

**Division Director Memo**  
**Division of Clinical Evaluation and Pharmacology/Toxicology**  
**Office of Tissues and Advanced Therapies**

<b>APPLICATION:</b> BLA 125643	<b>TRADE NAME:</b> YESCARTA
<b>APPLICANT/SPONSOR:</b> Kite Pharma, Inc.	<b>ESTABLISHED NAME:</b> axicabtagene ciloleucel
<b>SUBMISSION DATE:</b> 3/31/17	
<b>PDUFA DATE:</b> 11/29/17	<b>PRODUCT CLASS:</b> CAR-T Cells
<b>REVIEW DATE:</b> 10/16/17	<b>ROUTE:</b> Intravenous infusion

**INDICATION:** 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

**Review Team** (for comprehensive review team members from other offices, please see SBRA)

**Clinical:** Drs. Najat Bouchkouj and Yvette Kasamon (OCE); **Statistical:** Dr. Xue Lin; **Pharm/Tox:** Dr. Jinhua Lu; **Clin Pharm:** Xiaofei Wang; **CMC:** Drs. Mike Havert, Anna Kwilas, Graeme Price, Jakob Reiser, and Don Fink

**REVIEW SUMMARY:**

Kite Pharma, Inc. submitted this original BLA to seek marketing approval for YESCARTA *for the treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT)*. Due to lack of specific data to support the proposed indication, following review of the BLA, the proposed indication was modified to: *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.*

The primary evidence of safety and efficacy comes from the ZUMA-1 study, a multicenter, open-label, single-arm Phase 1/Phase 2 study conducted in 111 adult patients with aggressive B-cell NHL that was primary refractory, refractory to second or greater line of therapy, or relapsed within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The primary efficacy endpoint was the objective response rate (ORR) as analyzed in all subjects treated with a minimum of  $1.0 \times 10^6$  CAR-positive T cells/kg. Key secondary efficacy endpoints included best overall response (BOR), duration of response (DOR), and survival. The ORR as assessed by 1) an Independent Review Committee (IRC) was 72% (95% CI: 62, 81) and 2) by the investigator was 83% (95% CI: 74, 90). This represents an important clinical benefit for patients with relapsed/refractory non-NHL over existing salvage therapy as the ORR reported in patients with relapsed/refractory NHL is only 20-30%. The median duration of response (DOR) in subjects who achieved complete remission (CR) was not reached (95% CI: 8.1 months, not estimable [NE]) after a median follow-up of 7.9 months. The estimated median DOR for subjects who achieved partial remission (PR) was 2.1 months (95% CI: 1.3, 5.3).

Although there is no question as to the benefit of YESCARTA, significant risks to subjects were identified in ZUMA-1, the most significant were cytokine release syndrome (CRS) and neurologic toxicities. Ninety-four percent (94%) of subjects experienced CRS and 87% experienced neurologic adverse events. Other common adverse reactions occurring at an incidence of  $\geq 20\%$ , included fever, fatigue, headache, decreased appetite, chills, hypotension, tachycardia, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 49% of subjects and included CRS, neurologic toxicity, prolonged cytopenias (including neutropenia, thrombocytopenia, and anemia), and serious infections. Fatal cases of CRS and neurologic toxicity have occurred.

Although the benefit of YESCARTA in the studied population is impressive, significant safety concerns were identified that warrant a Risk Evaluation and Mitigation Strategy (REMS) to support a favorable benefit/risk profile. The proposed REMS is based on the Applicant's risk mitigation strategy employed during the study, which included: treatment with an IL-6 receptor antagonist (tocilizumab), on-site training for participating sites, restriction of study sites to certified centers, and close monitoring of subjects for safety events.

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The REMS will be a postmarketing requirement (PMR) and will include Elements to Assure Safe Use (ETASU) for the management of cytokine release syndrome and neurologic toxicity, training and assessment of sites and the use of tocilizumab. An additional PMR will be a postmarketing observational study to assess short and long-term toxicities of YESCARTA.

The overall benefit-risk profile of YESCARTA is favorable, and the REMS is intended to ensure that the benefits of YESCARTA outweigh the risks of CRS and neurologic toxicity.

Please see primary reviews from the clinical and statistical reviewers for details of the review. I concur with the clinical review team’s recommendation of Approval.

**OUTSTANDING ISSUES:**

There are no outstanding issues impacting Approval of the BLA; however, as discussed above, there will be Post-Marketing Requirements for REMS with ETASU and for an observational study.

**RECOMMENDED REGULATORY ACTION**

**APPROVAL**
                         
  **COMPLETE RESPONSE**
                         

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 Director  
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 Office of Tissue and Advanced Therapies  
 Center for Biologics Evaluation and Research  
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