BLA Clinical Review Memorandum

Application Type	Original Application
STN	125643
CBER Received Date	March 31, 2017
PDUFA Goal Date	November 29, 2017
Division / Office	CBER/Office of Tissues and Advanced Therapies; CDER/Office of Oncology and Hematology Products/Division of Hematology Products
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Yvette Kasamon, MD (Efficacy) Najat Bouchkouj, MD (Safety)
Review Completion Date / Stamped Date	October 5, 2017
Supervisory Concurrence	R. Angelo de Claro, MD Bindu George, MD Amy McKee, MD
Applicant	Kite Pharma, Inc.
Established Name	Axicabtagene ciloleucel (KTE-C19)
(Proposed) Trade Name	YESCARTA
Pharmacologic Class	CD19-directed, genetically-modified autologous T cell immunotherapy
Formulation(s), including Adjuvants, etc.	Cryopreserved injection containing human albumin, (b) (4) , and dimethylsulfoxide (b) (4) and supplied in one or more patient-specific infusion bags. Each bag (~68 mL) contains (b) (4) CAR T cells/kg.
Dosage Form(s) and Route(s) of Administration	Intravenous
Dosing Regimen	Single dose with a target of 2 x 10^6 CAR-positive T cells/kg (maximum 2 x 10^8 cells) administered by 30-minute IV infusion, and preceded by fludarabine and cyclophosphamide conditioning chemotherapy
Indication(s) and Intended Population(s)	Proposed: Treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma who are ineligible for autologous stem cell transplant Recommended: Treatment of adult patients with relapsed or refractory large B-cell lymphoma of the following types after two or more lines of systemic therapy: diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from follicular lymphoma
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
Allo	allogeneic
AR	adverse reaction
Auto	autologous
BLA	biologics license application
BOR	best overall response
CAR	chimeric antigen receptor
CMC	chemistry, manufacturing and controls
CI	confidence interval
CNS	central nervous system
CR	complete remission
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
eCTD	electronic common technical document
ECOG	eastern cooperative oncology group
EEG	electroencephalogram
ETASU	elements to assure safe use
FAS	full analysis set
FDA	food and drug administration
FL	follicular lymphoma
HLH/MAS	hemophagocytic lymphohistiocytosis/macrophage activation syndrome
HSCT	hematopoietic stem cell transplantation
IND	investigational new drug application
IPI	International Prognostic Index
ISS	integrated summary of safety
IQR	interquartile range
IRC	independent review committee
IR	information request
LTFU	long-term follow up
MedDRA	medical dictionary for regulatory activities
mITT	modified intention-to-treat
MMSE	mini mental status exam
NE	not evaluable, not estimable
NESI	neurotoxicity events of special interest
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	prescribing information/package insert
PK/PD	pharmacokinetics/pharmacodynamics

PMBCL	primary mediastinal B-cell lymphoma
PREA	pediatric research equity act
PR	partial remission
PS	performance status
PT	preferred term
RCR	replication competent retrovirus
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplantation
SD	stable disease
SOC	system organ class
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SPD	sum of the products of greatest diameter
TEAE	treatment-emergent adverse event

1. EXECUTIVE SUMMARY

The clinical review team recommends regular approval of axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma of the following types after two or more lines of systemic therapy: diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from follicular lymphoma.

Axicabtagene ciloleucel (KTE-C19) is a CD19-directed immunotherapy consisting of autologous T cells that have been transduced with a retroviral vector encoding an anti-CD19, *CD28/CD3-zeta* chimeric antigen receptor (CAR). The active substance comprises autologous T cells that have undergone *ex vivo* activation, gene transfer by a replication-deficient retroviral vector, and expansion to target human CD19, an antigen expressed by most malignant B-cells as well as all normal B-cells. The recommended regimen is a single dose of axicabtagene ciloleucel, with a target of 2×10^6 CAR-positive T cells/kg (maximum 2×10^8 CAR-positive T cells), administered by 30-minute IV infusion and preceded by fludarabine and cyclophosphamide conditioning for lymphodepletion.

Efficacy and safety are based on a single-arm, open-label, multicenter phase 1/2 study (ZUMA-1) that evaluated a single infusion of axicabtagene ciloleucel, preceded by conditioning chemotherapy, in 108 adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NHL). Eligible patients had refractory disease to the most recent therapy or relapse within one year after autologous (auto) hematopoietic stem cell transplantation (HSCT).

Efficacy

The submitted data meet the evidentiary standard of effectiveness for patients with large B-cell lymphoma that has relapsed or progressed after two or more lines of systemic therapy. In the phase 2 portion, 101 of 111 patients who underwent leukapheresis received axicabtagene ciloleucel. Most treated patients (76%) had DLBCL, 16% had transformed follicular lymphoma (FL), and 8% had primary mediastinal large B-cell lymphoma (PMBCL). 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 after autologous HSCT.

The regulatory recommendation is based on the complete remission (CR) rate and duration of response (DOR) demonstrated in the phase 2 portion, as determined by an independent review committee (IRC). On modified intention-to-treat (mITT) analysis, the objective response rate (ORR) was 72%, with a CR rate of 51% (95% CI: 41, 62) and median time to response of 0.9 months. On ITT analysis of all enrolled patients, the ORR was 66%, with a CR rate of 47% (95% CI: 37, 57).

With an estimated 7.9-month follow-up for DOR, the estimated median DOR among all responders was 9.2 months (95% CI: 5.4, NE). Response durations were longer in patients with a best overall response (BOR) of CR as compared to a BOR of partial remission (PR). Among patients achieving CR, the estimated median DOR had not been reached (95% CI: 8.1 months, NE), whereas the estimated median DOR among patients in PR was 2.1 months (95% CI: 1.3, 5.3).

Safety

ZUMA-1 study was the primary source of safety data and included a total of 108 subjects who were treated with KTE-C19 (seven subjects from Phase 1 and 101 subjects from Phase 2). Grade 3 or higher adverse reactions of interest included cytokine release syndrome (CRS) (13%), neurologic

toxicities (31%), febrile neutropenia (32%), prolonged cytopenias (28%), and infections (23%). Serious or fatal events of cerebral edema were reported in the 120-day safety update report.

During conduct of the ZUMA-1 study, life-threatening and fatal adverse reactions attributed to KTE-C19 were mitigated by mandated site and investigator training, careful site selection and monitoring, and instructions for early detection and management of the most serious complications. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and neurotoxicity, and a Risk Evaluation and Mitigation Strategy (REMS). FDA determined that the Communication Plan as proposed by the Applicant would not be sufficient; instead, a REMS with elements to assure safe use (ETASU) was the appropriate approach. The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies with emphasis on early recognition and treatment of CRS and neurotoxicity.

The theoretical concerns include an increased risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional mutagenesis. There were no events of RCR infection or insertional mutagenesis reported in the BLA.

Long-term safety after treatment with KTE-C19, particularly from the risk of insertional mutagenesis related secondary malignancies, remain a concern due to the limited follow up duration. Therefore, a postmarketing requirement (PMR) study is warranted. As a PMR, the Applicant agreed to conduct an observational registry study that will collect safety information for patients treated with marketed product, including key early adverse reactions and follow-up for 15 years for detection and evaluation of second malignancies. No routine collection of samples to evaluate for RCR is planned as part of this study.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Of the 135 subjects who were screened for Phase 1 and Phase 2 of the ZUMA-1 study, 119 were enrolled and underwent leukapheresis, 110 received conditioning chemotherapy and 108 subjects were treated with KTE-C19. The majority of the treated subjects were male (73 subjects, 68%), white (96 subjects, 89%), and not Hispanic or Latino (89 subjects, 82%). The median age was 58 years (range: 23 to 76 years), with 81 subjects (75%) < 65 years. One subject was treated in Israel and the remaining 107 subjects received their treatment in the U.S.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

DLBCL, which comprises 30-40% of NHLs, is fatal if not cured. PMBCL and transformed FL are typically treated along a DLBCL paradigm. Approximately half of all patients with aggressive B-cell NHL have relapsed or refractory (rel/ref) disease, with an estimated 10-15% of patients with DLBCL having primary refractory disease and an additional 20-30% relapsing after an initial objective response (Chaganti et al 2016). High-grade B-cell lymphomas with aberrations in MYC, BCL2 and/or BCL6, including “double hit” and “triple hit” lymphomas, are associated with an inferior prognosis, even in the newly diagnosed setting (Rosenthal and Younes 2017). Patients with untreated rel/ref aggressive B-cell lymphoma have a median survival of approximately 3-4 months. A recent meta-analysis (SCHOLAR-1 study, reviewed in Section 7.1.9) underscores the poor prognosis of patients with aggressive lymphoma that is refractory or relapses early after SCT. In

this analysis of > 500 patients, ORR to modern salvage therapy was only 20-30%, CR rates were < 15%, and the median overall survival (OS) was 6 months.

2.2 Currently Available, Pharmacologically Unrelated Treatments/Interventions for the Proposed Indication(s)

There are no approved therapies for patients with rel/ref, aggressive B-cell NHL. High-dose therapy with auto SCT is the usual standard for first relapse of *de novo* DLBCL, provided that the relapse is chemosensitive. Over 50% of such relapses, however, are chemoresistant (Gisselbrecht et al 2010). As in other hematologic malignancies, patients unable to achieve objective response to salvage therapy are generally not considered for SCT, as they are unlikely to benefit from the procedure. Although allogeneic (allo) SCT can produce long-term survival, if not cure, in a subset of patients, including after auto SCT failure, eligibility usually is contingent upon achievement of disease control with salvage therapy.

Combination chemotherapy is the mainstay of salvage therapy for aggressive lymphomas. Drug combinations used widely for salvage therapy of large B-cell lymphoma (LBCL) include ifosfamide/carboplatin/etoposide, etoposide/methylprednisolone/cytarabine/cisplatin, and dexamethasone/cytarabine/cisplatin, generally in combination with rituximab. These intensive regimens, however, are typically used as a bridge to HSCT and can be difficult to tolerate for extended cycles. There are no universally established treatment regimens for patients with rel/ref LBCL who are refractory to second- or later- line salvage regimens, ineligible for transplantation, or relapse after transplantation. Survival is especially poor in patients with primary refractory disease, resistant relapse, or relapse that occurs less than 1 year after SCT, with median survival measured in months.

2.3 Safety and Efficacy of Pharmacologically Related Products

No pharmacologically related products are approved for the proposed indication. General safety concerns with CD19-directed CAR T cells include CRS, neurotoxicity, and insertional mutagenesis and resultant secondary malignancies. CRS is an expected systemic reaction that coincides with immune activation and T-cell expansion. Characteristics include fever, fatigue, hypotension, tachycardia, hypoxia, capillary leak, and cardiac/renal/hepatic dysfunction. Inflammatory cytokines are elevated, particularly interleukin-6 (IL-6). Treatment is directed at signs and symptoms. In addition, investigators have reported that the anti-IL-6 receptor inhibitor tocilizumab moderated the course of CRS with rapid reversal of symptoms.

A pattern of neurologic dysfunction has been described with other CAR T cell products during clinical trials. It is characterized by encephalopathy, confusion, delirium, aphasia, obtundation, and seizures. More recently, cases of cerebral edema have been reported (Brudno et al, 2016).

For products that have been genetically modified by retroviral transduction, there are additional considerations related to possible generation of second malignancies. Early in the development of gene therapies, in the setting of modification of hematopoietic stem cells, there were reports of insertional oncogenesis with retrovirus transduction in patients receiving a genetically modified (retroviral vector) stem cells. T-cell leukemia developed in recipients of HSCT with gene-modified stem cells for severe combined immunodeficiency and chronic granulomatous disease, with cases reported up to 15 years after the procedure. CAR T-cell products can persist after treatment. This persistence theoretically can lead to an increased risk of insertional mutagenesis and a secondary malignancy.

Reviewer comment:

- **Reviews published on the toxicity of activated T-cell therapy provide an insight to the risks and management of the short-term toxicities such as CRS and neurotoxicity. Long-term risks associated with secondary malignancy remain theoretical but may augment a risk that already exists in a heavily pretreated cancer patient due to prior exposure to carcinogenic cytotoxic agents. Long-term follow-up programs that document the incidence of secondary malignancy, comparisons with known and established risks for the patients' baseline therapies, and evaluation of tumor tissue for the vector will be critical to delineate an accurate oncogenic risk profile for these products. These risks should be addressed in the label, the short-term risks of CRS and neurotoxicity should be addressed in the REMS with ETASU, and the long-term risk evaluated further in a postmarketing observational study.**

2.4 Previous Human Experience with the Product

None. Axicabtagene ciloleucel is a new molecular entity (NME) and has not been marketed in other countries.

2.5 Summary of Pre- and Post-Submission Regulatory Activity

IND 016278 investigates axicabtagene ciloleucel (KTE-C19) in aggressive B-cell lymphomas. Axicabtagene ciloleucel was granted orphan designation for DLBCL (3/2014), PMBCL (4/2016), and FL (4/2016) and received Breakthrough Therapy Designation in 12/2015 for refractory, aggressive NHL.

In a Type B pre-BLA meeting in 10/2016, FDA indicated that it was premature to submit a BLA on 12/30/2016 due to <6 month follow-up for efficacy in the ZUMA-1 study and fewer than the prespecified number of subjects in the primary analysis; FDA requested data on response and response duration after 6 months follow-up for all subjects. FDA also disagreed with including the (b) (4)
The Agency agreed to a rolling submission, which was initiated 12/2/2016.

After BLA submission, a teleconference was held 5/31/2017 due to inadequate follow-up for efficacy with 12/2016 (IRC) and 1/2017 (investigator) data cuts. Alignment was reached to submit updated efficacy data by 6/30/2017, using a 4/26/2017 cut-off date for both investigator and IRC assessments.

2.6 Other Relevant Background Information

None

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The overall submission quality and content were acceptable. Inadequacies, including different cutoff dates for investigator and IRC efficacy assessments, insufficient follow up for response duration, and dataset errors and omissions, were addressed through multiple information requests (IRs).

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant indicated that the clinical trials were conducted in accordance with good clinical practice. The submission integrity was acceptable.

3.3 Financial Disclosures

Covered clinical study (name and/or number): ZUMA-1		
Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 355 (24 PIs, 311 subinvestigators)		
Number of investigators who are applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (N/A)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (N/A)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (N/A)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Axicabtagene ciloleucel (KTE-C19) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare KTE-C19, a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising an anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory

domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19 expressing target cells.

4.2 Assay Validation

Per FDA Chemistry, Manufacturing and Controls (CMC) reviewer, the assays that were utilized for KTE-C19 manufacturing and cell persistence determination were validated.

4.3 Nonclinical Pharmacology/Toxicology

Per FDA Pharmacology and Toxicology reviewer: Anti-murine CD19 CAR T cells administered to mice after lymphodepletion (using total body irradiation) prevented engraftment of $CD19^+$ murine lymphoma cells and eliminated established $CD19^+$ lymphoma. Depletion of normal B cells was observed in the syngeneic mouse lymphoma model. This finding persisted for up to 209 days (last time point studied) after administration of the anti-murine CD19 CAR T cells. The mice did not show any overt signs of toxicity.

4.4 Clinical Pharmacology

The clinical pharmacology of KTE-C19 was evaluated separately by two review teams; Clinical Pharmacology and Pharmacometrics. See their full review for details.

4.4.1 Mechanism of Action

KTE-C19 is a CD19-directed genetically modified autologous T cell immunotherapy that binds to CD19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19-expressing target cells.

4.4.2 Human Pharmacodynamics (PD)

Per the CBER clinical pharmacology reviewer: In ZUMA-1, after KTE-C19 infusion, PD responses were evaluated over a 4 week interval by measuring transient elevation of cytokines, chemokines and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion and levels generally returned to baseline within 28 days. Due to the on target effect of KTE-C19, a period of B-cell aplasia is expected.

4.4.3 Human Pharmacokinetics (PK)

Per the CBER clinical pharmacology reviewer: Peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after KTE-C19 infusion. The median peak level of anti-CD19 CAR T cells in the blood (Cmax) were 41.9 cells/µL (range: 0.8 - 1513.7 cells/µL). The median area under the blood concentration vs. time curve from Day 0 to Day 28 ($AUC_{(0\text{-}28d)}$) was 462.3 days*cells/µL (range 5.1 – 14329.3 days*cells/µL). At 1 month after KTE-C19 infusion, the median blood level of anti-CD19 CAR T cells was 2.1 cells/µL (range: 0 – 167.4 cells/µL), and by 3 months, levels of anti-CD19 CAR T cells decreased to a median of 0.4 cells/µL (range: 0 – 15.8 cells/µL).

Age and gender had no significant impact on $AUC_{(0\text{-}28d)}$ and Cmax of KTE-C19. Some subjects required tocilizumab and corticosteroids for management of CRS and neurologic toxicities.

Subjects treated with tocilizumab had 173% and 231% higher YESCARTA $AUC_{(0\text{-}28d)}$ and Cmax respectively, as compared to subjects who did not receive tocilizumab. Similarly, subjects that received corticosteroids had 165% and 154% higher $AUC_{(0\text{-}28d)}$ and Cmax compared to patients who did not receive corticosteroids.

4.5 Statistical

The statistical reviewer verified that the key efficacy analyses reported by the Applicant were supported by the submitted data.

4.6 Pharmacovigilance

REMS
The available safety data suggest that a REMS with an ETASU is indicated, and the Applicant was sent a notification letter on August 1, 2017. The recommendation for REMS is to ensure that the benefits of KTE-C19 outweigh the risks of CRS and neurotoxicity. The REMS should include ETASU to train health care providers, pharmacies and prescribers and provide CRS and neurotoxicity related risk mitigation measures as follows:

For hospitals:

1. To become certified to dispense KTE-C19, hospitals must:
    a. Designate an authorized representative to complete the certification process by submitting a completed KTE-C19 REMS Program Hospital Enrollment Form on behalf of the hospital.
    b. Ensure the authorized representative is assigned to the program for KTE-C19 and oversees implementation and compliance with the KTE-C19 REMS Program requirements by the following:
        i. Complete the training and successfully complete a KTE-C19 REMS Program Knowledge Assessment.
        ii. Ensure all relevant staff involved in the prescribing, dispensing or administering of KTE-C19 are trained on the REMS Program requirements as described in the training materials, successfully complete a KTE-C19 REMS Program Knowledge Assessment, and maintain a record of training.
        iii. Goals of the training include: Informing prescribers and other staff about the risks, clinical manifestations, and management of CRS and neurotoxicity observed with KTE-C19 treatment.
    c. Put processes and procedures in place to ensure the following requirements are completed prior to dispensing and administering KTE-C19:
        i. Verify tocilizumab (two doses) is ordered and available for administration before a dose of KTE-C19 is administered.
        ii. Ensure that, during a pre-specified time period after product administration, procedures are in place to maintain availability to patients within close proximity to allow for rapid return to the certified hospital if symptoms of CRS or neurotoxicity develop. The REMS should include procedures to inform patients of the importance of being admitted to the hospital for KTE-C19 infusion and inpatient monitoring for a period of 7 days to monitor for CRS and neurologic toxicities. Patients also should be informed of the importance of remaining close to the administering certified hospital for a pre-specified period of time (i.e. 3-4 weeks) so that they can return if they develop symptoms of CRS or neurotoxicity.

iii. Ensure that the patient and family are given wallet cards to remind them of the signs and symptoms of CRS and neurotoxicity that require immediate medical attention.

2. As a condition of certification, the certified hospital must:
    a. Recertify in the KTE-C19 REMS Program if the hospital designates a new authorized representative. Procedures for routine re-education of all staff should be included in the REMS plan.
    b. Report any adverse events suggestive of CRS or neurotoxicity.
    c. Maintain documentation that all processes and procedures are in place and are being followed for the KTE-C19 REMS Program and provide this documentation upon request to the Applicant, FDA, or a third party acting on behalf of the Applicant or FDA.
    d. Comply with audits by the Applicant, FDA, or a third party acting on behalf of the Applicant or FDA to ensure that all processes and procedures are in place and are being followed for the KTE-C19 REMS Program.
    e. Dispense KTE-C19 to patients only after verifying that two doses of tocilizumab are available for each patient and ready for administration within 2 hours.

For the Applicant:

3. To implement KTE-C19 REMS Program in hospitals, the Applicant must:
    a. Ensure that hospitals that dispense KTE-C19 are certified, in accordance with the requirements described above.
    b. Provide interactive training (either in person or via live webcast) for healthcare providers who prescribe, dispense, or administer axicabtagene ciloleucel to ensure that the hospital can complete the certification process. Provide all the following mechanisms for hospitals to complete: enrollment, documentation of training, knowledge assessment, and certification. The KTE-C19 REMS Program should include a procedure for recertifying hospitals.
    c. Ensure that hospitals are notified when they have been certified by the KTE-C19 REMS Program.
    d. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the certified hospital. If different, the hospital must be required to re-certify with a new authorized representative.
    e. Provide the REMS materials listed below to all healthcare providers at new sites who: (1) attempt to order KTE-C19 and are not yet certified or (2) inquire about how to become certified:
        - KTE-C19 REMS Program Knowledge Assessment
        - Slides for Live Training/ Hospital Training material(s)
        - KTE-C19 REMS Program Hospital Enrollment Form
        - KTE-C19 REMS Program website
        - KTE-C19 Patient Wallet Card
        - KTE-C19 Adverse Reaction Guide

4. To further implement KTE-C19 REMS Program, the Applicant must:
    a. Ensure that KTE-C19 is only distributed to certified hospitals.
    b. Maintain a validated secure database of hospitals that are certified to dispense KTE-C19 in the KTE-C19 REMS Program.

c. Maintain records of axicabtagene ciloleucel distribution and dispensing to certified hospitals to meet the REMS requirements.
d. Maintain an Axicabtagene ciloleucel REMS Program Call Center and a REMS Program Website. The REMS Program Website must include the option to print the Package Insert, patient-directed labeling (Medication Guide), and KTE-C19 REMS materials. The KTE-C19 product website must include a prominent REMS-specific link to the KTE-C19 REMS Program Website. The KTE-C19REMS website must not link back to the product website(s).
e. Ensure that KTE-C19 REMS Program website is fully operational and the REMS materials listed in or appended to the KTE-C19 REMS document are available through the Axicabtagene ciloleucel REMS Program Website and by calling the KTE-C19 REMS Program Call Center.
f. Monitor that the certified hospitals are evaluating their training program on a regular basis to ensure the requirements of the KTE-C19 REMS Program are being met; institute corrective action if noncompliance is identified and decertify hospitals that do not maintain compliance with the REMS requirements.
g. Maintain, with certified hospitals, an ongoing annual audit plan, and audit all newly certified hospitals within 180 calendar days after the hospital places its first order for KTE-C19 to ensure that all processes and procedures are in place and functioning to support the requirements of the KTE-C19 REMS Program. The newly certified hospital must also be included in the Applicant's ongoing annual audit plan.
h. Take reasonable steps to improve implementation of and compliance with the requirements in the KTE-C19 REMS Program based on monitoring and evaluation of this program.

The pharmacovigilance plan includes a long term, prospective, non-interventional registry study in patients treated with KTE-C19. This PMR study will follow the recipients of KTE-C19 for 15 years to assess RCR, persistence, and the potential for insertional mutagenesis with KTE-C19 that is transduced with a retrovirus and the associate risk of secondary malignancy.

Reviewer comments:

- **The REMS with ETASU and the PMR study are the recommendation of the clinical review team with concurrence from the pharmacovigilance reviewers from CBER OBE, CDER DRISK, and the CBER Safety Working Group. The goal of the REMS is to assure that sites are prepared for the safety risks of KTE-C19 that were identified in the IND phase of product development. The PMR Registry Study addresses the theoretical concerns of insertional mutagenesis or the development of a KTE-C19 related second malignancy. The Applicant is proposing to enroll approximately 1000 patients, and the final sample size is under review.**

- **The clinical review team recommends that the label inform of the requirement for inpatient monitoring for seven days following administration of KTE-C19. This recommendation is based on the requirements in the protocol, the clinical data related to the timing of onset of neurological and CRS events and the need for medical intervention requiring in hospital management. See the safety analysis, Section 6.1.2.5, for details.**

- **Negotiations with the applicant are still ongoing regarding the final REMS and ETASU documents. Please refer to the action letter for final wording of the PMR.**

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED

5.1 Review Strategy

The ZUMA-1 study, conducted under IND 016278, served as the primary basis for the review. Data reviewed included the integrated summary of safety (ISS), summary of clinical safety (SCS), summary of clinical efficacy (SCE), individual clinical study reports (CSRs), patient narratives, numerous IRs, and data in the public domain. JMP 13 was used to reproduce key efficacy analyses, based on the submitted data analysis datasets, and to conduct additional exploratory analyses.

The clinical safety review was primarily based upon analysis of ZUMA-1 (KTE-101-C19) with a data cut-off date of Jan 27, 2017. The ZUMA-1 protocol design is described in Section 6.1.2. Because subjects' characteristics and treatment regimen were similar between Phase 1 and Phase 2 arms, safety analysis of ZUMA-1 was pooled and analyzed.

Supportive data from the study ZUMA-2 were used in the Integrated Summary of Safety (ISS) analysis. Data from ZUMA-3 and ZUMA-4 were reviewed but were not included in the ISS analysis, given the different patient population and safety profile in the two studies (refer to Table 2 for details). Data from the (b) (4) were reviewed but were not included in the ISS analysis given the difference in the products used in each study. The database lock for the 120-day safety update report (SUR) was April 26, 2017. The primary safety review was based on originally submitted data with a cut-off date of January 27, 2017. Key findings in the SUR are provided at the end of section 6.1.12.6.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Per Section 5.1.

5.3 Table of Studies / Clinical Trials

ZUMA-1 is the primary basis for the efficacy and safety review, as summarized in Table 1. Supportive safety studies are summarized in Table 2.

Table 1: Overview of Primary Study

Trial	Design	Population	Primary Endpoint	# Treated	Data cutoff
KTE-C19-101 (ZUMA-1) [a]	single-arm, open-label, multicenter phase 1/2 trial of single KTE-C19 infusion (~2 x 10^6 cells/kg) after fludarabine/Cy conditioning	Age ≥18 with aggressive B-cell NHL that is refractory or relapsed ≤ 1 y after auto SCT	ORR per investigator	Phase 1: 8 apheresed, 7 infused Phase 2: 111 apheresed, 101 infused	SCS: 1/27/17 Efficacy – original: 1/27/17 (investigator) 12/14/16 (IRC) Efficacy – updated: 4/26/17

[a] Phase 2 data primary, phase 1 data supportive.
Cy, cyclophosphamide

Table 2: Overview of Supportive Studies Providing Additional Safety Data

Trial	Design	Population	# Treated	Data cutoff
KTE-C19-102 (ZUMA-2)	single-arm, open-label, multicenter phase 2 study of KTE-C19 or KTE-C19 ((b) (4))[a] infusion (~2 x 10^6 cells/kg) after fludarabine/Cy conditioning	Age ≥18 y with Relapsed/refractory Mantle Cell Lymphoma (MCL)	16 leukapheresed 11 treated	1/27/17
KTE-C19-103 (ZUMA-3)	single-arm, open-label, multicenter phase 1/2 study of KTE-C19 ((b) (4) infusion (~0.5, 1 or 2 x 10^6 cells/kg) after fludarabine/Cy conditioning	Age ≥18 y with Relapsed/refractory adult B-precursor Acute Lymphoblastic Leukemia (ALL)	12 leukapheresed 11 treated	1/27/17
KTE-C19-104 (ZUMA-4)	single-arm, open-label, multicenter phase 1/2 study of KTE-C19 ((b) (4) infusion (~1 or 2 x 10^6 cells/kg) after fludarabine/Cy conditioning	Age 2-21 y with Relapsed/refractory Pediatric B-precursor Acute Lymphoblastic Leukemia (ALL)	5 leukapheresed 4 treated	1/27/17

[a] Both KTE-C19 and KTE-C19 ((b) (4) comprise anti-CD19 CAR T cells; the products differ in their manufacturing processes. In ZUMA-2, the first 10 subjects treated as of the data cutoff date were treated with KTE-C19.

In support of efficacy and safety, the Applicant also submitted preliminary data from (b) (4) The review team did not consider these data as supportive, because the product differs from KTE-C19.

5.4 Consultations

- CBER Office of Biostatistics and Epidemiology (OBE): see Section 4.6 for Pharmacovigilance, Post-Marketing Requirements and REMS ETASU.
- CDER Division of Risk Management (DRISK): see Section 4.6 for REMS ETASU.
- CBER/CDER Pharmacometrics. See the reviewers' full reviews for details.

5.4.1 Advisory Committee Meeting

This application was not presented to an Advisory Committee, because KTE-C19 is not the first biologic in its class.

5.4.2 External Consults/Collaborations

This application was not presented to external consultants or collaborators.

5.5 Literature Reviewed

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Phillip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995;333:1540-1545.

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Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-

cell lymphoma who fail second-line salvage regimens in the international CORAL study. *Bone Marrow Transplant* 2016; 51(1): 51-57.

Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. *Bone Marrow Transplant* 2017; 52(2): 216-221.

Zelenetz AD, Gordon LI, Wierda WG et al. NCCN Guidelines: B-Cell Lymphomas, Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed 26 May 2017.

6. DISCUSSION OF INDIVIDUAL STUDIES

6.1 ZUMA-1 (KTE-C19-101)

A phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma

First enrollment: 4/21/2015
Study status: ongoing
Centers: 24 (U.S. 23, Israel 1)
Original data cutoff: 1/27/2017 (safety; efficacy per investigator), 12/14/2016 (IRC)
Updated cutoff: 4/26/2017 (efficacy and safety)

6.1.1 Objectives

ZUMA-1 is a single arm, open-label, multicenter phase 1/2 study for refractory aggressive B-cell NHL, with a primary endpoint of ORR after a single infusion of KTE-C19 preceded by cyclophosphamide/fludarabine lymphodepleting chemotherapy.

6.1.2 Design Overview

A phase 1 portion enrolled eight patients, of whom seven were treated and received the recommended dose-schedule of lymphodepleting chemotherapy and KTE-C19. A single-arm phase 2 expansion followed to evaluate efficacy.

6.1.3 Population

Key Eligibility Criteria

- Aggressive B-cell NHL, including DLBCL, T-cell rich large B-cell lymphoma, PMBCL, and transformed FL, that is
  - Primary refractory,
  - Refractory (SD or PD as best response) to second or greater line of therapy, or
  - Relapsed ≤ 1 year after auto SCT

  An additional cohort (Cohort 3), consisting of relapsed/refractory, transplant-ineligible lymphoma, is not part of this submission.
- Prior therapy:
  - Anti-CD20 monoclonal antibody and anthracycline required
  - No prior CD19-directed therapy permitted
  - No prior allo SCT

- At least 6 weeks between auto SCT and CART infusion
- Age ≥ 18
- ECOG PS 0-1
- Evaluations:
  - Absolute lymphocyte count ≥ 100/µL, ANC ≥ 1000/µL, platelets ≥ 75,000/µL
  - AST and ALT ≤ 2.5 x ULN, bilirubin ≤ 1.5 mg/dL
  - CrCl ≥ 60 mL/min
  - EF ≥ 50%
- Comorbidities:
  - No infection that is uncontrolled or requires IV therapy
  - No active CNS disease
  - No significant autoimmune disease
  - No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
  - No cardiac events within previous year
  - No thromboembolic events within 6 months
  - No hypoxemia, significant pleural effusion, or significant EKG findings

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Leukapheresis: 12-15 liter apheresis with target collection of ~5-10 x 10^9 mononuclear cells
- Lymphodepleting chemotherapy (Days -5, -4, and -3):
  - Fludarabine 30 mg/m^2/day IV and cyclophosphamide 500 mg/m^2/day IV (+/- mesna), each for 3 concurrent days
- KTE-C19 infusion (Day 0):
  - Single dose administered inpatient, followed by ≥ 7 day inpatient observation
  - Target of 2 x 10^6 CAR-positive T cells/kg (maximum 2 x 10^8 cells), administered by 30-minute IV infusion
- Supportive care: CRS and neurotoxicity management guidelines are provided in the Appendix (Table 40 and Table 41, respectively).

In ZUMA-1, no bridging therapy was permitted between the time of leukapheresis and conditioning.

6.1.5 Directions for Use

Sites received an investigational product manual that details KTE-C19 storage and administration.

6.1.6 Sites and Centers

There were 24 sites, all but one being in the U.S.

6.1.7 Surveillance/Monitoring

Refer to the evaluation schedule in the Appendix (Table 42). After Month 3, disease assessments occur every 3 months until Month 18, then every 6 months until Month 60, then yearly. After 6 months, the protocol requires long-term follow for up to 15 years, including monitoring for RCR.

The protocol required the following assessments/interventions for neurotoxicity monitoring:

- A full neurological assessment at screening to establish a baseline with subsequent assessments before KTE-C19 administration on Day 0, on Day 1, and then every other day while hospitalized.
- Dedicating a single research staff member familiar with or trained in the administration of

the MMSE to conduct the assessment to minimize inter-rater variability.

Evaluation of any new onset ≥ Grade 2 neurotoxicity was to include a neurological examination (including a MMSE), brain MRI, electroencephalogram (EEG), and examination of the cerebrospinal fluid (CSF). In addition, subjects with ≥ Grade 3 neurotoxicity were to be monitored with continuous cardiac telemetry and pulse oximetry as clinically indicated.

6.1.8 Endpoints and Criteria for Study Success

Phase 2 primary endpoint: ORR per investigator, according to 2007 International Working Group criteria

Secondary endpoints include:
- BOR, DOR, and progression-free survival (PFS) per investigator
- ORR, BOR, and DOR per IRC
- OS
- Safety
- Correlative studies

6.1.9 Statistical Considerations & Statistical Analysis Plan

Refer to the statistical review.

Analysis population: In phase 2, the primary efficacy analyses involved the mITT population, defined as all patients treated with at least 1.0×10^6 CAR-positive T cells/kg.

Censoring for time-to-event endpoints: For the primary analyses of DOR and PFS, the Applicant censored patients at the last disease assessment prior to initiation of new anti-lymphoma therapy, with the exception of SCT. Patients were censored for SCT in sensitivity analyses.

Reviewer comments:

- **For a single-arm study, the primary efficacy analysis, rather than sensitivity analysis, should censor patients for DOR and PFS at the time of SCT. Accordingly, the analyses presented in Section 7 and the recommended prescribing information (PI) censor patients at the time of SCT.**

- **Correction of errors in the censoring of DOR and PFS required multiple IRs and dataset revisions.**

6.1.10 Study Population and Disposition

Refer to Sections 7.1.2 and 7.1.3.

6.1.11 Efficacy Analyses

Refer to Section 7.

Refer to the statistical review for results of the phase 2 interim analyses and the prespecified primary analysis based on 92 patients. The primary efficacy endpoints were met in each case. Two prespecified interim analyses of ORR, one for futility and one for efficacy, were conducted, based on a null ORR of ≤ 20% and an alternative ORR of ≥ 40%. The prespecified primary analysis

compared investigator-assessed ORR for 92 patients in the mITT analysis set to the null rate of 20% using a 1-sided exact binomial test. Nine additional patients were treated and thus are included in the mITT assessment of efficacy (N = 101).

6.1.12 Safety Analyses

6.1.12.1 Methods

The key materials used for the safety review included:

- The BLA application electronic submission
- Applicant submissions in response to the review teams' information requests
- Published literature
- Prior regulatory history

The clinical review of safety was primarily based upon analysis of ZUMA-1. The KTE-C19-101 datasets were used for the safety analysis. Because subjects' characteristics and treatment regimen were similar between Phase 1 and Phase 2 arms, safety analysis of ZUMA-1 consisted of the pooled analyses of both phases of the study.

Analyses by the clinical reviewer for safety were performed largely using JReview 11.0 and JMP 13 (SAS Institute, Inc.). All narratives and relevant CRFs were reviewed. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. AE severity was graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. CRS was reported and graded as a syndrome using a grading scale specific for CRS (Lee et al, 2014) and per CTCAE 4.03.However, for the purposes of the review the Lee criteria was used. Individual symptoms associated with CRS were also reported as AEs. Some AEs are presented, throughout the review memo, as grouped terms as defined by this reviewer. The complete list of FDA grouped terms is presented in Table 43.Unless otherwise specified all analyses and tables were generated by the FDA reviewer.

Safety analysis set included all subjects treated with any dose of KTE-C19. All AEs were collected from the start of leukapheresis until 90 days after KTE-C19 infusion. A severe adverse event (SAE) was defined as an AE that met at least one of the following serious criteria: fatal, life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, congenital anomaly/birth defect, or any other medically important serious event. SAEs were collected from screening. Treatment-emergent adverse events (TEAEs) were defined by the Applicant as occurring after the start of conditioning chemotherapy. However, for the purpose of this review, TEAEs (referred to in the review as AEs) were defined as all AEs occurring after the start of KTE-C19 administration. A separated analysis of AEs that occurred from Leukapheresis until the start of conditioning chemotherapy, and from the start of conditioning regimen until the day before KTE-C19 infusion, were conducted and presented separately. Similarly, adverse drug reactions (ADRs) were defined as any AE occurring after the start of KTE-C19 infusion regardless of relationship and causality with the investigational product. From Month 3 and until 24 months, or disease progression, whichever occurred first, only the following targeted AEs/SAEs were collected: hematologic events, neurologic events, infections, autoimmune disorders, and secondary malignancies.

Reviewer comment:

- **The Applicant's methodology for determining ADRs differs from the one the reviewer used. The Applicant defined ADRs as: 1) any AE with an incidence of ≥10% that is consistent with the pharmacology of the drug, temporality, and the consistency of the pattern of symptoms across studies/indications; 2) any AE with an incidence < 10% if the event is known to be associated with CAR-T therapies based on published literature or data from KTE-C19 studies, or if the AE was assessed by the Applicant as related to KTE-C19. This definition is subjective. Furthermore, the CAR-T cell therapy is preceded by conditioning chemotherapy; therefore, it is often difficult to parse out the causality of AEs. For the above-mentioned reasons and in order to decrease bias in this uncontrolled study, the reviewer considered any AE that occurred after initiating KTE-C19 treatment as an ADR.**

- **Negotiations are ongoing with the applicant regarding ADR definitions. Please refer to the package insert (PI for final version of the safety tables and AEs group terms.**

The safety population was based on combined data from seven subjects in Phase 1 and 101 subjects in Phase 2 who were enrolled in ZUMA-1 study and received KTE-C19 treatment. The median duration of follow up for safety was 218 days, with a range of nine to 581 days Table 3 below summarizes the baseline characteristics of this patient population.

Table 3: Demographics of the Safety Population

Characteristics [n (%)]	Statistics	Phase1	Phase2 Cohort1	Phase2 Cohort2	Total subjects
Evaluable population		**7 (6%)**	**77 (71%)**	**24 (22%)**	**108 (100%)**
Sex	F	2 (29%)	27 (35%)	6 (25%)	**35 (32%)**
	M	5 (71%)	50 (65%)	18 (75%)	**73 (68%)**
Age Group	<65 Years	4 (57%)	60 (78%)	17 (71%)	**81 (75%)**
	>=65 Years	3 (43%)	17 (22%)	7 (29%)	**27 (25%)**
Race	Asian	0 (0%)	1 (1%)	3 (13%)	**4 (4%)**
	Black or African American	1 (14%)	3 (4%)	1 (4%)	**5 (5%)**
	Other	0 (0%)	2 (3%)	1 (4%)	**3 (3%)**
	White	6 (86%)	71 (92%)	19 (79%)	**96 (89%)**
Ethnicity	Hispanic or Latino	1 (14%)	16 (21%)	2 (8%)	**19 (18%)**
	Not Hispanic or Latino	6 (86%)	61 (79%)	22 (92%)	**89 (82%)**
Country	ISR	0 (0%)	0 (0%)	1 (4%)	**1 (1%)**
	USA	7 (100%)	77 (100%)	23 (96%)	**107 (99%)**
ECOG Performance Status	0	4 (57%)	28 (36%)	14 (58%)	**46 (43%)**
	1	3 (43%)	49 (64%)	10 (42%)	**62 (54%)**
Retreat Safety Population	Y	1 (14%)	8 (10%)	1 (4%)	**10 (9%)**

Table 3: Demographics of the Safety Population

Characteristics [n (%)]	Statistics	Phase1	Phase2 Cohort1	Phase2 Cohort2	Total subjects
Retreat Modified ITT Pop	Y	0 (0%)	8 (10%)	1 (4%)	**9 (8%)**
Subject with DLT Occurrence in 30 Days	Y	1 (14%)	0 (0%)	0 (0%)	**1 (1%)**
Reason for Discontinuation from Treatment	Completed treatment	7 (100%)	77 (100%)	24 (100%)	**108 (100%)**
Reason for Discontinuation from Study	Death	4 (57%)	27 (35%)	3 (13%)	**34 (31%)**

Source: FDA analysis. ADSL dataset.
Abbreviations: Pop: Population; ECOG: Eastern Cooperative Oncology Group

Table 4 below lists the number of prior chemotherapy regimen subjects received prior to enrollment in the ZUMA-1 study. All subjects received prior anthracycline and anti-CD20 therapies. Twenty nine subjects (27%) received prior ASCT. Two subjects had primary refractory disease.

Table 4: Number of prior lines of therapy

Number of Prior Chemotherapy Regimen	Total Subjects N (%)
1	2 (2%)
2	30 (28%)
3	35 (32%)
4	29 (27%)
5	6 (6%)
>5	6 (6%)

Source: FDA analysis

Reviewer comment:

- **Because of the strict eligibility enrollment criteria in regards to performance status and end organ function, many typical patients with rel/ref B cell lymphoma would not qualify for this study.**

6.1.12.2 Overview of Adverse Events

Detailed safety data are available for the total of 108 subjects who were included in the safety analysis set. For the purposes of the safety review, “Day 0” refers to the day of KTE-C19 infusion. Throughout this review, some AEs are presented as grouped terms. The Applicant grouped certain terms when presenting the adverse reactions but didn’t use the grouped terms when analyzing all AEs. Moreover, the grouping was limited and occasionally missed cases. For example, certain AEs that were suggestive of a single clinical entity were sometimes termed using different dictionary derived terms (e.g. “hypoxia” and “oxygen saturation decreased”). Therefore, FDA utilized a

different grouping strategy for comprehensive analyses of AEs. Please refer to Table 43 for full list of FDA grouped terms. Example of FDA grouped terms includes:

Arrhythmia = Arrhythmia, Atrial fibrillation, Atrial flutter, Atrioventricular block, Bundle branch block right, Electrocardiogram QT prolonged, Extra-systoles, Heart rate irregular, Supraventricular extrasystoles, Supraventricular tachycardia, Ventricular arrhythmia, Ventricular tachycardia.
Encephalopathy = Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Hypersomnia, Leukoencephalopathy, Memory impairment, Mental status changes, Paranoia, Somnolence, Stupor.
Lung infection = Aspiration, Lung infection, Pneumonia, Pneumonia klebsiella, Pneumonia staphylococcal

All 108 subjects (100%) had at least one AE. An overview of all AEs with a data cutoff date of Jan 27, 2017 is presented in Table 5.

Table 5: Overview of Adverse Events in the Safety Analysis Set; (N = 108)

Adverse events	Subjects N (%)
Any AE	108 (100%)
Worst Grade ≥3	102 (94%)
Any SAE	56 (52%)
Worst Grade ≥3	48 (44%)
Any CRS	101 (94%)
Worst Grade ≥3	14 (13%)
Any Neurotoxicity	94 (87%)
Worst Grade ≥3	34 (31%)
Fatal AEs excluding PD	4 (4%)

Source: FDA analysis. ADAE dataset.
Abbreviation: AE, adverse event. SAE, serious adverse event. PD, progressive disease.
Note: CRS events were graded by Lee et al 2014. CRS grading is provided by the syndrome level.
AEs and SAEs are events that occurred after the administration of KTE-C19.

Table 6 below summarizes subjects with AEs by worse toxicity grade. The majority of the maximum toxicity grades were Grade 3 and 4 events. Grade 5 events included four AEs that lead to death, and 6 events of B-cell lymphoma (PD). See Section 6.1.12.3 for details regarding deaths that occurred during the ZUMA-1 study.

Table 6: Adverse Events by Worst Toxicity Grade

Adverse Events Worst Toxicity Grade	Subjects N (%)
Any tox grade	108 (100%)
1	0 (0%)
2	6 (6%)
3	29 (27%)
4	63 (58%)
5	10 (9%)

Source: FDA analysis

Incidence of AEs by system organ class (SOC) are presented in Table 7.

Table 7: Most Frequent AEs (≥5%) per MedDRA SOC in the Safety Analysis Set; (N = 108)

Body System Organ Class **AE**	**All Grades** **N (%)**	**Grades 3 or higher** **N (%)**
Blood and lymphatic system disorders		
Neutropenia	86 (80%)	79 (73%)
Anemia	63 (58%)	46 (43%)
Thrombocytopenia	59 (55%)	42 (39%)
Leukopenia	46 (43%)	43 (40%)
Lymphopenia	23 (21%)	22 (20%)
Cardiac disorders		
Tachycardia	62 (57%)	2 (2%)
Arrhythmia	25 (23%)	8 (7%)
Sinus Bradycardia	7 (6%)	0 (0%)
Cardiac failure	7 (6%)	5 (5%)
Eye disorders		
Vision Blurred	5 (5%)	0 (0%)
Gastrointestinal disorders		
Diarrhea	41 (38%)	4 (4%)
Nausea	37 (34%)	0 (0%)
Vomiting	28 (26%)	1 (1%)
Constipation	25 (23%)	0 (0%)
Abdominal Pain	15 (14%)	1 (1%)
Dry Mouth	13 (12%)	0 (0%)
Abdominal Distension	7 (6%)	0 (0%)
General disorders and administration site conditions		
Fever	93 (86%)	17 (16%)
Fatigue	50 (46%)	3 (3%)
Chills	43 (40%)	0 (0%)
Edema	21 (19%)	1 (1%)
Asthenia	10 (9%)	2 (2%)
Pain	9 (8%)	1 (1%)
Non-Cardiac Chest Pain	7 (6%)	0 (0%)
Immune system disorders		
Immunoglobulins Decreased	16 (15%)	0 (0%)
Infections and infestations		
Infections Pathogen unspecified	28 (26%)	17 16%)

Body System Organ Class **AE**	**All Grades** **N (%)**	**Grades 3 or higher** **N (%)**
Viral infection	17 (16%)	4 (4%)
Bacterial infection	14 (13%)	10 (9%)
Lung infection*	13 (12%)	11 (10%)
Fungal infection	5 (5%)	0 (0%)
Injury, poisoning and procedural complications		
Fall	7 (6%)	0 (0%)
Investigations		
Weight Decreased	17 (16%)	0 (0%)
Metabolism and nutrition disorders		
Decreased Appetite	48 (44%)	2 (2%)
Hypocalcemia	35 (32%)	7 (6%)
Hypoalbuminemia	35 (32%)	1 (1%)
Hyponatremia	34 (31%)	9 (8%)
Hypokalemia	33 (31%)	2 (2%)
Hypophosphatemia	29 (27%)	22 (20%)
Hyperglycemia	21 (19%)	5 (5%)
Dehydration	12 (11%)	3 (3%)
Hypomagnesaemia	11 (10%)	0 (0%)
Hyperkalemia	8 (7%)	0 (0%)
Musculoskeletal and connective tissue disorders		
Motor Dysfunction	20 (19%)	1 (1%)
Back Pain	16 (15%)	1 (1%)
Myalgia	15 (14%)	1 (1%)
Pain in Extremity	13 (12%)	1 (1%)
Arthralgia	11 (10%)	0 (0%)
Neck Pain	6 (6%)	0 (0%)
Bone Pain	5 (5%)	1 (1%)
Neoplasms benign, malignant		
B-Cell Lymphoma	6 (6%)	6 (6%)
Nervous system disorders		
Encephalopathy	62 (57%)	31 (29%)
Headache	49 (45%)	1 (1%)
Tremor	34 (31%)	2 (2%)
Dizziness	22 (20%)	0 (0%)
Aphasia	19 (18%)	7 (6%)
Dysgeusia	8 (7%)	0 (0%)
Ataxia**	8 (7%)	1 (1%)

Body System Organ Class AE	All Grades N (%)	Grades 3 or higher N (%)
Psychiatric disorders		
Delirium	18 (17%)	7 (6%)
Insomnia	15 (14%)	
Anxiety	12 (11%)	1 (1%)
Renal and urinary disorders		
Renal Insufficiency	13 (12%)	5 (5%)
Urinary Incontinence	7 (6%)	1 (1%)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	35 (32%)	12 (11%)
Cough	32 (30%)	0 (0%)
Dyspnea	21 (19%)	3 (3%)
Pleural Effusion	14 (13%)	2 (2%)
Pulmonary Edema	10 (9%)	3 (3%)
Oropharyngeal Pain	8 (7%)	1 (1%)
Nasal Congestion	6 (6%)	0 (0%)
Skin and subcutaneous tissue disorders		
Rash	10 (9%)	0 (0%)
Pruritus	8 (7%)	0 (0%)
Vascular disorders		
Hypotension	62 (57%)	16 (15%)
Hypertension	16 (15%)	6 (6%)
Thrombosis	11 (10%)	1 (1%)

Source: FDA analysis. ADAE dataset.
*Lung infection group term includes: Aspiration, Lung infection, Pneumonia, Pneumonia klebsiella and Pneumonia staphylococcal.
**Three ataxia events were classified in the general disorders system by the Applicant as “gait disturbance”. These events are included in this table under the nervous system disorders. Please refer to Section 6.1.12.5 (neurotoxicity) for more details.

Overall, 44 subjects (41%) had ongoing AEs at the time of the data cutoff, and eight subjects (7%) had ongoing AEs of G≥3 that were all related to cytopenia.

Reviewer comment:

- **The overall AEs noted after KTE-C19 treatment are of acceptable severity given subjects’ advanced stage of the disease. Infections and cytopenias are also known risks from lymphodepletion chemotherapy and pre-existing conditions as discussed below.**

A separate analysis was performed to identify the incidence of AEs and G≥3 AEs during the

leukapheresis and conditioning chemotherapy periods respectively. As expected, increased AEs that are related to chemotherapy side effects such as nausea, vomiting, decreased appetite and cytopenia was observed in the conditioning chemotherapy period. See below.

Leukapheresis period:
This period was defined from the day of leukapheresis until the day before the start of conditioning chemotherapy. The leukapheresis population included 119 subjects. Table 8 below summarizes the AEs that occurred in this period.

Table 8: Adverse Events in the Leukapheresis Period (≥5%)

Adverse Events	Subjects N (%)
Any AE	75 (63%)
Anemia	19 (16%)
Lymphopenia	14 (12%)
Leukopenia	13 (11%)
Thrombocytopenia	12 (10%)
Hypokalemia	11 (9%)
Hyperglycemia	10 (8%)
Neutropenia	10 (8%)
Nausea	9 (8%)
Constipation	8 (7%)
Fatigue	8 (7%)
Hypoalbuminemia	8 (7%)
Cough	7 (6%)
Fever	7 (6%)
Anxiety	6 (5%)
Decreased Appetite	6 (5%)
Edema	6 (5%)
Pain	6 (5%)

Source: FDA analysis. ADAE dataset.

Grade 3 or higher AEs occurred in 35 subjects (29%) and mainly included cytopenias.

Conditioning chemotherapy period:
This period was defined from the first day of chemotherapy administration until Day -1 (the day prior to KTE-C19 infusion). The conditioning chemotherapy population included 110 subjects. Table 9 below summarizes the AEs that occurred in this period.

Table 9: Adverse Events in the Chemotherapy Conditioning Period (≥5%)

Adverse Events	Subjects N (%)
Any AE	96 (87%)
Nausea	39 (35%)
Anemia	30 (27%)
Leukopenia	30 (27%)
Thrombocytopenia	27 (25%)
Lymphopenia	26 (24%)
Neutropenia	23 (21%)
Hypoalbuminemia	21 (19%)
Constipation	17 (15%)
Fatigue	17 (15%)
Diarrhea	15 (14%)
Hyperglycemia	13 (12%)
Hypocalcemia	13 (12%)
Decreased Appetite	12 (11%)
Hypomagnesemia	12 (11%)
Vomiting	12 (11%)
Edema	11 (10%)
Fever	10 (9%)
Hyponatremia	9 (8%)
Hypophosphatemia	8 (7%)
Tachycardia	8 (7%)
Cough	6 (5%)
Dyspnea	6 (5%)
Hypertension	6 (5%)
Hypotension	6 (5%)
Abdominal Pain	5 (5%)
Headache	5 (5%)
Hypokalemia	5 (5%)
Insomnia	5 (5%)
Pleural Effusion	5 (5%)

Source: FDA analysis. ADAE dataset.

Grade 3 or higher AEs occurred in 57 subjects (52%) and mainly included cytopenias.

6.1.12.3 Deaths

The reviewer reviewed all narratives and CRFs to confirm the cause of death. In addition to the narratives themselves, the Applicant provided their adjudication of the proximate and/or root cause of death in each case. FDA considered the cause of death to be the underlying malignancy when supported by worsening of disease by imaging, biopsy, autopsy or description of other objective evidence.

The majority of the deaths were due to the progressive disease (30 subjects, 28%). Four deaths were considered by FDA to be related to treatment with KTE-C19, and these are summarized in Table 10. Two of these deaths occurred within 30 days of KTE-C19 infusion. Additionally, the reviewer identified one death that occurred within 30 days and was reported by the Applicant as

due to progressive disease. However, the subject had evidence of CRS as well at the time of death. See narrative below for subject 101-010-001 (Deaths in subjects treated with KTE-C19).

Deaths in subjects not treated with KTE-C19:
In the Phase 2 study, 10 subjects were enrolled but not treated with KTE-C19. These 10 subjects included eight subjects who underwent leukapheresis and two subjects who underwent leukapheresis and received conditioning chemotherapy. Eight of these 10 subjects died. Six subjects died due to PD. One subject (Subject 101-001-003) died from myelodysplastic syndrome (MDS) that occurred one year after starting other therapy off study. One subject (Subject 101-016-002) died from tumor lysis syndrome (TLS) that was considered related to conditioning chemotherapy. Narratives for the two subjects who died due to an AE are listed below:

Subject 101-001-003: was a 56-year-old Asian male with Stage 2 DLBCL. He underwent leukapheresis but subsequently withdrew from the study due to suspected intestinal obstruction and therefore did not meet the eligibility criteria. The subject subsequently enrolled in another trial and died due to chemotherapy-related MDS.

Subject 101-016-002: was a 45-year-old white male with Stage 3 transformed FL who developed Grade 4 TLS one day after starting conditioning chemotherapy. He did not receive the third dose of conditioning chemotherapy nor KTE-C19. The subject developed aspiration pneumonia, septic shock, acute kidney injury, gastrointestinal perforation and bleeding, and subsequently died two days after conditioning chemotherapy. He had PD per imaging study performed prior to his death.

Death in subjects treated with KTE-C19:
A total of 34 subjects who were treated with KTE-C19 died; four subjects in Phase 1 and 30 subjects in Phase 2. Thirty subjects died of PD and four died due to AEs. Three deaths occurred within 30 days of KTE-C19 infusion; two due to AEs and one due to PD. Table 10 below depicts a summary of all deaths in the safety analysis set. Subjects IDs are provided for subjects who died due to an AE or within 30 days of KTE-C19 infusion.

Table 10: Deaths in the Safety Analysis Set; (N = 108)

	ZUMA-1 N (%)	Subject ID	Cause of Death	Study Day of Death*
All Deaths	**34 (32%)**			
Adverse events	4 (4%)			
		101-009-001	Intracranial hemorrhage/CRS	16
		101-009-007	Anoxic brain injury/cardiac arrest/CRS	34
		101-003-006	(HLH/MAS)/CRS	40
		101-022-003	Pulmonary embolism	15
Progressive disease	30 (28%)			
		101-010-001	PD/Possible CRS	9

Source: FDA analysis. ADSL dataset.
*Study Day 0 = Day of KTE-C19 infusion
Abbreviations: HLH/MAS: Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome, CRS: Cytokine Release Syndrome, PD: progressive disease.

Narratives for subjects who died due to an AE or within 30 days of KTE-C19 treatment are listed below:

Subject 101-009-001: was a 29-year-old black female with Stage 3 DLBCL who died on Day 16 with intracranial hemorrhage. The subject developed Grade 4 CRS, acute cardiac failure, encephalopathy, sepsis and acute kidney injury which required dialysis. On Day 16, the subject was on maximum oxygen and vasopressor support and no longer responsive with dilated and fixed pupils. An autopsy revealed intracranial hemorrhage. The subject had thrombocytopenia and was on heparin for DVT prophylaxis at the time of death.

Subject 101-009-007: was a 63-year-old white male with Stage 4 transformed FL who died due to sequelae of cardiac arrest leading to irreversible anoxic brain injury. Four days following axicabtagene ciloleucel infusion, the subject developed Grade 3 encephalopathy followed by Grade 4 CRS consisting of acidosis and cardiac arrest while undergoing an arterial line placement, leading to anoxic brain injury. After the cardiac event, the subject had acute kidney injury and was placed on continuous veno-venous hemodialysis (CVVHD). He later experienced atrial fibrillation, hypotension and multiple subacute brain infarcts. Due to a lack of recovery of neurologic status, he was enrolled in hospice care and he died on Day 34. Autopsy report indicated acute myocardial infarction, recurrent DLBCL, and multiple brain infarcts.

Subject 101-003-006: was a 66-year-old white female with Stage IV DLBCL who died of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) on Day 40. The subject developed Grade 3 CRS, encephalopathy, pneumonia, pleural effusion, decreased left ventricular function, pancytopenia, hyperferritinemia and direct hyperbilirubinemia. Bone marrow biopsy on Day 29 showed hypocellularity but no evidence of HLH; however, she was started on dexamethasone and etanercept for suspected HLH. Encephalopathy worsened on Day 37 and the subject died on Day 40. The autopsy report showed DLBCL, pneumonia, and mild-moderate hemophagocytosis in lymph nodes, spleen, liver and bone marrow which was consistent with HLH. The subject did not have any genetic predisposition by next-generation sequence analysis of 14 HLH associate genes.

Subject 101-022-003: 51-year-old white male with stage 3 transformed FL who had pulmonary embolism (PE) on Day 15. The subject developed Grade 1 CRS Grade 1 and Grade 3 neurotoxicity. He was started on enoxaparin on Day 14 for deep vein thrombosis (DVT) prophylaxis. On Day 15, the subject developed acute respiratory distress and hypotension leading to pulseless electrical activity (PEA) and cardiac arrest. An autopsy demonstrated a massive saddle pulmonary embolism. Risk factors for venous thromboembolism in this subject were malignancy and obesity.

Subject 101-010-001: was a 64-year-old white, female with Stage 4 DLBCL who died of disease progression on Day 9. The subject developed CRS Grade 1 from Day 2 to Day 4 for which she received tocilizumab. On Day 7, the subject experienced acute tachypnea, tachycardia, metabolic acidosis, acute kidney injury and Grade 2 CRS. She received another dose of tocilizumab. On Day 8, she developed hypotension, shock, and acute respiratory failure. She was on mechanical ventilation, vasopressor support and continuous renal replacement therapy (CRRT). She received corticosteroids for possible CRS. She was afebrile. On Day 9, the subject experienced ventricular tachycardia and cardiac arrest. She developed disseminated intravascular coagulation (DIC) and died on the same day. An autopsy showed rapidly progressive disease.

Reviewer comments:

- **The following four subjects, 101-009-001, 101-003-006, 101-009-007, and 101-010-001 all died in the setting of CRS, irrespective of their primary cause of death. Therefore, this information will be included in the label.**

- **Subject 101-011-001 is listed as having died due to an AE, but died from PD (ZUMA-1 Dataset Errata).**

6.1.12.4 Nonfatal Serious Adverse Events

For the purpose of this review and as clarified earlier, SAEs were defined as any serious AE that occurred after the start of KTE-C19 administration. SAEs occurred in 56 of 108 subjects (52%). All subjects were hospitalized for a minimum of seven days per protocol. Seventeen of a total of 108 subjects (16%) were admitted to the intensive care unit (ICU). Table 11 summarizes all SAEs and Grade ≥3 SAEs.

Table 11: Subject Incidence of SAEs in the Safety Analysis Set; (N = 108)

SAEs	All grades N (%)	Grades 3 or higher N (%)
Any	**56 (52%)**	**48 (44%)**
Encephalopathy	23 (21%)	21 (19%)
Lung Infection	10 (9%)	2 (2%)
Fever	8 (7%)	8 (7%)
Neutropenia	7 (6%)	6 (6%)
B-Cell Lymphoma	6 (6%)	6 (6%)
Arrhythmia	6 (6%)	4 (4%)
Cardiac Failure	6 (6%)	4 (4%)
Urinary Tract Infection	4 (4%)	4 (4%)
Renal Insufficiency	3 (3%)	3 (3%)
Aphasia	3 (3%)	3 (3%)
Cardiac Arrest	3 (3%)	3 (3%)
Hypotension	3 (3%)	3 (3%)
Hypoxia	3 (3%)	3 (3%)
Clostridium Difficile Infection	3 (3%)	3 (3%)
Delirium	3 (3%)	3 (3%)
Headache	2 (2%)	1 (1%)
Myelodysplastic Syndrome	2 (2%)	2 (2%)
Lactic Acidosis	2 (2%)	2 (2%)
Dyspnea	2 (2%)	2 (2%)
Pulmonary edema	2 (2%)	2 (2%)
Herpes	2 (2%)	2 (2%)
Fatigue	1 (1%)	0 (0%)
Intracranial hemorrhage	1 (1%)	1 (1%)
Brain Injury	1 (1%)	1 (1%)
Escherichia Bacteremia	1 (1%)	1 (1%)
HLH	1 (1%)	1 (1%)
Hypercalcemia	1 (1%)	1 (1%)
Hypertension	1 (1%)	1 (1%)

SAEs	All grades N (%)	Grades 3 or higher N (%)
Hypophosphatemia	1 (1%)	1 (1%)
Bone Pain	1 (1%)	1 (1%)
Carcinoma In Situ	1 (1%)	1 (1%)
Immunoglobulins Decreased	1 (1%)	0 (0%)
Klebsiella Infection	1 (1%)	1 (1%)
Device Related Infection	1 (1%)	1 (1%)
Lethargy	1 (1%)	0 (0%)
Bacterial Sepsis	1 (1%)	1 (1%)
Motor Dysfunction	1 (1%)	1 (1%)
Cytomegalovirus Infection	1 (1%)	1 (1%)
Back Pain	1 (1%)	1 (1%)
Edema	1 (1%)	0 (0%)
Pain In Extremity	1 (1%)	1 (1%)
Pancytopenia	1 (1%)	1 (1%)
Pleural Effusion	1 (1%)	1 (1%)
Presyncope	1 (1%)	0 (0%)
Bone Marrow Failure	1 (1%)	1 (1%)
Aspiration (lung infection)	1 (1%)	1 (1%)
Dehydration	1 (1%)	1 (1%)
Seizure	1 (1%)	1 (1%)
Sepsis	1 (1%)	1 (1%)
Shock	1 (1%)	1 (1%)
Soft Tissue Infection	1 (1%)	1 (1%)
Squamous Cell Carcinoma	1 (1%)	1 (1%)
Thrombocytopenia	1 (1%)	1 (1%)
Thrombosis	1 (1%)	1 (1%)
Troponin T Increased	1 (1%)	1 (1%)
Acidosis	1 (1%)	1 (1%)

Source: FDA analysis. ADAE dataset.
Abbreviation: SAEs: severe adverse events. HLH: Hemophagocytic lymphohistiocytosis

6.1.12.5 Adverse Events of Special Interest (AESI)

Cytokine Release Syndrome (CRS)
CRS occurred in 101/108 subjects (94%), 13% of whom experienced Grade 3 or higher (severe, life threatening or fatal) CRS. Among subjects who died after receiving KTE-C19, four had CRS events at the time of death (see section 6.1.12.3 for details). The median time to onset was 2 days (range 1 to 12 days) and the median time to resolution of CRS was 8 days (range for the duration of CRS:1 to 57 days) (Q1, Q3*: 5, 13 days). Manifestation of CRS included fever, hypotension, hypoxia, tachycardia and chills. Serious events that may be associated with CRS include acute kidney injury, cardiac arrhythmias including atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). CRS was graded based on the modified Lee 2014 criteria. The median time to onset of Grade ≥ 3 in subjects who experienced at least Grade 3 toxicities was 2 days. The median duration of Grade ≥ 3 CRS was 10.5 days.

Forty-five percent (49/108) of subjects received tocilizumab, 19 of whom received more than one dose. See more details in the concomitant medication section. Please refer to Appendix I for CRS grading as per Lee 2014 criteria and Appendix II for CRS management guidance that was used during the clinical studies.

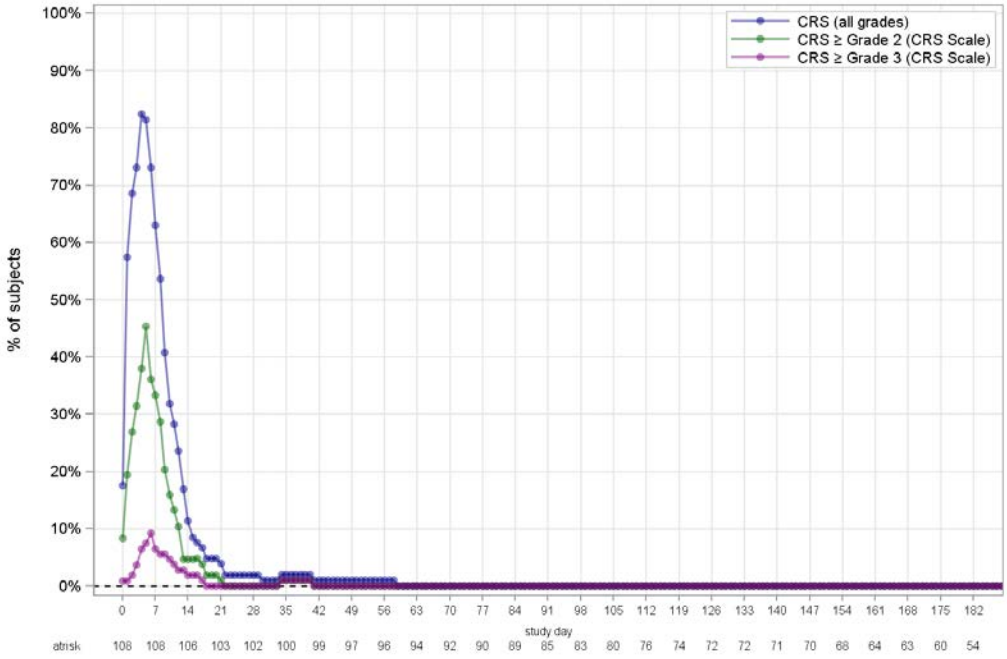
Reviewer comments:

- ***Quartile 1 (Q1 = 25th percentile) and Quartile 3 (Q3 = 75th percentile). The proposed Package Insert (PI) will include the CRS duration range and will not include the Q1-Q3 information, because the range might be more useful to the health care provider.**

- **The Applicant's definition of CRS duration was calculated as "the number of days from the first onset of CRS syndrome to the last stop date of CRS syndrome, with the non-event date in between subtracted (ie: [stop date of last CRS – Start date of first CRS +1] – number of non-event days in between)". This definition is not acceptable, because in many instances, while reviewing the CRFs and subjects' narratives, we confirmed that certain CRS individual symptoms in some subjects remained despite the investigator/Applicant's claim that CRS had resolved. Therefore, for the purpose of this review, CRS duration was calculated without subtracting the non-event date in between. The CRS duration was calculated based on earliest day in the study period and final study day that event was noted. This analysis includes the subjects who were retreated with KTE-C19.**

The majority of CRS symptoms resolved at the time of the data cutoff except for the four subjects who had CRS events at the time of their death. See Figure 1, which illustrates the time course of CRS onset and duration by grade.

Figure 1: CRS Time Course by Grades



Source: FDA analysis. SAS ADAE XC.

Reviewer comment:

- **The Applicant indicated that 100 subjects (93%) had CRS events. However, the reviewer identified one additional subject (ID: 101-009-008) who presented with CRS symptoms but was not flagged for CRS in the ADAE datasets, and therefore was missed by the Applicant. Review of his narrative and CRF indicates that he experienced Grade 1 CRS (fever, tachycardia, headache, elevated IL6 levels and nausea). Nausea started on Day –4 and continued until other CRS symptoms resolved on Day 29. The subject did not receive any tocilizumab. He died of PD on Day 173.**

Table 12: CRS Toxicity Grade

Worst CRS Toxicity Grade	Subjects N (%)
CRS Any Grade	101 (94%)
Grade 1	42 (39%)
Grade 2	45 (42%)
Grade 3	9 (8%)
Grade 4	4 (4%)
Grade 5	1 (1%)

Source: FDA analysis. XC dataset.

The most common CRS symptoms included fever, hypotension, tachycardia, hypoxia, and chills. Table 13 and Table 14 present the individual CRS symptoms.

Table 13: CRS Individual Symptoms

CRS AEs	Subjects N (%)
Fever	84 (78%)
Hypotension	44 (41%)
Tachycardia	30 (28%)
Hypoxia	24 (22%)
Chills	22 (20%)
Renal Insufficiency	6 (6%)
Fatigue	6 (6%)
Headache	6 (6%)
Arrhythmia	6 (6%)
Cardiac Failure	5 (5%)
Vomiting	4 (4%)
Myalgia	4 (4%)
Neutropenia	4 (4%)
Diarrhea	3 (3%)
Pulmonary edema	3 (3%)
Dyspnea	3 (3%)
Hypertransaminasemia	2 (2%)
Asthenia	2 (2%)
Decreased Appetite	2 (2%)
Metabolic Acidosis	2 (2%)
Edema	2 (2%)
Tachypnea	2 (2%)
Nasal Congestion	1 (1%)
Cough	1 (1%)
CRS	1 (1%)
Oliguria	1 (1%)
Hyperhidrosis	1 (1%)
Cardiac Arrest	1 (1%)
HLH	1 (1%)
Syncope	1 (1%)
Anal Incontinence	1 (1%)
Nausea	1 (1%)
Troponin T Increased	1 (1%)
Acidosis	1 (1%)

Source: FDA analysis. ADAE dataset.
Abbreviation: HLH: Hemophagocytic lymphohistiocytosis

Table 14: CRS Individual Symptoms Grade ≥3

CRS AEs	Subjects N (%)
Any Grade ≥3	**36 (33%)**
Fever	13 (2%)
Hypoxia	10 (9%)
Hypotension	10 (9%)
Neutropenia	4 (4%)
Cardiac Failure	3 (3%)
Arrhythmia	3 (3%)
Renal Insufficiency	3 (3%)
Metabolic Acidosis	2 (2%)
Diarrhea	1 (1%)
Oliguria	1 (1%)
Cardiac Arrest	1 (1%)
Acidosis	1 (1%)
HLH	1 (1%)
Syncope	1 (1%)
Tachycardia	1 (1%)
Troponin T Increased	1 (1%)

Source: FDA analysis. ADAE dataset.
Abbreviation: HLH: Hemophagocytic Lymphohistiocytosis

Table 15: CRS SAEs

CRS SAEs	Subjects N (%)
Any	**14 (13%)**
Arrhythmia	4 (4%)
Cardiac Failure	4 (4%)
Hypoxia	3 (3%)
Renal Insufficiency	2 (2%)
Hypotension	1 (1%)
HLH	1 (1%)
Cardiac Arrest	1 (1%)
Pyrexia	1 (1%)
Acidosis	1 (1%)
Troponin T Increased	1 (1%)

Source: FDA analysis. ADAE dataset.
Abbreviation: HLH: Hemophagocytic Lymphohistiocytosis

Of the 101 subjects who had CRS events, seven subjects received a second treatment with KTE-C19. When indicated, these subjects were considered as separate subjects. Four of these subjects had CRS Grade 4 and three had CRS Grade 2.

Neurotoxicity
FDA neurotoxicity analysis differs from the Applicant's. FDA's neurotoxicity analysis included all events from the nervous system disorders and psychiatric disorders that occurred, regardless of the Applicant's attribution as "neurological flag". The analyses also captured few events misclassified under other organ system class and not captured by the Applicant as neurologic

events (i.e., three ataxia events were classified as gait disturbance under "General disorders"). Additionally, certain AEs were collated into a larger category (e.g., encephalopathy, delirium, etc...)

Ninety-four/108 subjects (87%) experienced one or more neurotoxicity events. Seven subjects were retreated with KTE-C19 and experienced neurotoxicity with the first and/or the second treatment. Thirty-four subjects (31%) experienced Grade 3 or higher (severe or life threatening) events.

The following neurotoxicity events of special interest (NESI) occurred in ≥10% of subjects: anxiety, aphasia, delirium, dizziness, encephalopathy, headache, insomnia and tremor. A total of 91/108 (84%) subjects experienced one or more of these events. These NESI were a cluster of neurological symptoms or signs that were associated with immunotherapies based on the literature review.

The median time to onset of any neurotoxicity was 5 days (range 1 to 17 days). The median duration was 15 days (Q1, Q3: 8, 33 days). Although the median time to resolution was 15 days, prolonged Grade 3 encephalopathy was noted up to 182 days post-infusion (ID 101-003-018) (maximum duration of 173 days) and Grade 1 dizziness was noted up to 174 days (maximum duration of 162 days) post-infusion.

The median time to onset of neurotoxicity Grade 3 or higher was 3 days and the median duration was 26 days.

Reviewer comments:

- **The clinical review team defined the term "encephalopathy" based on literature review. Encephalopathy was grouped based on the following terms: "Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Hypersomnia, Leukoencephalopathy, Memory impairment, Mental status changes, Paranoia, Somnolence and Stupor". The Applicant did not provide a definition for encephalopathy and rather listed the above symptoms individually. Therefore, the incidence of encephalopathy in this review is higher than the Applicant's.**

- ***Quartile 1 (Q1 = 25th percentile) and Quartile 3 (Q3 = 75th percentile). The proposed PI will include the neurotoxicity duration range and will not include the Q1-Q3 information because the range might be more useful to the health care provider.**

- **This reviewer identified three subjects who had "gait disturbance" events listed under "General disorders and administration site conditions". The term gait disturbance was grouped by FDA analysis with the term ataxia. The following is a summary of these subjects:**
    - **Subject 101-003-016 had encephalopathy (max toxicity Grade 3), which was neuro-flagged, from Day 5-21. He developed ataxia Grade 2 from Day 21-32.**
    - **Subject 101-003-024 had Grade 1 confusion on Day 8 which resolved on the same day. He also developed Grade 1 gait disturbance from Day 8-9.**
    - **Subject 101-017-001: the subject developed Grade 1 gait disturbance from Day -1 to Day 124. The investigator attributed the event to the conditioning regimen.**

Table 16: Neurotoxicity (All AEs)

Neuropsychiatric Symptoms	Subjects N (%)
Any symptom	**94 (87%)***
Encephalopathy	62 (57%)
Headache	49 (45%)
Tremor	34 (31%)
Dizziness	22 (20%)
Aphasia	19 (18%)
Delirium	18 (17%)
Insomnia	15 (14%)
Anxiety	12 (11%)
Dysgeusia	8 (7%)
Ataxia	7 (6%)
Speech Disorder	4 (4%)
Dysarthria	4 (4%)
Seizure	4 (4%)
Neuropathy	3 (3%)
Lethargy	3 (3%)
Paresis	2 (2%)
Post Herpetic Neuralgia	2 (2%)
Myoclonus	2 (2%)
Depression	2 (2%)
Presyncope	2 (2%)
Dyscalculia	2 (2%)
Hypoesthesia	2 (2%)
Hyperesthesia	1 (1%)
Adjustment Disorder	1 (1%)
Loss Of Consciousness	1 (1%)
Meningismus	1 (1%)
Mood Altered	1 (1%)
Motor Dysfunction	1 (1%)
Intracranial Hemorrhage	1 (1%)
Grimacing	1 (1%)
Amnesia	1 (1%)
Poor Sucking Reflex	1 (1%)
Dyskinesia	1 (1%)
Cerebellar Infarction	1 (1%)
Psychomotor Hyperactivity	1 (1%)
Brain Injury	1 (1%)
Bradyphrenia	1 (1%)
Syncope	1 (1%)
Abnormal Dreams	1 (1%)
Vagus Nerve Disorder	1 (1%)

Source FDA analysis. ADAE dataset.
*Note: Three “gait disturbance” events from “General system” were grouped by FDA with ataxia.

Table 17: Neurotoxicity Grade ≥3

Neuropsychiatric Symptoms G ≥3	Subjects N (%)
Any G ≥3	**34 (31%)**
Encephalopathy	31 (29%)
Delirium	7 (6%)
Aphasia	7 (6%)
Speech Disorder	3 (3%)
Tremor	2 (2%)
Dysarthria	2 (2%)
Ataxia	1 (1%)
Intracranial Hemorrhage	1 (1%)
Headache	1 (1%)
Poor Sucking Reflex	1 (1%)
Psychomotor Hyperactivity	1 (1%)
Seizure	1 (1%)
Grimacing	1 (1%)
Brain Injury	1 (1%)
Syncope	1 (1%)
Anxiety	1 (1%)

Source: FDA analysis.

Table 18: Neurotoxicity Grade

Worst Neurotoxicity Grade	
Any Toxicity Grade	**94 (87%)**
Grade 1	38 (35%)
Grade 2	22 (20%)
Grade 3	30 (28%)
Grade 4	2 (2%)
Grade 5	2 (2%)

Source: FDA analysis.

Two subjects had Grade 5 neurotoxicity, one had anoxic brain injury due to cardiac arrest and the other one had intracranial hemorrhage in setting of severe thrombocytopenia while on prophylaxis anticoagulation therapy.

Distribution of neurotoxicity events of special interest by grades and type of neurotoxicity are listed in Table 19.

Table 19: NESI Distribution by Maximum Toxicity Grade in the Safety Analysis Set (N = 108)

	Maximum Toxicity Grade			
AE	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Anxiety	8 (7%)	3 (3%)	1 (1%)	0 (0%)
Aphasia	5 (5%)	7 (6%)	7 (6%)	0 (0%)
Delirium	5 (5%)	6 (6%)	7 (6%)	0 (0%)
Dizziness	20 (19%)	2 (2%)	0 (0%)	0 (0%)
Encephalopathy	18 (17%)	13 (12%)	28 (26%)	3 (3%)
Headache	38 (35%)	10 (9%)	1 (1%)	0 (0%)
Insomnia	10 (9%)	5 (5%)	0 (0%)	0 (0%)
Tremor	28 (26%)	4 (4%)	2 (2%)	0 (0%)
Subjects	**38 (35%)**	**20 (19%)**	**30 (28%)**	**3 (3%)**

Source: FDA analysis.

Table 20 summarizes the neurotoxicity events of special interest of any grade. One subject may have experienced more than one grade of events.

Table 20: NESI Distribution by Toxicity Grade (N = 92) *

FDA Term	Grade 1	Grade 2	Grade 3	Grade 4
Anxiety	8	3	1	0
Aphasia	11	12	8	0
Delirium	18	13	10	0
Dizziness	23	2	0	0
Encephalopathy	82	56	55	3
Headache	54	12	1	0
Insomnia	11	5	0	0
Tremor	37	4	2	0
Total Events	**244**	**107**	**77**	**3**

*92 subjects of the 108 safety evaluable set experienced NESI.

The majority of neurotoxicity symptoms resolved by the data cutoff date. The Applicant reports that only one subject had unresolved neurotoxicity of Grade 1 memory impairment. However, the reviewer identified ten additional neurotoxicity events that remained unresolved. These events were all low grade with toxicity Grade 1 or 2, and were largely isolated events or events that were not associated with other neurological or psychiatric symptoms. Therefore, they are unlikely to be related to KTE-C19. The event of “altered mood” occurred in a subject while receiving conditioning regimen in the retreatment period.

Reviewer comments:

- **The group term used by the Applicant to classify the categories of Steroids and Vasopressors was reviewed and deemed reasonable (Page 548/1294 of the CSR).**

- **The attribution of concomitant medication use to whether it was used for management of CRS vs. neurotoxicity was determined by the Applicant.**

Table 23: Tocilizumab Use

Medication	Total Use	CRS Toxicity Grade	Subjects N (%)
Tocilizumab	**49 (45%)**	Grade 1	9 (8%)
		Grade 2	26 (24%)
		Grade 3	9 (8%)
		Grade 4	3 (3%)
		Grade 5	1 (1%)
		No CRS	1 (1%)

Source: FDA analysis. ADCM dataset.

Tocilizumab was administered to 49 subjects (45%). Forty-eight of these subjects had CRS events, and one subject (ID 101-002-004) was not flagged for CRS. However, this subject had the following relevant symptoms at the time when he received the two doses of tocilizumab: fever, hypoxia, and increased IL6 levels. Therefore, this subject could have CRS event (Grade 2 if using Lee criteria) for which he received tocilizumab.

Of the 49 subjects who received tocilizumab, 30 subjects received one dose, 13 subjects received two doses, two subjects received three doses, two subjects received four doses and two subjects received five doses.

Reviewer comment:

- **The protocol-specified dose and frequency of tocilizumab administration is consistent with the prescribing information (PI) for tocilizumab. A maximum of three doses of tocilizumab in a 24-hour period was administered every 8 hours with a maximum of 4 doses. The proposed PI will be consistent with the doses prescribed in ZUMA-1 and in the PI for tocilizumab.**

Infection

Infection of any Grade occurred in 38% of subjects, and Grade 3 or higher occurred in 23% of subjects.

Table 24: Infection Incidence by High Level Group Term

Infections High Level Group Term	Any Grade	G 3 or higher
All Infections	**41 (38%)**	**25 (23%)**
Infections Pathogen unspecified	28 (26%)	17 (16%)
Viral infection	17 (16%)	4 (4%)
Bacterial infection	14 (13%)	10 (9%)
Fungal infection	5 (5%)	0 (0%)

Source: FDA analysis. ADAE Dataset

Grade 3 or higher infections included the following terms:

Table 25: Infection Grade ≥3

High Level Group Term	High Level Term	Subjects N (%)
Bacterial infectious disorders	Bacterial Sepsis Clostridium Difficile Infection Escherichia Bacteremia Klebsiella Infection Lung Infection	1 (1%) 6 (6%) 1 (1%) 1 (1%) 2 (2%)
Infections - pathogen unspecified	Device Related Infection Localized Infection Lung Infection Osteomyelitis Sepsis Soft Tissue Infection Urinary Tract Infection	2 (2%) 1 (1%) 9 (8%) 1 (1%) 1 (1%) 1 (1%) 5 (5%)
Respiratory disorders NEC	Lung Infection	1 (1%)
Viral infectious disorders	Cytomegalovirus Infection Herpes Parvovirus Infection	1 (1%) 3 (3%) 1 (1%)

Source: FDA analysis. ADAE Dataset

Lung infection occurred in 13/108 (12%) subjects; 11 Subjects had Grade 3 or higher lung infection. Five subjects had ongoing infections at the time of death (IDs: 101-001-006, 101-003-006, 101-003-007, 101-009-001, 101-010-001).

Prolonged cytopenia ≥30 days
Fever neutropenia occurred in 36% of subjects and Grade ≥3 occurred in 32% of all subjects. Table 26 lists prolonged cytopenia events which lasted longer than 30 days.

Table 26: Prolonged Cytopenia Grade ≥3

FDA grouped terms	Subjects N (%)
Any prolonged cytopenia G ≥3	**30 (28%)**
Thrombocytopenia	19 (8%)
Neutropenia	16 (15%)
Anemia	3 (3%)

Source: FDA analysis. ADAE ISS Dataset.

B cell aplasia
Grade 1 or 2 hypogammaglobulinemia occurred in 16/108 (15%) subjects. Grade ≥3 hypogammaglobulinemia were not observed.

Secondary malignancies
There are to date, no reports of secondary malignancy in any subject in the ongoing long-term follow-up study. There were two reported cases of myelodysplastic syndrome (MDS) noted in the clinical studies that were reviewed and considered as not related by the FDA clinical reviewer.

Cardiac toxicity

Table 27: Cardiac Disorders

FDA grouped terms	Subjects N (%)
Any cardiac disorder	**74 (69%)**
Tachycardia	62 (57%)
Arrhythmia	23 (21%)
Pulmonary edema	10 (9%)
Sinus bradycardia	7 (6%)
Cardiac arrest	4 (4%)
Cardiac failure	3 (3%)
Palpitations	1 (1%)
Cardiomegaly	1 (1%)

Table 28: Cardiac Disorders Grade ≥3

FDA grouped terms	Subjects N (%)
Any cardiac disorder G ≥3	**14 (13%)**
Arrhythmia	6 (6%)
Cardiac arrest	4 (4%)
Cardiac failure	3 (3%)
Pulmonary edema	3 (3%)
Tachycardia	2 (2%)

Source: FDA analysis. ADAE Dataset

Electrocardiogram QT prolongation was observed in 3 subjects (IDs: 101-002-012, 101-002-018, 101-009-009). Grade 4 cardiac events were observed in 5 subjects, four of which were cardiac arrests and one of arrhythmia. There were no Grade 5 cardiac events, with the exception of subject 101-009-007 who experienced cardiac arrest leading to anoxic brain injury and death.

Renal toxicity
Renal insufficiency was seen in 13/108 (12%) subjects, and Grade ≥3 in 5 (5%) subjects. Three subjects experienced kidney injury that required dialysis.

Respiratory failure
Four subjects required endotracheal intubation or mechanical ventilation for the management of respiratory failure.

Hospitalization
The protocol required mandatory hospitalization on the day of KTE-C19 infusion and for a minimum of seven days post infusion. The median duration of hospitalization was 13 days (95% CI 12, 14). The observed range of the duration of hospitalization was 7 to 62 days. Thirty nine % and 14% of subjects in the safety population remained hospitalized on Days 14 and 21 respectively.

Table 21: Unresolved Neurotoxicity Events at the Data Cutoff*

FDA Grouped Terms	Reported Terms	Subjects N (%)
Any unresolved neurotoxicity		**11 (10%)**
Abnormal Dreams		1 (1%)
Dizziness		3 (3%)
Encephalopathy	Memory impairment	1 (1%)
Insomnia		4 (4%)
Mood Disorders	Mood altered	1 (1%)
	Anxiety	1 (1%)
Post Herpetic Neuralgia		1 (1%)

Source: FDA analysis, ADAE dataset.
*Data cutoff date of January 27, 2017

Relationship between neuropsychiatric events and CRS events
To evaluate the relationship of neurotoxicities to CRS, neurotoxic events of special interest that occurred within 60 days were used in this analysis, because some of the neurotoxicities occurred late and were isolated (e.g. transient dizziness occurred 175 days post infusion and considered by the FDA reviewer as not related to the product). For analysis purposes, subjects who received a second infusion and experienced CRS and/or neurotoxicities in the post infusion period following the second infusion were considered to have events separate from those occurring following the first infusion.

There were 90 subjects who had neurotoxicity events with onset that occurred within 60 days of KTE-C19 infusion; and 96 subjects when counting subjects who received a second infusion separately.

104 subjects experienced a total of 111 CRS and/or neurotoxicity events (seven of the 111 events of CRS and/or neurotoxicity events occurred in subjects who received a second infusion. Of the 111 subjects, 21 experienced only CRS events but no neurotoxicity events. Five subjects experienced neurotoxicity events without CRS.

A total of 85 subjects experienced CRS and neurotoxicity. Of these, 75% (64/85) of subjects experienced neurotoxicity events that occurred after CRS onset, and 25% (21/85) of subjects experienced neurotoxicity events before the onset of CRS.

Ten subjects had neurotoxicities that began after CRS had resolved. Therefore, 63% (54/85) neurotoxicities occurred during the CRS events.

Figure 2 below illustrates the relationship and time course of CRS and neurotoxicity.

Table 29: Maximum Grade of NESI and Timing of Onset

Days Post Infusion	Grade 1	Grade 2	Grade 3	Grade 4
0	5	2	1	0
1	6	7	12	1
2	3	2	2	1
3	3	3	3	1
4	6	2	5	0
5	2	1	4	0
6	3	0	3	0
7	**1**	**2**	**0**	**0**
8	1	0	0	0
9	2	1	0	0
12	1	0	0	0
13	1	0	0	0
16	1	0	0	0
42	1	0	0	0
56	1	0	0	0
71	1	0	0	0
94	1	0	0	0

Source: FDA analysis. Abbreviation: NESI: neurotoxicity events of special interest

Reviewer comments:

- **Grade 2 or greater NESI require treatment with dexamethasone. As noted in the table above, all but one Grade ≥2 NESI occurred within 7 days following the infusion. One subject was noted to have onset of Grade 2 tremor and headache on Day 9. Subjects were to remain hospitalized for ongoing KTE-C19 related events of fever, hypotension, hypoxia, or ongoing central neurologic toxicity, if severity was greater than Grade 1, or if deemed necessary by the treating investigator. See protocol description "Surveillance/Monitoring section" above (section 6.1.7) for details regarding neurotoxicity monitoring during the clinical study.**

- **The Applicant's proposed management guidance for neurotoxicity, which we will include in the label, recommends the initiation of steroids treatment with the onset of any Grade 2 neurotoxicity. All of the Grade 2 neurological events (except one which was related to headache and tremor that started on Day 9) occurred on or within 7 days after the infusion, and would be eligible for steroids treatment as per the current protocol. Almost all delayed neurotoxicity events were Grade 1.**

- **The reviewer recommends requiring inpatient infusion and monitoring of patients receiving KTE-C19 for a period of 7 days post infusion. The reviewer also recommends that the REMS include information regarding mandatory hospitalization and inpatient monitoring for 7 days following product infusion.**

The recommendations for hospitalization are based on:

- **The median time to onset of CRS was 2 days and neurotoxicity was 5 days. The onset of these events was rapid.**
- **Management of Grade ≥ 2 CRS and neurotoxicity require immediate intervention.**
- **Fatal cases of CRS and neurotoxicity have occurred after receiving KTE-C19.**
- **The feasibility of conducting MMSE and full neurological exams by patient's caregivers, the requirement for increased frequency of neurologic exams following the onset of Grade 1 neurologic events, and the observation that Grade 1 or higher neurologic events occurred in a majority of subjects (91 of 108 subjects- please refer to Table 19).**

The recommendation for the duration of 7 days of in-patient hospitalization is based on:

- **The observation that all but one Grade ≥ 2 neurologic event occurred within 7 days post infusion.**
- **Re-admissions to the hospital for delayed neurologic or CRS related events did not occur in the majority of subjects. Of the 108 subjects, all but two subjects required re-admission for Grade 2 headache and Grade 3 encephalopathy. No re-admissions occurred for delayed CRS events.**
- **An abbreviated duration and need for hospitalization could be re-evaluated as data from ZUMA-1 and other ongoing studies of KTE-C19 become available.**

Additionally, because the majority of all grade AEs, CRS and neurologic toxicities occurred within the first four weeks post-infusion, the review team recommends that all patients remain within proximity (the definition of proximity is under labeling negotiations) of the certified treating hospitals for 4 weeks following product infusion. This recommendation will be included in the proposed Package Insert (PI).

120-Day Safety Update

A 120-Day safety update to the BLA was submitted on Jul 31, 2017, which included events that occurred after the original Jan 27, 2017 cutoff date, through April 26, 2017. The safety profile remained consistent with what was observed in the original submission with the exception of two cases of cerebral edema. The following describes the narrative for these subjects:

- Subject 101-025-012 was enrolled in ZUMA-1 Cohort 3. He was a 21 year old male diagnosed with rapidly progressing Stage IVB rel/ref PMBCL who presented with CRS Grade 3 on Day 6 consisting of hypotension, acute kidney injury, cardiac failure and cardiomyopathy. On Day 6, the subject developed encephalopathy Grade 2 which progressed rapidly to G4 on Day 7 when he became obtunded and unresponsive. An initial head CT scan showed on evidence of cerebral edema or herniation. A repeat CT scan was performed three hours later which showed diffuse cerebral edema and bilateral uncal herniation. The subject subsequently died on Day 9. A retrospective analysis of the baseline levels of cytokines and chemokines in serum and cerebrospinal fluid (CSF) suggested a significant pre-existing underlying inflammatory process.

- Subject 102-003-019 was enrolled in ZUMA-2 Study. He was a 65 year old male with Stage IV rel/ref MCL who developed rapidly progressive Grade 4 encephalopathy on Day 4. Head

CT showed no cerebral edema. He subsequently developed seizures. Brian MRI was performed 15 hours after the initial CT scan and showed cerebral edema. The subject was extubated on Day 11 and the event of Grade 4 cerebral edema resolved on Day 20.

Reviewer comment:

- **These two cases of cerebral edema were not included in the datasets and in the reviewer's analyses tables because they occurred after the data cutoff.**

6.1.12.6 Clinical Test Results

The most comment Grade 3 or higher laboratory abnormalities included: lymphopenia, leukopenia, neutropenia, anemia, thrombocytopenia and hypophosphatemia. See Table 30 for detailed listing of all laboratory abnormalities.

Table 30: Shift Analyses of Laboratory AEs Grade ≥3

Parameter	Subjects N (%)
Lymphopenia	108 (100%)
Leukopenia	104 (96%)
Neutropenia	100 (93%)
Anemia	71 (66%)
Thrombocytopenia	63 (58%)
Hypophosphatemia	56 (52%)
Hyponatremia	27 (25%)
Hypoalbuminemia	25 (23%)
Uric acid increased	23 (21%)
Direct Bilirubin increased	17 (16%)
Hypokalemia	13 (12%)
Alanine Aminotransferase increased	13 (12%)
Aspartate Aminotransferase increased	12 (11%)
Hyperglycemia	12 (11%)
Bilirubin increased	10 (9%)
Hypocalcemia	10 (9%)
Hypermagnesemia	6 (6%)
Creatinine increased	5 (5%)
Alkaline Phosphatase increased	2 (2%)
Hypernatremia	1 (1%)
Hyperkalemia	1 (1%)

Source: FDA Analysis. New ADLB Dataset

Reviewer comment:

- **The laboratory abnormalities are more detailed in the labs dataset as compared to the AE dataset. Therefore, the label will include a separate table for laboratory abnormalities that are derived from the new ADLB dataset.**

6.1.12.7 Dropouts and/or Discontinuations

Among the eight subjects who were enrolled in Phase 1 and underwent leukapheresis, seven subjects received KTE-C19. One subject discontinued prior to receiving conditioning chemotherapy

due to disease progression. Of the seven remaining subjects one received KTE-C19 dose less than the target dose and six received the target dose. Therefore, 6 subjects were evaluable for DLTs and all seven subjects were evaluable for safety.

Among 111 subjects who were enrolled in Phase 2 and underwent leukapheresis, 103 subjects received conditioning regimen and 101 subjects were treated with KTE-C19. Of the 10 subjects who didn't receive KTE-C19; three subjects died prior to KTE-C19, two didn't receive it due to non-measurable disease, and five due to AEs likely related to the disease [intestinal obstruction, pleural effusion and hypoxia, spinal column stenosis, deep vein thrombosis (DVT), and ecthyma complicated by sepsis (which occurred in a subject treated with conditioning regimen)].

The primary reason for study discontinuation following KTE-C19 was death (refer to Table 10).

6.1.13 Study Summary and Conclusions

Refer to Sections 1, 7.1.11 (efficacy), 8.6 and 10 (safety), and 11.

Safety:
Of 108 subjects in the safety evaluable set, ≥ Grade 3

- CRS occurred in 13%
- Neurologic toxicities occurred in 31%
- Febrile neutropenia occurred in 32%
- Prolonged cytopenias occurred in 28%, and
- Infections occurred in 40% of subjects.

Additionally,

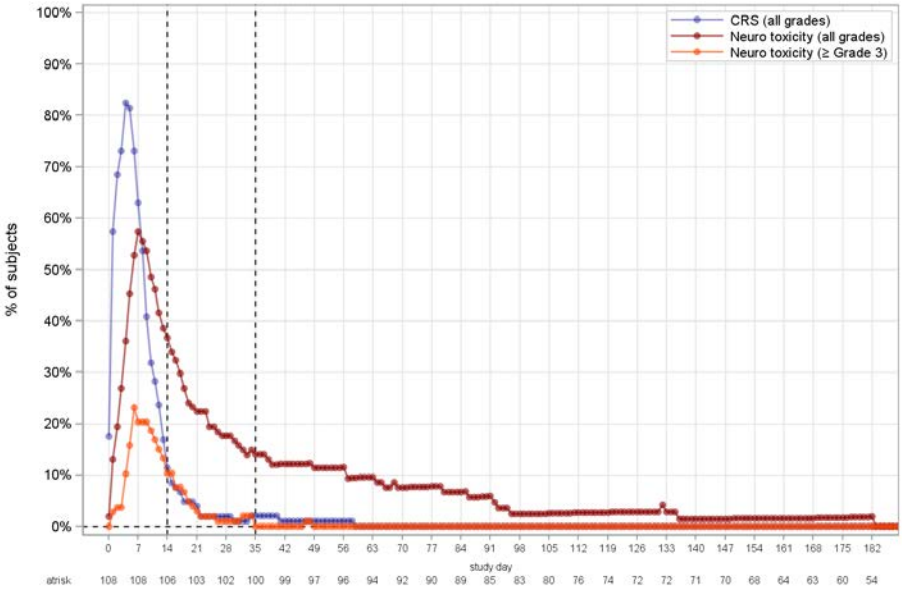
- Life-threatening (Grade 4) or fatal events of cerebral edema have been reported with KTE-C19.

During conduct of ZUMA-1, life-threatening and fatal adverse reactions caused by KTE-C19 were mitigated by mandated site and investigator training, careful site selection and monitoring, instructions for early detection and management of the most serious complications and a requirement for in-patient administration and in-patient monitoring for seven days following the infusion. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and neurotoxicity, and a REMS. FDA determined in consultation with the OBE and CDER DRISK that the Communication Plan as proposed by the Applicant would not be sufficient; instead, a REMS with ETASU is the appropriate approach. The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies with emphasis on recognition and treatment of CRS and neurotoxicity.

Long-term safety after treatment with KTE-C19 remains a concern. Due to the lack of long-term safety data in the BLA, additional study postmarketing is warranted.

The Applicant agreed to conduct an observational registry study that will collect safety information for patients treated with the marketed product. Collection of key early adverse reactions and follow-up for 15 years for detection and evaluation of second malignancies is planned in this post-marketing requirement (PMR) study. Routine collection of samples to evaluate for RCR is not planned as part of this PMR.

Figure 2: CRS and Neurotoxicity Time Course



Source: FDA analysis. SAS, ADAE XC datasets

Reviewer comment:

- **The duration of neurotoxicity is calculated based on the earliest date of onset of any of the neurologic events that were group under the neurologic events of special interest (NESI) and the final end date for any of the neurological events that were grouped in the NESI. Thus the duration of NESI should be interpreted with caution keeping this caveat in mind. Thus in some subjects the duration of NESI appears prolonged and these "outliers" were the result of persistent but less serious clinical events such as anxiety and/or insomnia.**

Concomitant medication

Concomitant medications are medications that were started following the first dose of KTE-C19 and prior to hospital discharge.

Table 22: Concomitant Medications

Medication	Any use	To manage CRS	To manage neurotoxicity
Steroids	31 (29%)	6 (6%)	18 (17%)
Tocilizumab	49 (45%)	18 (17%)	39 (36%)
Vasopressors	18 (17%)	14 (13%)	
Immunoglobulins	6 (6%)		
Steroids and Tocilizumab	29 (27%)		
Steroids or Tocilizumab	51 (47%)		
Other immunosuppressive agents*	2 (2%)	1 (1%)	

Source: FDA analysis. ADCM, ADHO datasets.

*Anakinra (interleukin 1 [IL1] receptor antagonist) in 1 subject (which was used to manage CRS) and Etanercept (Tumor Necrosis Factor Alpha (TNFα) inhibitor in 2 subjects.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication: Relapsed or Refractory Aggressive B-cell NHL

7.1.1 Methods of Integration

The efficacy determination is based on one single-arm, multicenter clinical trial (ZUMA-1). Efficacy results in de novo DLBCL, transformed FL, and PMBCL were integrated for the main analysis, which comprises all 101 patients in the phase 2 mITT population.

7.1.2 Demographics and Baseline Characteristics

Table 31 summarizes the baseline patient and disease characteristics of the phase 2 mITT population. The median age was 58, with ~25% of patients being aged ≥ 65. The majority of patients (76%) had a diagnosis per investigator of de novo DLBCL, 16% had transformed FL, and 8% had PMBCL. Diagnoses by central review were generally concordant with diagnoses by investigator.

This was an especially poor-risk group of patients, with a median of three prior lines of therapy. Although only two patients received study treatment for primary refractory disease, ~25% of had a history of primary refractory disease, more than half had refractoriness to ≥ 2 consecutive lines of therapy, ~25% had refractoriness to ≥ 3 consecutive lines, and 25% had prior auto SCT. However, all patients had an ECOG PS of 0 or 1 per protocol requirement.

Reviewer comment:

- **The International Prognostic Index (IPI), which was evenly balanced between lower-risk and higher-risk disease, does not, in the reviewer's opinion, accurately reflect the extent of poor-risk disease in this population.**

Table 31: Baseline Characteristics of mITT Population (N = 101)

Parameter		**Phase 2 mITT population (N = 101)**	
Proportion of enrolled patients		101/111	(91%)
Demographics			
Age, y	Median (range)	58	(23, 76)
	≥ 65	24	(24%)
Sex	Male	68	(67%)
Race	White	90	(89%)
	Black	4	(4%)
	Other	7	(7%)
ECOG performance status	0-1	101	(100%)
Baseline Parameters			
Diagnosis per investigator	de novo DLBCL	77	(76%)
	transformed FL	16	(16%)
	PMBCL	8	(8%)
Double or triple hit	Yes	32	(32%)
Detectable tumor CD19 expression	Documented	74	(73%)
	No	8	(8%)
	Not tested	19	(19%)
Prior lines of systemic therapy [a]	Median (range)	3	(1, 10)
	1	2	(2%)
	2	29	(29%)
	3	30	(30%)
	4	28	(28%)
	≥ 5	12	(12%)
Prior auto SCT	Yes	25	(25%)
Refractoriness to most recent therapy [b]	Primary refractory	2	(2%)
	Refractory to 2nd or greater line	78	(77%)
	Relapse ≤ 12 mo after auto SCT	21	(21%)
History of refractoriness	Ever primary refractory	26	(26%)
	Refractory to ≥ 2 consecutive lines	54	(54%)
	Refractory to ≥ 3 consecutive lines	26	(26%)
Extranodal disease at study baseline	Yes	70	(69%)
Bulky disease at study baseline	Yes	17	(17%)
IPI at study baseline	0-2 (low or low-intermediate risk)	53	(52%)
	3-4 (high-intermediate or high risk)	48	(48%)
	5	0	(0%)

Source: FDA clinical reviewer
[a] Salvage chemotherapy and auto SCT were counted as separate regimens.
[b] Termed the "refractory subgroup." Unless relapse occurred ≤ 12 months after auto SCT, the refractory subgroup was determined by the last time criteria for the particular subgroup were met.

7.1.3 Subject Treatment and Disposition

Treatment and disposition of the phase 2 population (N = 111) is summarized in Table 32. Of the eight patients (8%) who underwent leukapheresis but not conditioning, one had KTE-C19 manufacturing failure. The median time from apheresis to site delivery was 17 days (maximum 51).

Three patients proceeded to SCT in remission (two in CR, one in PR per investigator) after one dose of KTE-C19; 10 patients received allo SCT after either one dose or two doses of KTE-C19.

Table 32: Phase 2 Population: Treatment and Disposition

Variable		Result
Enrolled (full analysis set), n	Yes	111
Leukapheresed, n	Yes	111
Conditioning received, n	Yes	103 (93%)
	No	8 (8%)
Reason conditioning not given, n	KTE-C19 manufacturing failure, then death from PD	1
	Death from PD	1
	Non-PD SAEs after leukapheresis	4
	No measurable disease	1
KTE-C19 received, n [a]	Yes	101 (91%)
Reason KTE-C19 not given after conditioning	Death from tumor lysis syndrome	1
	Sepsis	1
KTE-C19 dose (10^6 CART/kg) [b, c]	Median	2.0
	Range	1.1, 2.2
	Q1, Q3	1.9, 2.0
KTE-C19 CD4:CD8 ratio [d]	Median	0.9
	Range	0.0, 5.8
	Q1, Q3	0.5, 1.9
Days from apheresis to product delivery	Median	17
	Range	14, 51
	Q1, Q3	16, 18
Days from apheresis to infusion	Median	24
	Range	16, 73
Second KTE-C19 dose received, n	Yes	10
Subsequent allo SCT	Yes	10
Allo SCT after 1st CART dose (before PD)		3
Allo SCT after 2nd CART dose, with or without intervening therapy for PD		7
Subsequent auto SCT	Yes	2 [e]

Source: FDA clinical reviewer
[a] Same as mITT population.
[b] In patients treated twice, refers to first dose.
[c] Supplied dose and administered dose were the same.
[d] Missing in two patients.
[e] After PD.

Reviewer comment:

- **ZUMA-1 did not permit bridging therapy between leukapheresis and conditioning. However, the manufacturing time for KTE-C19, which can take (b) (4) , is notable and is potentially prohibitive for patients with rapidly progressive lymphoma.**

7.1.4 Analysis of Primary Endpoint

Table 33 demonstrates the overall ORR, per investigator and IRC, after one dose of KTE-C19. The primary analysis was based on the 101 patients in the phase 2 population who received the intended dose of KTE-C19 (N = 101). On modified intention-to-treat (mITT) analysis, the ORR per IRC was 72%, with a CR rate of 51% (95% CI: 41, 62) and median time to response of 0.9 months. ORR per IRC had 79% concordance (K = 0.41) with ORR per investigator (source: summary report of updated efficacy analysis, Section 3.2.1).

Table 33 also presents a sensitivity analysis of response, using as the denominator all patients in the phase 2 population who were enrolled and leukapheresed, irrespective of receipt of KTE-C19 (N = 111). On this true ITT analysis, the ORR per IRC was 66%, with a CR rate of 47% (95% CI: 37, 57).

Table 33: Overall Response after One Dose of KTE-C19

Parameter	Phase 2 mITT population (N = 101)		Phase 2 full analysis set (N = 111)	
	Investigator	IRC	Investigator	IRC
Objective response, n (%)	84 **(83%)**	73 **(72%)**	**76%**	**66%**
(95% CI) [a]	(74, 90)	(62, 81)	(67, 83)	(56, 75)
Best response, n (%)				
Complete Remission	55 **(54%)**	52 **(51%)**	**50%**	**47%**
(95% CI)	(44, 64)	(41, 62)	(40, 59)	(37, 57)
Partial Remission	29 (29%)	21 (21%)	25%	19%
(95% CI)	(20, 39)	(13, 30)	(18, 35)	(12, 27)
SD	19 (19%)	19 (19%)	17%	17%
PD	5 (5%)	7 (7%)	5%	6%
Not evaluable	2 [b] (2%)	2 (2%)	11%	11%
Time to response (days)				
Median (range)	29 (24, 183)	28 (24, 190)		
Q1, Q3	(28, 31)	(28, 30)		

Source: FDA clinical reviewer
Data cut: 4/2017
[a] Exact binomial CI (Clopper-Pearson method)
[b] Not evaluable due to early death

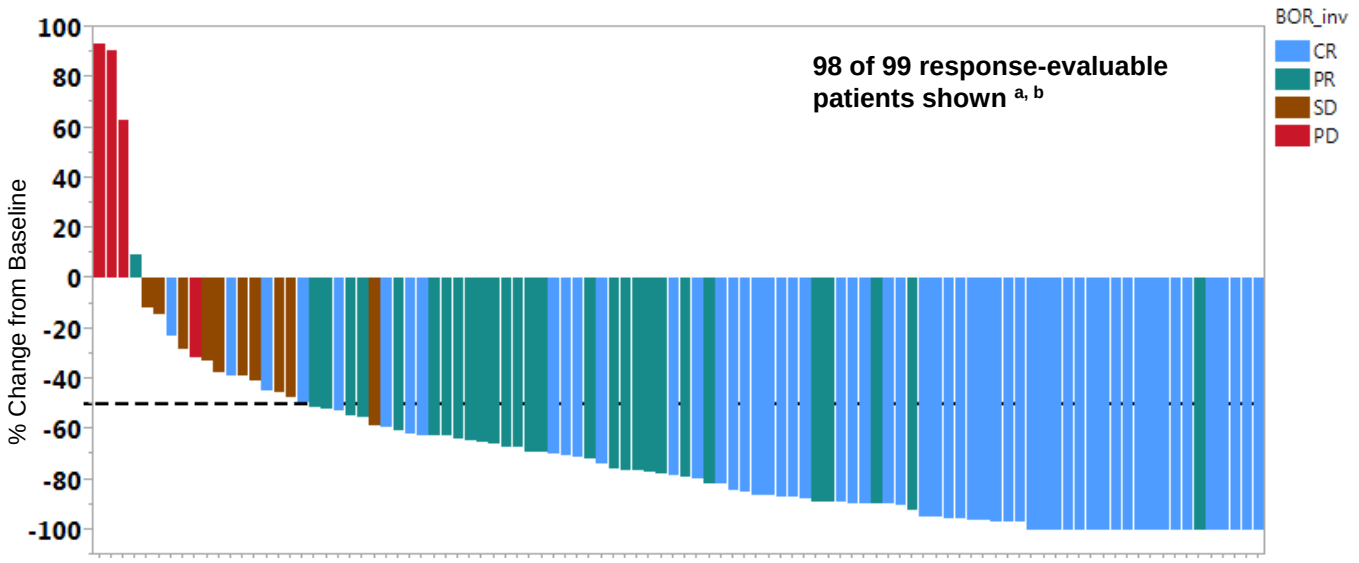
Waterfall plots for the mITT population, displaying the maximal % reduction in disease burden in relation to BOR, are shown in Figure 3. Disease burden is represented by the sum of the products of greatest diameter (SPD).

Reviewer comment:

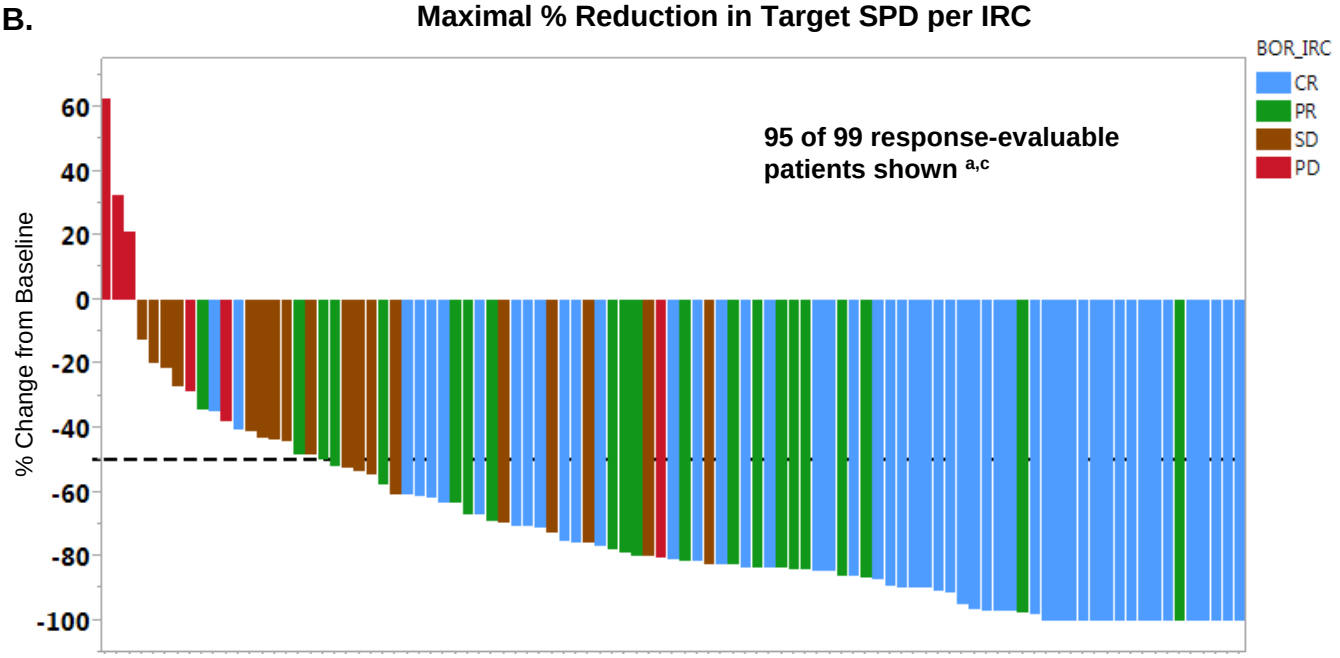
- **Particularly for an open-label, single-arm study, efficacy per IRC is preferable over efficacy per investigator for regulatory decisions. This minimizes bias and, especially when differentiating metabolic CR from PR, may improve accuracy. Thus, although the primary endpoint of ZUMA-1 was ORR per investigator, the clinical review team recommends that efficacy per IRC be prioritized for regulatory decisions.**

Figure 3: Waterfall Plot (mITT Population)

A.



B.



Source: FDA clinical reviewer.
Data cut, 4/2017
[a] Of 101 patients in the mITT population, 99 were evaluable for response.
[b] One additional patient had PD, without post-baseline tumor measurements reported.
[c] Additional patients not shown due to non-measurable disease per IRC.

7.1.5 Analysis of Secondary Endpoints

Response Rate on Intention-to-Treat Analysis

Per Section 7.1.4, Table 33.

Duration of Response

DOR per investigator and IRC, based on the updated efficacy analysis, is shown in Table 34 and Figure 4. With an estimated 7.9-month follow-up for DOR, the estimated median DOR per IRC was 9.2 months (95% CI: 5.4, NE). Evaluation of DOR remains limited by the large amount of censoring before 6 months. Of the 44 patients censored for DOR per IRC, only 7 (16%) were censored due to receipt of subsequent anticancer therapy before PD (source: FDA analysis). Thus, longer follow-up would better inform DOR in most responders (> 80%).

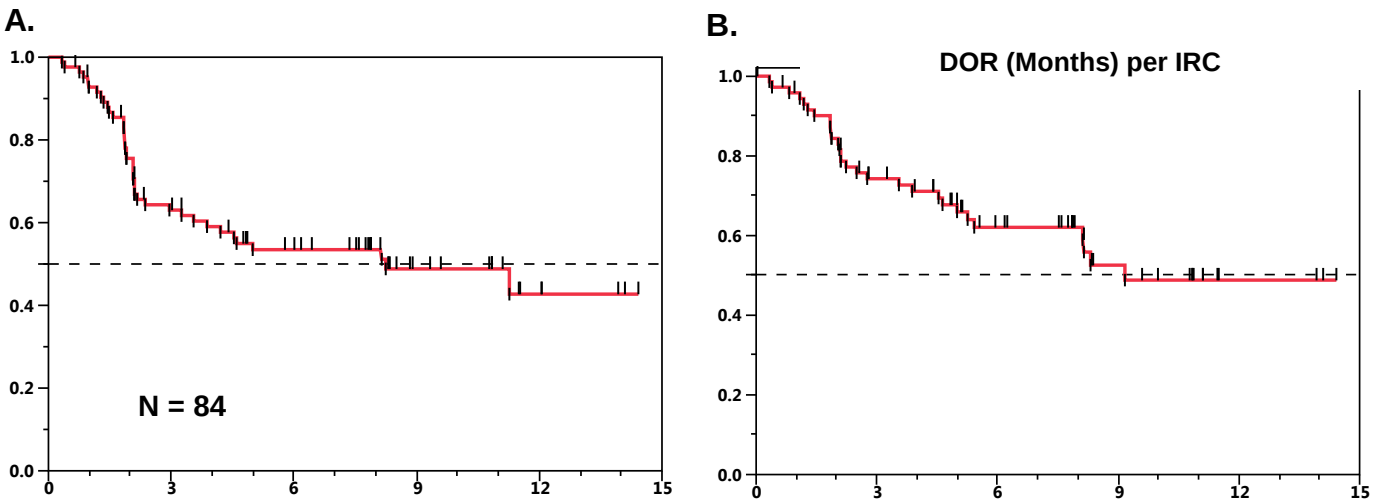
Table 34: Duration of Response (mITT)

Parameter	**Phase 2 mITT population (N = 101)**	
	Investigator	**IRC**
Number of responders	84	73
DOR (months),[a] censored for SCT		
Estimated median (95% CI)	8.2 (3.5, NE)	9.2 (5.4, NE)
Range	(0.0+, 14.4+)	(0.0+, 14.4+)
# censored for DOR	44/84 (52%)	44/73 (60%)
Follow up for DOR (months)		
Estimated median (95% CI)	8.3 (7.6, 9.3)	7.9 (6.2, 9.6)
DOR if BOR is CR (months) [b]		
Estimated median (95% CI)	NE (8.2, NE)	NE (8.1, NE)
Range	(0.4, 14.4+)	(0.4, 14.4+)
# censored for DOR	37/55 (67%)	36/52 (69%)
DOR if BOR is PR (months)		
Estimated median (95% CI)	1.9 (1.4, 2.1)	2.1 (1.3, 5.3)
Range	(0.3, 9.3+)	(0.0+, 8.4+)
# censored for DOR	7/29 (24%)	8/21 (38%)

Source: FDA clinical reviewer
Data cut: 4/2017 (7/12/17 submission)
[a] In responders, measured from date of first objective response using reverse Kaplan-Meier method. For all efficacy analyses presented, DOR was censored for SCT in the absence of PD.
[b] In these patients, median follow-up for DOR per IRC was 7.9 months (95% CI: 7.5, 10.8).

N = 73

Figure 4: Duration of Response (mITT Population)



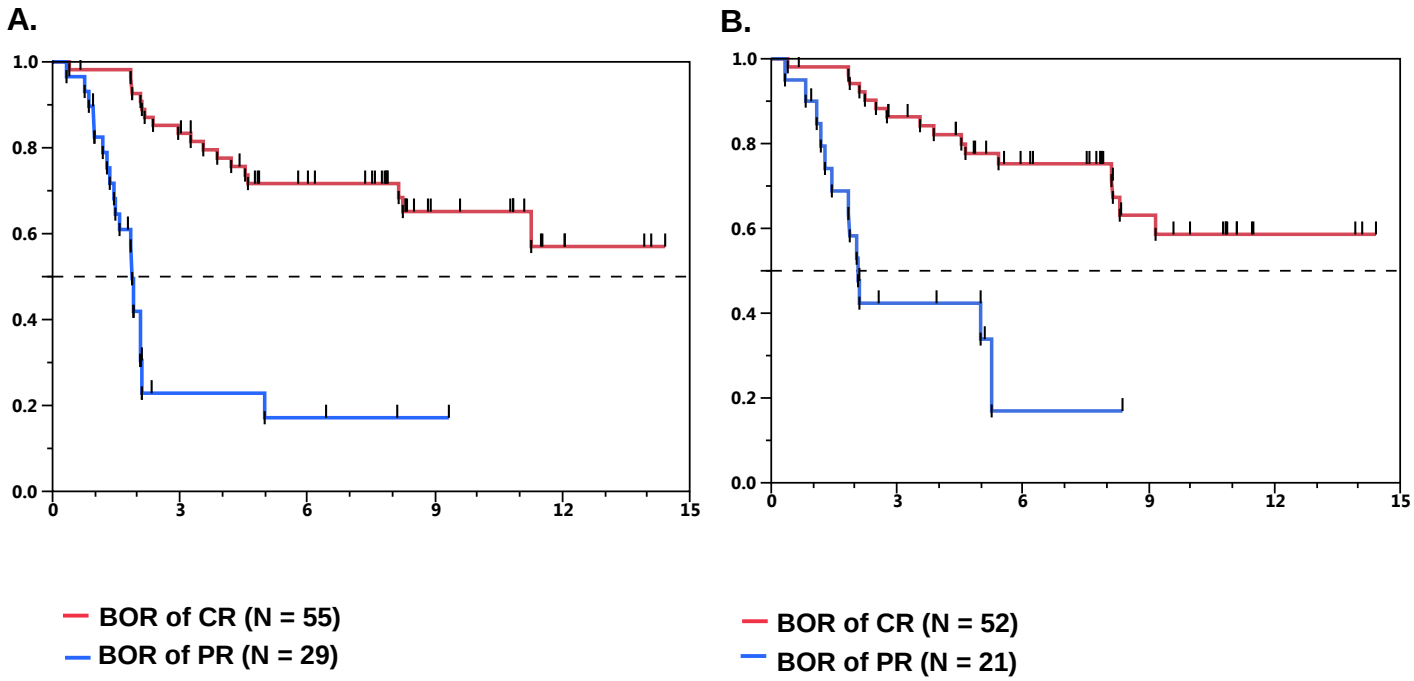
Source: FDA clinical reviewer
Data cut, 4/2017; dataset received 7/12/17
This analysis censors patients at the time of SCT.

Response durations tended to be substantially longer in patients with a BOR of CR, as compared to a BOR of PR (Figure 5). Among patients achieving CR, the estimated median DOR had not been reached (95% CI: 8.1 months, NE), whereas the estimated median DOR among patients in PR was 2.1 months (95% CI: 1.3, 5.3).

Reviewer comments:

- **Despite the more recent data-cut, the evaluation of DOR remains limited due to an excessive amount of censoring before 6 months.**
- **Because of early censoring, the estimate for median DOR, particular for patients with a BOR of CR, is potentially unstable. Longer follow-up would be required to characterize the durability of the treatment effect.**
- **Despite this limitation, in this poor-risk group of patients, the magnitude and observed durations of the treatment effect, among those with a BOR of CR, is clinically meaningful (Table 34, Figure 5). The observed benefit is less clear for patients with a BOR of PR, as these responses tend to be less durable. Therefore, although the primary endpoint of ZUMA-1 was ORR, the clinical review team recommends that the regulatory decision be made on CR rate and DOR.**

Figure 5: DOR According to Best Overall Response (mITT Population)



Source: FDA clinical reviewer
Data cut, 4/2017; dataset received 7/12/17.
This analysis censors patients at the time of SCT.

Progression-Free and Overall Survival

Survival data are immature, as shown by the large degree of early censoring in Kaplan-Meier curves of PFS and OS for the phase 2 mITT population (Figure 6). Interpretation of these data is further limited because they are from a single-arm trial. Per the FDA clinical reviewer:

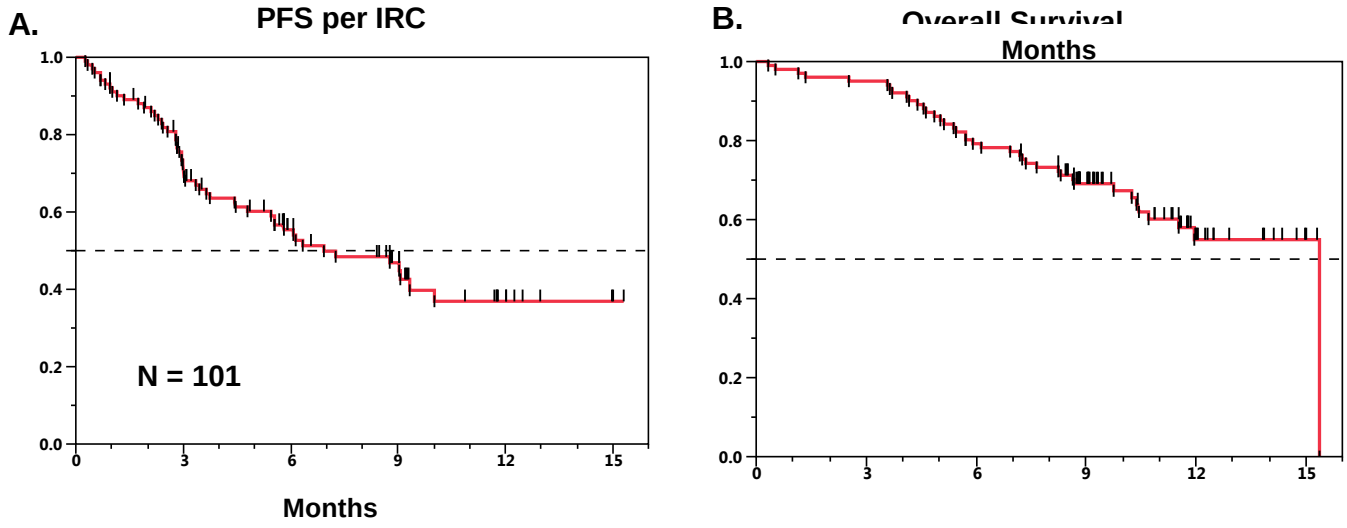
- With an estimated 8.8 month follow-up for PFS per IRC, the estimated median PFS after KTE-C19 infusion was 6.9 months (95% CI: 4.8, 10.0), the six-month probability of PFS was 55% (95% CI: 45, 65), and 49% of observations were censored.
- With an estimated 11.1 month follow-up for OS, the estimated median OS after KTE-C19 infusion was 15.4 months (95% CI: 10.7, 15.4), the six-month probability of survival was 79% (95% CI: 70, 86), and 61% of observations were censored.

Reviewer comment:

- **The results for time-to-event endpoints such as survival should be interpreted with caution. Because these data are from an uncontrolled clinical trial, it is unclear to what extent the outcomes can be attributed to the treatment effect of the drug. Follow-up is also immature.**

N = 101

Figure 6: PFS and OS (mITT Population)



Source: FDA clinical reviewer
Data cut: 4/2017 (7/12/17 submission for OS, 8/4/2017 submission for PFS)
Survival is measured from the date of KTE-C19 infusion.

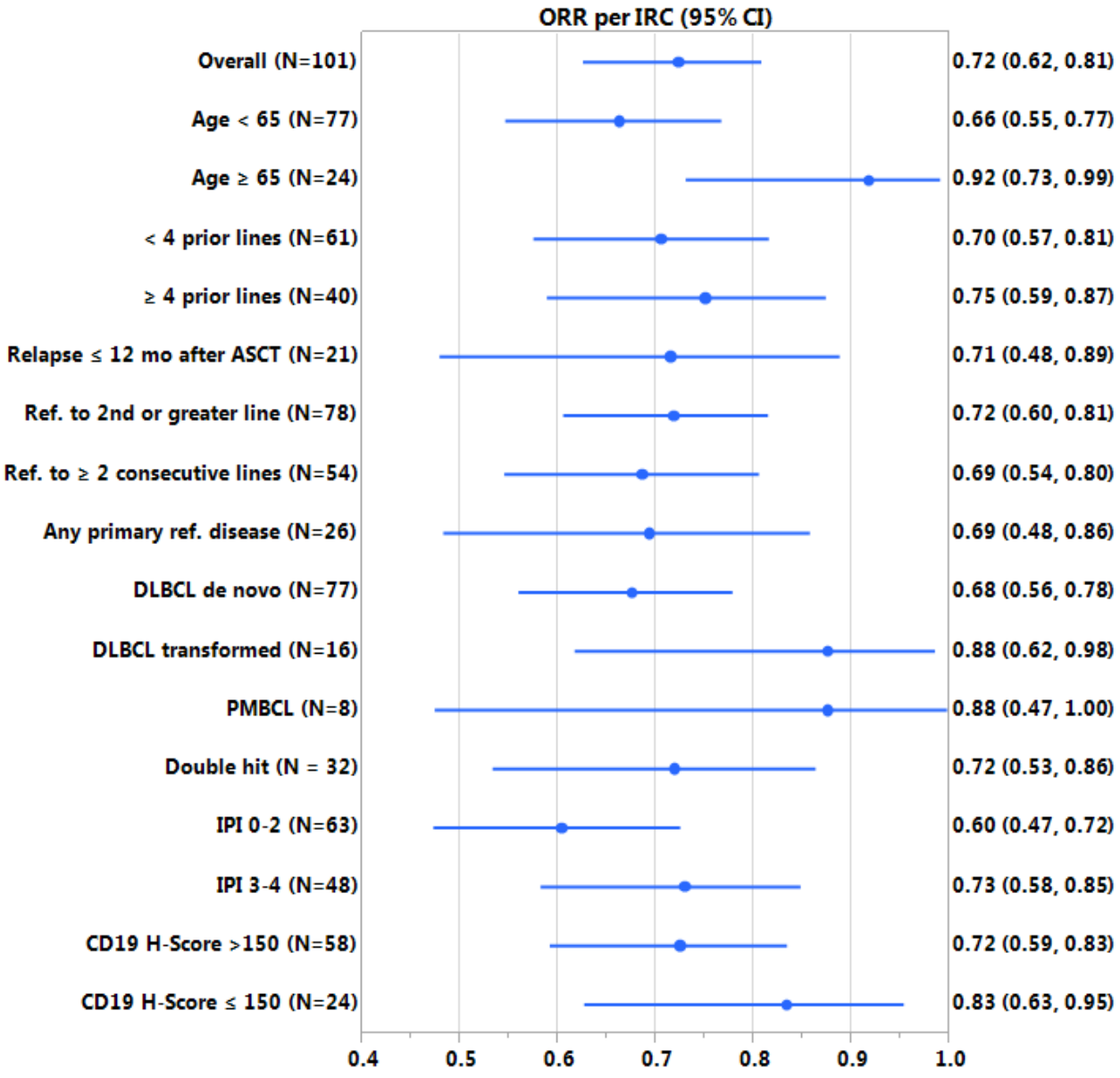
7.1.6 Other Endpoints

Not applicable

7.1.7 Subpopulations

A forest plot of ORR per IRC, in relation to key patient or disease characteristics, is shown in Figure 7. Sample size limits the subgroup analyses of ORR and precludes meaningful subgroup analyses of CR rate. Nevertheless, the magnitude of the treatment effect, based on ORR, was consistent across major subgroups including extent of prior therapy (≥ 4 vs fewer lines), outcome of most recent therapy (refractory to second– or greater– line, vs early relapse after SCT), the presence of double-hit, and amount of tumor CD19 expression (high vs low). Of eight patients with undetectable tumor CD19 expression, five had CR and one had PR per IRC.

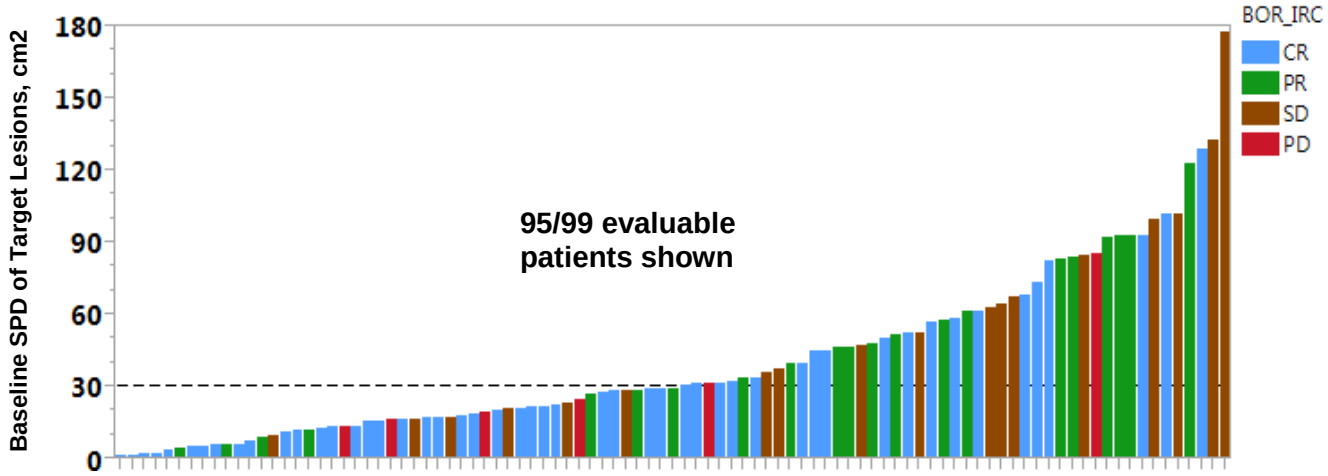
Figure 7: Forest Plot of ORR per IRC (mITT Population)



Source: FDA clinical reviewer
Data cut: 4/2017

Response was also achieved in patients with higher as well as lower tumor burdens at baseline (Figure 8).

Figure 8: Response (IRC) According to Baseline Tumor Burden (mITT Population)



Source: FDA clinical reviewer
Data cut: 4/2017

7.1.8 Persistence of Efficacy

DOR is reviewed in Section 7.1.5.

7.1.9 Product-Product Interactions

In the phase 2 mITT population, unadjusted subgroup analysis of ORR per investigator showed a similar treatment effect in recipients of tocilizumab or steroids, as compared to patients who did not receive tocilizumab or steroids (source: CSR Figure 14.1.6.3).

7.1.10 Additional Efficacy Issues/Analyses

Exposure-response
In the phase 2 mITT population, on unadjusted analysis the Applicant reported a positive association between CAR T cell expansion (peak numbers post infusion, area under the curve) and achievement of an objective response per investigator (source: CSR Table 14.9.3.1).

Response in phase 1 cohort
Seven of eight patients enrolled in the phase 1 portion of ZUMA-1 received KTE-C19. Of these seven, five had an objective response (4 CR, 1 PR) per investigator (source: FDA analysis). Thus, the ORR was consistent with that observed in the phase 2 cohort.

Response after retreatment
Ten patients received a second dose of KTE-C19 due to PD after initial response. Per FDA analysis:

- By IRC, three (30%) had an objective response on mITT analysis: three CR, six no response, one not evaluated.
- By investigator, six (60%) had an objective response: three CR, three PR, three no response, one not evaluated.

Follow-up for DOR after retreatment is immature.

Reviewer comments:

- **In patients retreated with KTE-C19, the discordance in response assessment per IRC vs investigator is notable.**
- **In the reviewer's opinion, the numbers of patients retreated and their extent of follow-up are insufficient to support an efficacy claim or to warrant mention in Section 14 of the PI.**

SCHOLAR-1 study

The Applicant conducted a companion study (SCHOLAR-1) to characterize outcomes with standard therapies for refractory or relapsed aggressive B-NHL, provide context for interpreting ZUMA-1 results, and confirm the prespecified control response rate (20%). This retrospective study pooled patients from two randomized phase 3 trials (CORAL, NCIC-CTG LY.12) and two observational cohorts; 636 patients were identified with aggressive B-cell lymphoma (median age 55; most with de novo DLBCL) who received salvage therapy for primary refractory disease (28%), refractoriness to later-line therapy (49%), or relapse ≤ 12 months after auto SCT (22%). Of these, 523 patients (88% with de novo DLBCL, all having prior anthracycline and anti-CD20 monoclonal antibody) were evaluable for the primary endpoint of response per investigator. ORR to salvage therapy ranged from approximately 20% to 30%, with CR rates of <15% (Table 35). Response rates were consistently poor across major subgroups (Table 35). DOR was not assessed. Among 603 patients assessed for survival, the median OS was 6.3 months, with six-month, one-year, and two-year survival estimates of 53%, 28%, and 20%, respectively (source: SCHOLAR-1 technical report).

Table 35: Outcomes in the SCHOLAR-1 Response-Evaluable Subset

Group	N	ORR (95% CI, %) per investigator		CR rate (95% CI, %) per investigator	
All patients	523	26%	(21, 31)	7%	(3, 15)
Diagnosis: de novo DLBCL	459	26%	(22, 31)	7%	(3, 15)
Refractoriness to last therapy					
Primary refractory	101	24%	(16, 33)	7%	(1, 39)
Refractory to 2nd or later line	316	27%	(21, 34)	10%	(5, 17)
Relapsed ≤ 12 mo after auto SCT	91	30%	(22, 41)	14%	(5, 30)
Any primary refractory disease	245	18%	(11, 28)	3%	(1, 7)
Refractory to ≥ 2 consecutive lines	321	1%	(<1, 11)	<1	(0, 2)

Source: SCHOLAR-1 technical report

7.1.11 Efficacy Conclusions

The submitted data meet the evidentiary standard of effectiveness for patients with large B-cell lymphoma that has relapsed within one year of auto SCT or was refractory to second- or later-line salvage therapy. This conclusion is based on CR rate and DOR, as determined by the IRC, in 101

patients with particularly poor-risk disease. This benefit is clinically meaningful, and the overall benefit/risk acceptable in this population of patients who otherwise would have few, if any, treatment options.

However, the Applicant seeks a broad indication for patients with rel/ref "aggressive B-cell NHL", without specified minimum number of prior lines of therapy, and characterizes the intended population as "ineligible for autologous SCT". In the clinical reviewer's opinion, the evidentiary standard of effectiveness has not been met for the Applicant's proposed indication statement. For further discussion, refer to Section 11.4.

For presentation of efficacy in labeling, refer to Section 11.5.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

See Section 6.1.12.1

8.2 Safety Database

8.2.1 Studies Used to Evaluate Safety

In light of the difference in the population and safety profile of subjects from ZUMA-3 and ZUMA-4, and the investigational product characteristics used in the (b) (4) study, the 108 subjects from ZUMA-1 comprise the safety population set and should be used as the safety population for labeling purposes.

In ZUMA-2, bridging therapy with steroids or continuation of ibrutinib (small-molecule inhibitor of Bruton's tyrosine kinase) was permitted at the discretion of the investigator. Bridging therapy was not permitted in ZUMA-1. A total of 25 of 37 subjects enrolled in ZUMA-2 were treated with KTE-C19 or KTE-C19 ((b) (4) The first 10 subjects in ZUMA-2 were treated with KTE-C19. Fifteen subjects were treated with KTE-C19 ((b) (4)

Reviewer comment:

- **The Applicant verified discrepancy regarding the number of subjects in ZUMA-2 who were treated with KTE-C19 vs. KTE-C19 ((b) (4) in response to an IR (amendment 48). The use of bridging chemotherapy and the limited number (n=10) of subjects who received KTE-C19 limit the ability to pool data with the ZUMA-1 study for pooled safety analyses.**

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

See Section 1.1 and 6.1.12.1. The overall demographics were similar to subjects in ZUMA-1.

8.2.3 Categorization of Adverse Events

See Section 6.1.12.2.

8.3 Caveats Introduced by Pooling of Data Across Studies

There were no pooled data. See Section 8.2.1.

8.4 Safety Results

8.4.1 Deaths

One subject ((b) (6)) in the ZUMA-2 study died of fatal organizing pneumonia that occurred after the data cutoff. The event occurred on Day 37 following infusion of KTE-C19 ((b) (4)

8.4.2 Nonfatal Serious Adverse Events

See section 8.4.4

8.4.3 Study Dropouts/Discontinuations

According to the 120-Day safety update, a total of 37 subjects were enrolled and underwent leukapheresis in ZUMA-2 by the cutoff date. Twenty-eight subjects were treated with the conditioning regimen, and 25 subjects received treatment with the investigational product.

8.4.4 Common Adverse Events

The small sample sizes in the current analyses precluded definitive conclusions regarding rates for adverse events. However, the incidences of SAEs, Grade ≥3 AEs, CRS, neurologic events, and infections were similar across studies.

8.4.5 Clinical Test Results

Not applicable

8.4.6 Systemic Adverse Events

See Section 8.4.4

8.4.7 Local Reactogenicity

Not applicable

8.4.8 Adverse Events of Special Interest

See Section 8.4.4

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

None

8.5.2 Time Dependency for Adverse Events

See Section 6.1.12.5

8.5.3 Product-Demographic Interactions

See Section 6.1.12.1

8.5.4 Product-Disease Interactions

Not applicable

8.5.5 Product-Product Interactions

Not applicable

8.5.6 Human Carcinogenicity

No carcinogenicity or genotoxicity studies have been conducted with KTE-C19.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.5.8 Immunogenicity (Safety)

The immunogenicity of KTE-C19 was evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. None of the subjects treated developed antibodies after infusion.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable

8.6 Safety Conclusions

The safety data from ZUMA-2 is consistent with the key adverse events noted in ZUMA-1.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Hepatic and renal impairment studies of KTE-C19 were not performed.

9.1.1 Human Reproduction and Pregnancy Data

No data in pregnant women are available. No animal reproductive studies have been conducted with axicabtagene ciloleucel. Refer to the PIs for cyclophosphamide and fludarabine.

9.1.2 Use During Lactation

It is unknown whether axicabtagene ciloleucel is excreted in human milk.

9.1.3 Pediatric Use and PREA Considerations

There are no pediatric data in the intended population. The application does not trigger PREA, as axicabtagene ciloleucel is an NME with orphan designation.

9.1.5 Geriatric Use

There are too few subjects to evaluate whether and to what extent efficacy and safety differ in subjects aged ≥ 65 vs < 65 years.

The overall incidence of Grade 3 or higher AEs was similar between subjects ≥ 65 year old and <65 year old except for the higher rate of encephalopathy, lymphopenia and hypophosphatemia observed in subjects ≥ 65 years of age. Please refer to Table 36.

Table 36: AEs Grade ≥3 by Age Group

AE Term	<65 Years (N = 81) (%)	≥ 65 years (N = 27) (%)
Any G ≥3	77 (95%)	25 (93%)
Encephalopathy	20 (25%)	11 (41%)
Hypophosphatemia	14 (17%)	8 (30%)
Lymphopenia	12 (16%)	10 (40%)
Delirium	3 (4%)	4 (16%)
Aphasia	7 (9%)	0 (0%)

Source: FDA analysis

The rate of CRS was similar between the two age groups, as was the rate of hypotension and tachycardia. However, more events of fever and hypoxia were observed in the older age group. See Table 37 below.

Table 37: CRS AEs Incidence ≥10% by Age Group

AE Term	<65 Years (N=81) (%)	≥ 65 Years (N = 27) (%)
Any CRS	76 (94%)	25 (93%)
Fever	61 (75%)	23 (85%)
Hypoxia	16 (20%)	8 (30%)
Chills	21 (26%)	1 (4%)

Source: FDA analysis

Table 38: ZUMA-1 Safety Analysis by Age Group

AE Worst Toxicity Grade	<65 Years (N = 81) (%)	≥ 65 Years (N = 27) (%)
Any	**81 (100%)**	**27 (100%)**
1	0 (0%)	0 (0%)
2	4 (5%)	2 (7%)
3	23 (28%)	6 (22%)
4	47 (58%)	16 (59%)
5	7 (9%)	3 (11%)

Source: FDA analysis

Reviewer comment:

- **Clinical trials of KTE-C19 did not include sufficient numbers of subjects aged 65 years and older to reach definitive conclusions that support extrapolation of safety data from subjects < 65 years of age to ≥ 65 years of age. The decision to treat a subject ≥ 65 years of age should therefore be left to the discretion of the treating physician.**

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None

10. CONCLUSIONS

Refer to Sections 1, 7.1.11, 6.1.13, and 11.

Safety:
Overall, the adverse events of CRS and neurotoxicity associated with KTE-C19 therapy are serious and can be fatal. Treatment algorithms to mitigate these AEs as implemented in the study permits the benefits of treatment to outweigh these risks. In addition, the potential for insertional mutagenesis and resultant secondary malignancies exist.

Measures to reduce or further assess the risk to patients include:

1) Warnings and precautions for the key safety issues identified in ZUMA-1
2) Treatment algorithms for the management of these toxicities
3) Hospitalization of patients for 7 days
3) REMS with an ETASU to assure the safe use of KTE-C19
4) A postmarketing observational study that is a requirement to follow recipients of the commercial product for short and long-term toxicity.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The following table summarizes the risk/benefit considerations for axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma of the following subtypes after two or more lines of systemic therapy: DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from FL.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Aggressive B-cell NHLs are fatal if not cured. In DLBCL that is refractory or that relapses within 1 year after auto SCT, salvage regimens produce ORRs of 20-30%, with <15% CR and an estimated median OS of 6 months.	• There is a need for effective and safe salvage therapies for relapsed or refractory, aggressive B-cell NHL
Unmet Medical Need	• There are no approved therapies for patients with relapsed/refractory, aggressive B-cell NHL.	• Patients with relapsed or refractory, aggressive B-cell NHL have unmet medical needs.

Clinical Benefit	• In a single-arm, multicenter study (ZUMA-1) for patients with relapsed/refractory, aggressive B-cell NHL, lymphodepleting chemotherapy followed by a single dose of KTE-C19 (target, 2 x 10^6 CAR-positive T-cells/kg) produced:
	  • On mITT analysis of 101 patients, an ORR per IRC of 72%, with CR rate of 51% (95% CI: 41, 62) and median time to response of 0.9 months
	  • On true ITT analysis of 111 patients, an ORR per IRC of 66, with 47% CR
	  • An estimated median DOR of 9.2 months (95% CI: 5.4, NE), with 7.9-month median follow-up
	  • An estimated median DOR that was not reached in patients who achieved CR (95% CI: 8.1 months, NE); in patients with a BOR of PR, the estimated median DOR was 2.1 months
		• Based on CR rate and DOR, KTE-C19 at the recommended dose-schedule has clinically meaningful activity in relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.
		• There are too few patients to assess the benefit/risk of KTE-C19 for the treatment of primary refractory disease.

Risk	• Major AEs associated with KTE-C19 were cytokine release syndrome (CRS), neurologic toxicities, prolonged cytopenias, infectious complications, cardiac events, and hypogammaglobulinemia.	• All the evidence indicates that the risk of KTE-C19, while substantial, does not outweigh the benefit to adult patients with rel/ref B-cell NHL
Risk Management	• The most substantial risks of KTE-C19 are CRS and neurologic toxicity . These were mitigated in the trial by careful site selection and training of investigators. • There are theoretical risks of secondary malignancy in this genetically modified immunotherapy based on the potential for replication competent retrovirus due to the retrovirus and insertional mutagenesis.	• The risks associated with KTE-C19 warrant boxed warnings, a REMS with ETASU and a long-term follow-up study. • The registry postmarketing study will follow 1000 recipients of the commercial product for 15 years for secondary malignancy and other short-term AEs.

11.2 Risk-Benefit Summary and Assessment

Axicabtagene ciloleucel is associated with a favorable risk/benefit balance for the recommended indication. A summary of key efficacy and safety results is provided in Sections 1 and 11.1.

11.3 Discussion of Regulatory Options

Efficacy
Based on the adequate number of patients evaluated, the magnitude and durability of the treatment effect, and the high unmet medical need, the clinical review team recommends regular, rather than accelerated, approval on the basis of the ZUMA-1, single-arm, multicenter clinical trial.

Safety
The safety profile for KTE-C19 warrants a REMS with ETASU. In the IND phase, the Applicant selected sites for expertise, conducted site training, and had close medical monitoring to assure that the unique adverse events were not only treated appropriately but that patients and medical staff were educated on the risk particularly of CRS and neurotoxicity. There are additional long-term safety concerns due to the use of the retroviral vector. We will ask the Applicant to comply with a PMR study for short and long-term toxicity with an observational focus. Lastly, the label will be inclusive of the risks and will include risk mitigation strategies for CRS and neurotoxicity, including mandatory hospitalization and inpatient monitoring after KTE-C19 infusion.

11.4 Recommendations on Regulatory Actions

Regulatory recommendations regarding efficacy

Proposed indication: Treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma who are ineligible for autologous stem cell transplant

Recommended indication: Treatment of adult patients with relapsed or refractory large B-cell lymphoma of the following types after two or more lines of systemic therapy: diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from follicular lymphoma

The clinical review team recommends approval for the revised indication above. The rationale for the changes is as follows:

- *Lines of prior therapy:* The Applicant seeks an indication for relapsed/refractory disease (b) (4) As such, the review team recommends an indication for relapsed or refractory disease after two or more lines of systemic therapy.

- *Characterization of the intended population:* The Applicant seeks an indication for patients who are ineligible for auto SCT. However, transplant ineligibility was not the entry criterion for the ZUMA-1 efficacy population. The term “transplant ineligible” is also problematic because of its

ambiguity, since reasons for transplant ineligibility include not only failure to achieve the remission typically required for SCT, but presence of prohibitive comorbidities. The latter, in turn, may increase the risks or reduce the tolerability of KTE-C19.

- *Diagnoses in the indication statement:* The Applicant seeks a broad indication for "aggressive B-cell NHL," a term that encompasses many types of lymphoma that were not studied, such as Burkitt lymphoma. The clinical review team considered an indication in DLBCL, the most common subtype studied. However, in the 2016 World Health Organization (WHO) classification of lymphoma (Swerdlow et al, Blood 2016), "DLBCL" is not an official diagnostic category; rather, the categorization contains "DLBCL not otherwise specified" and a variety of other "large B cell" and "high grade" lymphomas, with double-hit lymphomas included in the latter.

  For the indication statement, the review team thus recommends the term "large B-cell lymphoma" and specifying the main types that were studied in ZUMA-1, namely: DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from FL. It is recognized that "large B-cell lymphoma" is not an official WHO diagnosis, and that variants with a similar prognosis in the relapsed/refractory setting, such as T-cell rich large B-cell lymphoma, would be excluded. Alternatively, rather than in the indication statement, the specific types of lymphoma studied in ZUMA-1 could be described in the efficacy section of the PI.

Regulatory recommendations regarding safety

The review team recommends regular approval for axicabtagene ciloleucel (Yescarta) under an ETASU REMS.

11.5 Labeling Review and Recommendations

The following are recommendations for the YESCARTA PI based on this review:

Indication: Regular approval for the treatment of adult patients with relapsed or refractory large B-cell lymphoma of the following types after two or more lines of systemic therapy: diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, and DLBCL arising from follicular lymphoma.

Dosing and administration

- The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells.
- YESCARTA will be administered as inpatient only. Patients will be monitored in inpatient settings for 7 days.
- Patients will be instructed to remain within proximity of the certified treating hospital for a total of 4 weeks post YESCARTA infusion.

Safety

- Inclusion of all 108 patients, from Phase 1 and Phase 2 who received treatment, into the safety population.
- Modification to the warning and precautions sections to include details regarding CRS, neurologic toxicity, serious infections, prolonged cytopenias, hypogammaglobulinemia, and

secondary malignancies.
- Add section 5.3 to describe the REMS.
- Update the rate of adverse reaction according to the FDA group terms.

Efficacy
- Designate CR rate and DOR per IRC as the basis of the efficacy determination.
- Present efficacy according to IRC, rather than investigator.
- Present response rate according to both a mITT and true ITT analysis.
- In recipients of subsequent SCT, censor DOR at the time of SCT.
- Expand the description of ZUMA-1 eligibility criteria to inform prescribing.
- Remove the following from Section 14:
  - Survival data
  - Efficacy after retreatment with KTE-C19
  - Data from study NCI 09-C-0082 of a related anti-CD19 CAR-T product
  - SCHOLAR-1 meta-analysis

Reviewer comment:
- **Labeling negotiations with the Applicant are ongoing at the time of completion of this review.**

11.6 Recommendations on Postmarketing Actions

The Applicant is planning to conduct a postmarketing registry study which we will consider a PMR. This study is observational and focuses on short-term toxicity, documenting adverse events, and long-term follow-up for evaluation of secondary malignancies. No routine study for RCR is planned. The plan is to enroll approximately 1000 patients and follow each patient for 15 years.