] Additional information regarding the REMS program can be found at www.YescartaTecartusREMS.com.

Please see enclosed prescribing information for approved indications and additional considerations.[1] The information below is being provided in consideration of standing request for data submission to NCCN guidelines panel. Kite recommends the use of its products in accordance with the FDA-approved prescribing information.

Rationale

Adult patients with relapse or refractory ALL have poor prognosis with 1-year overall survival (OS) rate of 26% after first salvage which progressively declines with successive lines of treatment.[2] Despite the recent advances with approval of novel immunotherapeutic agents, survival rates remain poor in adult relapse or refractory ALL patients with a median overall survival (OS) of less than 8 months.[3-4]

ZUMA-3 is a phase 1/2, single-arm, open-label, multicenter study evaluating the safety and efficacy of TECARTUS, an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adults with relapsed/refractory B-ALL.[5,6] Eligible patients were ≥18 years of age and had relapsed/refractory B-ALL with morphologic disease in the bone marrow (>5% blasts) at study entry. Relapsed/refractory disease was defined as one of the following: primary refractory; first relapse following a remission lasting ≤12 months; relapsed or refractory after ≥2 prior lines of therapy; or relapsed after allogeneic stem-cell transplant (allo-SCT). Prior blinatumomab use was

permitted as part of ZUMA-3 inclusion criteria. The primary endpoint was the overall complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate by independent review.

Patients underwent leukapheresis followed by conditioning chemotherapy with fludarabine 25 mg/m^2 IV on days: -4, -3, -2 and cyclophosphamide 900 mg/m^2 IV on day -2.[1] This was followed by infusion of brexu-cel at a target dose of 1x 10^6 CAR T-cells/kg. Seventy-one patients were enrolled and leukapheresed; six of these patients did not receive TECARTUS due to manufacturing failure, eight patients were not treated primarily due to adverse events following leukapheresis, two patients underwent leukapheresis and received lymphodepleting chemotherapy but were not treated with TECARTUS, and one patient treated with TECARTUS was inevaluable for efficacy.[1] Among the remaining 54 efficacy-evaluable patients, the median time from leukapheresis to product delivery was 16 days (range: 11 to 39 days) and the median time from leukapheresis to TECARTUS infusion was 29 days (range: 20 to 60 days).

Of the 54 patients who were efficacy evaluable, the median age was 40 years (range: 19 to 84 years), 61% were male, and 67% were White, 6% were Asian, 2% were Black or African American, and 2% were American Indian or Alaska Native.[1] At enrollment, 46% had refractory relapse, 26% had primary refractory disease, 20% had untreated second or later relapse, and 7% had first untreated relapse. Among prior therapies, 43% of patients were previously treated with allo-SCT, 46% with blinatumomab, and 22% with inotuzumab. Twenty-six percent of patients were Philadelphia chromosome positive (Ph+). Fifty (93%) patients had received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden.

The efficacy of TECARTUS was established on the basis of complete remission (CR) within 3 months after infusion and the duration of CR (DOCR).[1] Twenty-eight (51.9%) of the 54 evaluable patients achieved CR, and with a median follow-up for responders of 7.1 months, the median DOCR was not reached. The median time to CR was 56 days (range: 25 to 86 days). The CR/CRi rate in the efficacy evaluable patients (N=54) was 64.8%. All efficacy evaluable patients had potential follow-up for ≥ 10 months with a median actual follow-up time of 12.3 months (range: 0.3 to 22.1 months).

The safety of TECARTUS was evaluated in the Phase 1/2 ZUMA-3 study, in which a total of 78 patients with relapsed/refractory ALL received a single dose of CAR-positive T cells (1 x 10^6 anti-CD19 CAR T cells/kg) that was weight-based.[1] Grade ≥3 CRS occurred in 26% of patients and grade ≥3 neurological events (NE) occurred in 35% of patients. Three patients with ALL had ongoing CRS events at the time of death. Six patients had ongoing neurologic events at the time of death. The most common (≥ 10%) Grade 3 or 4 reactions were fever, febrile neutropenia, hypotension, encephalopathy, cytokine release syndrome, hypoxia, and infection with pathogen unspecified.[1] Fatal adverse reactions occurred in 5% (4/78) of patients including cerebral edema, sepsis, and fungal pneumonia. Of the 4 patients who had fatal adverse reactions: one patient with fatal pneumonia had pre-existing pneumonia prior to study enrollment, and one patient with fatal sepsis had prolonged cytopenia and immunosuppression from prior therapies and underlying disease.

Amongst responders reported in the ZUMA-3 primary analysis, minimal residual disease (MRD) negativity rate was 97% at 10^{-4} sensitivity with sample unavailable for 1 patient. *[,5,6] CR/CRi rate was generally consistent across all evaluable subgroups. The median duration of response (DOR) both with and without censoring patients at subsequent allo-SCT was 12.8 months. Median OS and median relapse-free survival (RFS) were 18.2 months and 11.6 months respectively.[5,6]

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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*MRD- negativity rate was a secondary endpoint in the ZUMA-3 trial. The MRD assay used in this trial has not been analytically validated in accordance with FDA guidance. These data are not in USPI.

Enclosures

TECARTUS® Prescribing Information[1] and referenced literature[2-6]

References

1. TECARTUS® (brexucabtagene autoleucel). Prescribing information. Kite Pharma, Inc; 2021.
2. Gokbuget N, Dombret H, Ribera J, et al. International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia. *Hematologica.* 2016;101(12):1524-1533. doi: 10.3324/haematol.2016.144311
3. Topp MS, Gokbuget N, Zugmaier G, et al. Long-term survival of patients with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab. *Cancer.* 2021;127:554-559. doi: 10.1002/cncr.33298
4. Kantarjian H, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. *Cancer.* 2019;125:2474-2487. doi: 10.1002/cncr.32116
5. Shah BD, Ghobadi A, Oluwole OO, et al. Phase 2 Results of the ZUMA-3 Study Evaluating KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, in Adult Patients With Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. Oral presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; June 4, 2021; Virtual Meeting.
6. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed/refractory adult B-cell acute lymphoblastic leukemia. *Lancet.* 2021