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Application Type	Efficacy Supplement BLA
STN	125703/91
CBER Received Date	April 1, 2019
PDUFA Goal Date	October 1, 2021
Division / Office	DB/OBE
Committee Chair	Najat Bouchkouj
Clinical Reviewer(s)	Najat Bouchkouj
Project Manager	Crystal Melendez
Priority Review	Yes
Reviewer Name(s)	Xue Lin
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Lead, FDA/CBER/OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
Applicant	Kite Pharma
Established Name	KTE-X19
Trade Name	TECARTUS
Pharmacologic Class	CD19-directed genetically-modified autologous T cell
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	The target dose is 1×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 1×10^8 CAR-positive viable T cells.
Proposed Indication(s) and Intended Population(s)	adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

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GLOSSARY

ASCT autologous stem cell transplant
BLA Biologics Licensure Application
BOR best overall response
CI confidence interval
CR complete remission
CRi complete remission with incomplete hematologic recovery
CRS cytokine release syndrome
CSR clinical study report
DLBCL diffuse large B cell lymphoma
DOR duration of remission
FAS full analysis set
IEAS interim efficacy analysis set
IRC independent review committee
IV intravenous
NCI National Cancer Institute
NHL non-Hodgkin lymphoma
ORR overall remission rate
OS overall survival
PFS Progression-free survival
r/r relapsed/refractory
SCT stem-cell transplantation

1. EXECUTIVE SUMMARY

This efficacy supplement Biologics Licensure Application (sBLA) seeks licensure of KTE-X19 for the treatment of adult patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia (r/r B-ALL). KTE-X19 is an engineered autologous T cell immunotherapy. KTE-X19 received FDA BLA approval in July 2020 for the indication of adult patients with relapsed/refractory mantle cell lymphoma (r/r MCL).

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study, ZUMA-3. The primary efficacy endpoint is overall complete remission (OCR) rate, which is defined as the proportion of subjects with either a complete remission (CR) or a complete remission with an incomplete hematologic recovery (CRi), as assessed by an independent review committee (IRC).

The primary evidence of efficacy is based on the ZUMA-3 efficacy evaluable set, which included subjects who received at least one dose of KTE-X19 in Phase 2 and had measurable disease post bridging therapy. The FDA clinical review team re-adjudicated the disease response, based on which the OCR rate was 65% (95% CI: 50.6%, 77.3%) for the efficacy evaluable set with 54 subjects and the lower limit of the 95% confidence interval was above the pre-set null hypothesis rate of 40%. The CR rate were 54% (95% CI: 39.6%, 67.4%).

The follow-up time for the duration of remission (DOR) ranged from 1 day (no adequate disease assessment beyond initial response) to 16 months with a median of 5 months. The estimated median DOR was 13.6 months (95% CI: 9.4, NE). Seventy-seven percent (95% CI: 55.7%, 89.2%) of responders were estimated to remain in remission 6 months after initial response.

The safety analysis set included 55 subjects who received at least one dose of KTE-X19 in Phase 2. Deaths occurred in 42% of subjects. Treatment-emergent Serious Adverse Events (SAE) were reported in 76% of subjects. The most common adverse event of special interest was Cytokine Release Syndrome (CRS) which was reported in 89% of KTE-X19 infused subjects in Phase 2.

Study ZUMA-3 met its primary efficacy endpoint: the pre-specified null hypothesis of 40% OCR rate was rejected. The statistical analysis results provide sufficient evidence to support the applicant's proposed indication for KTE-X19 in this BLA supplement.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Based on information submitted by the applicant, ALL is a heterogeneous group of lymphoid disorders resulting from the clonal proliferation of immature lymphocytes of B- or T-cell lineage in the blood, bone marrow, and other organs. The disease occurs with a bimodal age distribution, with 55% of cases diagnosed in patients < 20 years old and 28% of cases diagnosed in adult patients ≥ 45 years. In the United States, approximately 6,000 new ALL cases are diagnosed per year, and approximately 1,500 deaths from ALL occur per year.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

According to the applicant, while initial complete remission (CR) rates in adults are high (80% to 90%) most patients eventually relapse. Second-line chemotherapy yields remissions in approximately 20% to 40% of patients, with the remission rate being lower in patients who relapse within 12 months of an initial response. Although allo-stem-cell transplantation (SCT) serves as a meaningful option for patients with r/r ALL, only a minority of patients are eligible for transplant, and few of these patients achieve a meaningful remission.

In the adult r/r setting, the FDA approved blinatumomab and inotuzumab. In the pediatric and young adult r/r setting, the FDA approved Tisagenlecleucel.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the major pre-submission regulatory activities associated with this BLA.

Table 1. Major pre-submission regulatory activities

Meeting Topic (Type)	Discussion Points	Format	Timeframe	Meeting Information Package / FDA Responses
Initial Multidisciplinary BTD Meeting (Type B)	Planned regulatory interactions; key aspects of the planned registration package; Phase 2 portion of ZUMA-3	Teleconference	15 May 2018	SN 0168 / CRMTS #11116
CMC meeting (Type B)	Discuss key aspects of Module 3 of the planned BLA	Teleconference	Meeting was removed from communication plan as it was not needed.	NA
Format/content of the sBLA (Type B)	Format and content of the planned sBLA for r/r ALL	Written Responses	07 April 2020	SN 0333 / CRMTS #12400
Pre-sBLA Meeting (Type B)	Discussion of the topline data from Phase 2 portion of ZUMA-3	Teleconference	02 February 2021	SN 0417/ CRMTS # 13038

(Source: original Table 4 Section 2.5 clinical overview BLA 125703/91)

Table 2 summarizes the major post-submission regulatory activities associated with this sBLA.

Table 2. Major post-submission regulatory activities

Milestone	Date
DCC Receipt Date	April 1, 2021
Filling Letter issued	May 28, 2021
Mid-Cycle Meeting	July 9, 2021
PUDUFA Action Due Date	October 1, 2021

(Source: FDA statistical reviewer)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from study ZUMA-3, which is the focus of this review memo.

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

The basis of this statistical memo is clinical study reports and data sets submitted in module 5 of the BLA submission.

5.3 Table of Studies/Clinical Trials

Table 3 summarizes the studies included in the BLA submission.

Table 3. Studies supporting the proposed indication in the BLA submission

Type of Study	Description of Study	eCTD Location of Data Included in the sBLA
Efficacy and Primary Safety		
KTE-C19-103 (ZUMA-3)	Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r B-ALL	ZUMA-3 Primary Analysis CSR (m5.3.5.2); Summary of Clinical Safety (m2.7.4); Summary of Clinical Efficacy (m2.7.3); Summary of Clinical Pharmacology (m2.7.2); Summary of Biopharmaceutic Studies and Associated Analytical Methods (m2.7.1); Pharmacokinetics, Pharmacodynamics, and Translational Medicine Report (m5.3.4.2)
Supporting Safety		
KTE-C19-102 (ZUMA-2)[a]	Phase 2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r MCL	Summary of Clinical Safety (m2.7.4)
KTE-C19-104 (ZUMA-4)[b]	Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in pediatric and adolescent subjects with r/r B-ALL or r/r B-cell NHL	Summary of Clinical Safety (m2.7.4)
KTE-C19-108 (ZUMA-8)[c]	Phase 1, multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with r/r CLL or SLL	Summary of Clinical Safety (m2.7.4)
KT-US-472-0118 (ZUMA-18)[d]	Multicenter, open-label, expanded access study of KTE-X19 for the treatment of adult subjects with r/r B-cell malignancies	Summary of Clinical Safety (m2.7.4)

Abbreviations: B-ALL, B-cell precursor acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CSR, clinical study report; eCTD, electronic Common Technical Document; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; r/r, relapsed/refractory; sBLA, supplemental Biologics License Application; SLL, small lymphocytic lymphoma.

a Ten subjects treated with axicabtagene ciloleucel in ZUMA-2 were not included in the safety analysis.

b One subject with non-Hodgkin lymphoma in ZUMA-4 was enrolled and treated with KTE-X19 at a target dose of 1×10^6 cells/kg. The data for this subject were not included in the tables and listings prepared for the Summary of Clinical Safety.

c No subjects with r/r SLL in ZUMA-8 were included in the safety analysis since they were not treated with KTE-X19 by the data cutoff date for ZUMA-3 primary analysis.

d ZUMA-18 Cohort 2 enrolled subjects whose commercially manufactured KTE-X19 did not meet commercial release specifications and were therefore considered out-of-specification products. Only subjects in Cohort 1 were included in the safety analysis.

(Source: Original Table 2 Section 2.5 clinical overview BLA 125703/91)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (Study ZUMA-3)

6.1.1 Objectives

The primary objective of Phase 1 was to evaluate the safety of KTE-X19.
The primary objective of Phase 2 was to evaluate the efficacy of KTE-X19, as measured by the OCR rate, defined as the combined rate of CR and CRi in adult subjects with r/r B-ALL.

6.1.2 Design Overview

ZUMA-3 was a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in subjects with r/r B-ALL.
During Phase 1, approximately 3-12 subjects with high burden r/r ALL disease who were evaluable for DLT were to be assessed to evaluate the safety of KTE-X19.
During Phase 2, approximately 50 subjects in the modified-intention to treat (mITT) set were to be assessed to evaluate the efficacy and safety of KTE-X19.

Each subject was to proceed through the following study periods:

- Screening
- Enrollment/leukapheresis
- Bridging chemotherapy and cerebrospinal fluid (CSF) prophylaxis period
- Conditioning chemotherapy
- Investigational product treatment
- Post-treatment assessment
- Long-term follow-up

6.1.3 Population

All eligible subjects must have had r/r B-ALL defined as at least 1 of the following: primary refractory disease, first relapse following a remission lasting ≤ 12 months, r/r disease after second-line or higher therapy, or r/r after allo-SCT (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment). All subjects must have had morphological disease in the bone marrow (> 5% blasts). Subjects with Ph+ disease were eligible if they were intolerant to TKI therapy or if they had r/r disease despite treatment with at least 2 different TKIs. Subjects must age 18 years or older.

Detailed inclusion and exclusion criteria are in Section 5 of the study protocol.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects underwent leukapheresis and optional conditioning chemotherapy before they received KTE-X19 cell infusion.

6.1.6 Sites and Centers

This study was to be conducted at 32 study centers in the US, Canada, France, Germany, and the Netherlands.

6.1.7 Surveillance/Monitoring

An independent Data Safety Monitoring Board (DSMB) were to review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion.

6.1.8 Endpoints and Criteria for Study Success (Phase 2)

Primary endpoint: OCR rate per independent review

The study protocol also included several secondary efficacy endpoints:

- Minimal Residual Disease (MRD) negative rate
- CR rate, CRi rate per independent review
- Duration of remission (DOR)
- Overall complete remission rate (CR+CRi) using the investigator assessment
- Allogeneic stem cell transplant (Allogeneic SCT) rate
- Overall survival (OS)
- Relapse-free Survival (RFS)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypotheses:

Primary hypothesis: H_0: overall complete remission rate $\leqslant 0.4$

Key secondary hypothesis: $H_{0:}$ Minimum Residual Disease (MRD) Negative Rate $\leqslant 0.3$

Key secondary hypothesis was tested only if the test for the primary hypothesis was statistically significant at the one-sided 0.025 significance level.

Analysis populations

a. Full Analysis Set: all enrolled (leukapheresed) subjects
b. Modified Intent-To-Treat (mITT) analysis set: all subjects enrolled and treated with KTE-X19 in Phase 2
c. Safety analysis set: all subjects treated with any dose of KTE-X19

Statistical methods

Primary endpoint

The rate of best response of CR and CRi were tabulated. CIs were calculated about the OCR rate, as well as the CR rate and CRi rate separately, with the Clopper-Pearson method.

Other secondary endpoints

a. Rate of MRD− Remission

The MRD− remission rate and 95% CIs were calculated.

b. Duration of response (DOR)

For subjects who experience CR or CRi per independent review, DOR was defined as the time between their first complete response per independent review to relapse or any death in the absence of documented relapse. Subjects who did not meet the criteria for relapse and who have not died were censored at the last evaluable disease assessment or disease status follow up assessment.

DOR was derived using disease assessments obtained on study prior to initiation of new anticancer therapy and allo-SCT (excluding resumption of tyrosine kinase inhibitor (TKI)). The DOR for subjects who undergo allo-SCT while in remission was censored at the last evaluable disease assessment prior to the allo-SCT; the DOR for subjects who undergo other new anticancer therapies in the absence of documented relapse was censored at the last evaluable disease assessment prior to the new anticancer therapies.

The primary analysis of DOR used the Kaplan-Meier method, and estimate of the median DOR, and 2-sided 95% CIs were generated. Estimates of the proportion of subjects who remained in response at 3-month intervals were provided. The number of subjects censored and the reasons for censoring was summarized.

c. Relapse free survival (RFS)

RFS for the mITT analysis set was defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause. RFS for all enrolled subjects in the FAS is defined as the time from enrollment to the date of disease relapse or death from any cause. Subjects who have not achieved a CR or CRi at the analysis data cutoff will be evaluated as having an RFS event at Day 0 for RFS analysis on mITT set, or at the date of enrollment for RFS analysis on FAS set. Subjects not meeting the criteria for relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date or disease status follow up assessment.

d. Overall survival (OS)

Kaplan-Meier plots, estimate of the median OS, and 2-sided 95% CIs were generated. Estimates of OS rates at 3-month intervals were provided. The number of subjects censored and the reasons for censoring were summarized.

<u>Sample size</u>

A sample size of 50 KTE-X19 subjects in Phase 2 provided about 93% power to distinguish an active therapy with a 65% true response rate from a therapy with a response rate of 40% or less, with a 1-sided alpha level of 0.025.

<u>Interim analyses</u>

The interim analysis were to be conducted after 20 subjects in the mITT analysis set in Phase 2 have had the opportunity to be followed for 30 days after the KTE-X19 infusion. This interim analysis was for safety only.

As part of its oversight of the study, the DSMB also will assess whether to pause enrollment in Phase 2 after 10, 20, and 35 subjects enrolled in Phase 2 have been treated with KTE-X19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following is met:

- Subject incidence of the following Grade 4 KTE-X19-related AEs lasting more than 7 days is > 33%:
  - Neurotoxicity
  - CRS (per Lee 2014 criteria)
  - Other nonhematological SAE
  - Treatment-related infection

Subgroup analysis

Subgroup analyses were planned based on age, sex, race, and a variety of other baseline clinical characteristics.

Missing data

The method for handling missing data is described in the definition for each efficacy endpoint.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographics of subjects who received at least one dose of KTE-X19 in Phase 2 are summarized in Table 4. Most subjects (75%) received treatment in the US. Seventy-five infused subjects (67%) were white. Forty-seven (85%) of infused subjects were younger than 65, and 60% of participants were male.

Table 4. Subject Demographics (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
Age (years)	
n	55
Mean (STDEV)	42.2 (16.1)
Median	40.0
Min, Max	19, 84
Age category, n (%)	
< 65 Years	47 (85)
≥ 65 Years	8 (15)
Sex, n (%)	
Male	33 (60)
Female	22 (40)
Ethnicity, n (%)	
Hispanic or Latino	11 (20)
Not Hispanic or Latino	42 (76)
Missing	2 (4)
Race, n (%)	
American Indian or Alaska Native	1 (2)
Asian	3 (5)
Black or African American	1 (2)
White	37 (67)
Other	9 (16)
Missing	4 (7)
Country of enrolled sites, n (%)	
Germany	3 (5)
France	10 (18)
Netherlands	1 (2)
United States	41 (75)

Data cutoff date = 09Sep2020.
(Source: original Table 9 CSR report body BLA 125703/91)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Baseline disease characteristics of subjects who received at least one dose of KTE-X19 in Phase 2 are summarized in Table 5. The median number of prior therapies was 2 (min=1, max=8), 42% of subjects had prior allo-SCT, 45% had prior Blinatumomab and 22% had inotuzumab.

Table 5. Subject Baseline Characteristics (Phase 2 Safety Analysis Set)

	Phase 2 (N=55)
ECOG Performance Status, n (%)	
0	16 (29)
1	39 (71)
Number of lines of prior therapy, n (%)	
1	10 (18)
2	19 (35)
3	14 (25)
4	10 (18)
5	1 (2)
8	1 (2)
median	2.0
Min, max	1, 8
Prior Blinatumomab, n(%)	
Yes	25 (45)
No	30 (55)
Prior inotuzumab, n(%)	
Yes	12 (22)
No	43 (78)
Prior allogeneic Stem Cell Transplant n(%)	
Yes	23 (42)
No	32 (58)
Relapsed or refractory to 2nd or greater line therapy, n (%)	
Yes	45 (82)
No	10 (18)

(source: abbreviated Table 13 CSR report body BLA 125703/91)

6.1.10.1.3 Subject Disposition

Detailed subject disposition is listed in Table 6 for the full analysis set. In Phase 2, 71 subjects were enrolled and 55 (77%) were treated with KTE-X19.

Table 6. Subject Disposition (Phase 2 Full Analysis Set)

	Total (N = 71)
Subjects Enrolled, n (%)	71
Subjects received bridging therapy, n (%)	64 (90)
Subjects Treated with Conditioning Chemotherapy, n (%)	57 (80)
Subjects not treated with conditioning chemotherapy nor with KTE-X19, n (%)	14 (20)
Adverse event	7(10)
Product not available	1 (1)
Partial consent withdrawn	1 (1)
Other [a]	5 (7)
Subjects did not initiate KTE-X19 infusion after conditioning chemotherapy, n (%)	2 (3)
Adverse event	1 (1)
Other	1 (1)
Subjects Treated with KTE-X19, n (%)	55 (77)
Primary reason for ending study for subjects Not treated with KTE-X19 n (%)	14 (20)
Investigator decision	3 (4)
Death	10 (14)
Other	1 (1)
Primary reason for ending study for subjects treated with KTE-X19, n (%)	23 (32)
Death	20 (28)
Full consent withdrawn	3 (4)
Actual Follow-up Time from KTE-X19 Dose (month)	
N	55
Median (Q1, Q3)	12.4 (7.6,17.2)
Min, Max	0.3, 22.1

Cutoff=09Sep2020

a Three subjects did not meet eligibility criteria, 1 subject experienced clinical deterioration after product was not successfully manufactured from 3 leukapheresis attempts, and 1 subject was considered not clinically stable to proceed with CAR T-cell therapy after product was not successfully manufactured from the initial leukapheresis attempt.

(source: abbreviated Table 9 report body, Clinical Study Report, BLA 125703/91)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

One subject in the mITT set didn't have bone marrow blasts post-bridging, and the FDA clinical review team considered this subject not evaluable for efficacy analyses. Excluding this subject from the mITT set, the efficacy evaluable set has 54 subjects.

Table 7 presents OCR rate after one dose of KTE-X19 in Phase 2 in efficacy evaluable set. The FDA clinical review team re-adjudicated the disease response, based on which the OCR rate was 65% (95% CI: 50.6%, 77.3%) for the efficacy evaluable set and the lower limit of the 95% confidence interval was above the pre-set null hypothesis rate of 40%. The CR rate were 54% (95% CI: 39.6%, 67.4%) and the CRi rate was 11% (95% CI: 4.2%, 22.6%).

As a supportive analysis, using all subjects who were enrolled as the denominator regardless of exposure to KTE-X19, the ORR was 51% (95% CI: 38.6%, 62.8%), with a CR rate of 42% (95% CI: 30.6%, 54.6%).

Table 7. Best Response per IRC (Efficacy Evaluable Set)

	Phase 2 Efficacy Evaluable set (N=54)
OCR (CR+CRi), n (%)	35 (65**%**)
(95% CI*)	(50.6%, 77.3%)
Best response, n (%)	
Complete remission (95% CI*)	29 (54**%**) (39.6%, 67.4%)
Complete remission with incomplete hematologic recovery (95%CI*)	6 (11%) (4.2%, 22.6%)
CRh	0
BFBM	6 (11%)
PR	0
NR	6 (11%)
Relapse	3 (6%)
Not evaluable	3 (6%)

*Clopper-Pearson exact confidence interval

(Source: FDA statistical reviewer)

The applicant reported that the OCR rate per investigator assessment with 55 subjects was 72.7% (95% CI: 59%, 84%), with a CR rate of 60.0% (95% CI: 46%, 73%), which were consistent with the rates based on the central assessment.

6.1.11.2 Analyses of Secondary Endpoints

MRD- Remission rate

The clinical team reported a 46% MRD- remission rate (95% CI: 33%, 60%), the lower limit is above the 30% null rate.

Duration of remission (DOR)

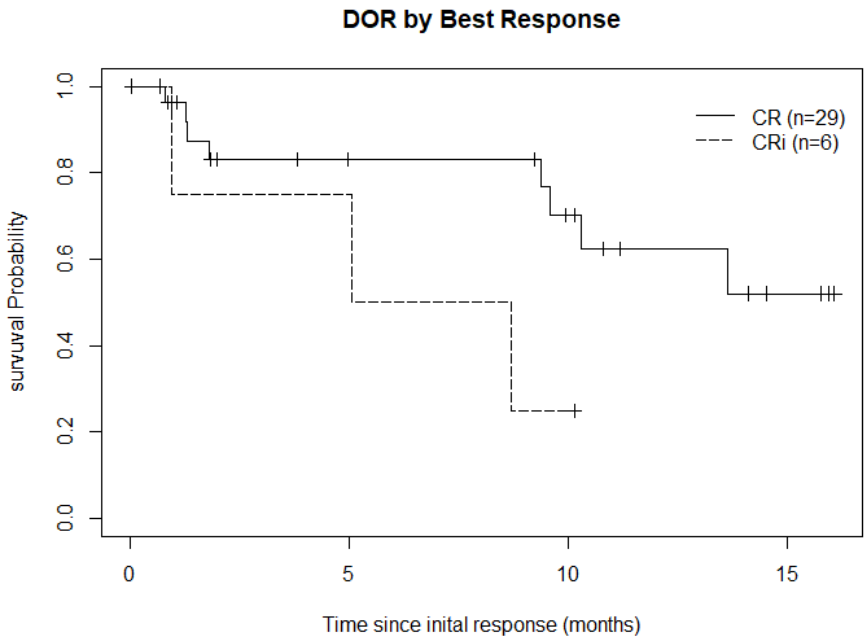
Table 8 summarizes the primary analysis of the DOR based on FDA re-adjudication. The follow-up time ranges from 1 day (no adequate disease assessment beyond initial response) to 16 months with a median of 5 months. The estimated median DOR was 13.6 months (95% CI: 9.4, NE). 77% (95% CI: 55.7%, 89.2%) of responders are estimated to remain in remission 6 months after initial response. CR responders appears to have longer DOR than CRi responders, however, the sample size for CRi is too small to make any meaningful conclusion.

Table 8. DOR results FDA adjudication (Efficacy evaluable set)

	Phase 2 Efficacy Evaluable Set (N=54)
Number of responders	35
Duration of response (months) Estimated median (95% CI)	13.6 (9.4, NE)
Median follow-up time (min, max)	5.0 (0.03+, 16.07+)
Percentage censored	69%
Remain in remission	12 (34%)
Allogeneic SCT	8 (23%)
Other new anti-cancer therapy	3 (9%)
Missing > 2 disease assessments	1 (3%)
DOR if BOR is CR (months)	
Estimated median (95% CI)	NE (9.6, NE)
Median follow-up time (min, max)	5.0 (0.03+, 16.07+)
Percentage censored	72%
DOR if BOR is CRi (months)	
Estimated median (95% CI)	6.9 (1.0, NE)
Median follow-up time (min, max)	3.0 (0.03+, 10.2+)
Percentage censored	50%
DOR landmarks (months) % (95% CI) KM estimation	
3- month	82% (62.0, 92.1)
6- month	77% (55.7, 89.2)
9- month	72% (50.0, 86.0)
12- month	55% (31.2, 73.8)

(Source: FDA statistical reviewer)

Figure 1. DOR by BOR

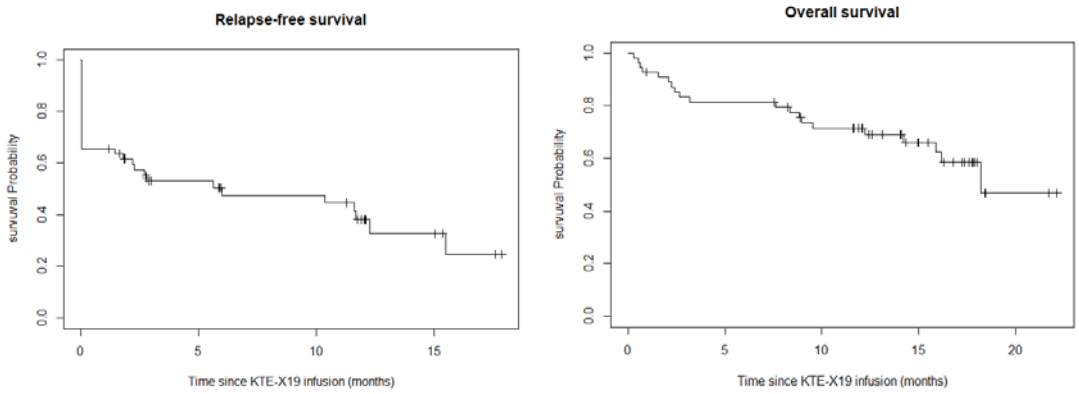


(Source: FDA statistical reviewer)

Progression-free survival and Overall survival

See Figure 2 for Kaplan-Meier curves of RFS (left panel) and OS (right panel) for the mITT population. The estimated median RFS was 6.0 months (95% CI: 1.8, 14.2), and the estimated median OS was 18.2 months (95% CI: 15.9, NE). Survival data from a single arm study needs to be interpreted with caution because it cannot be known with certainty what the control results would have been had there been a control group in the study.

Figure 2. Kaplan-Meier curves for RFS and OS (mITT)



(Source: FDA statistical reviewer)

6.1.11.3 Subpopulation Analyses

OCR appears to be consistent across race, ethnicity, age category and sex (Table 9).

Table 9. ORR by age group, ethnicity, race and sex (efficacy evaluable set)

Subgroup		Subgroup size (N=54) n (%)	Responders n (%)	95% CI[a] (%)
Age	<65 years	46 (85%)	27 (59%)	(43%, 73%)
	>=65 years	8 (15%)	8 (100%)	(63%, 100%)
Sex	Female	21 (39%)	12 (57%)	(34%, 78%)
	Male	33 (61%)	23 (70%)	(51%, 84%)
Race	White	36 (67%)	25 (69%)	(52%, 84%)
	Asian	3 (6%)	3 (100%)	(29%, 100%)
	Black or African American	1 (2%)	1 (100%)	(3%, 100%)
	American Indian or Alaska Native	1 (2%)	1 (100%)	(3%, 100%)
	Other	9 (17%)	3 (33%)	(7%, 70%)
	Unknown	4 (7%)	3 (75%)	(19%, 100%)
Ethnicity	Hispanic or Latino	11 (20%)	5 (45%)	(17%, 77%)
	Not Hispanic or Latino	41 (76%)	29 (71%)	(54%, 84%)
	Unknown	2 (4%)	1 (50%)	(1%, 100%)
Overall	54 (100%)	54 (100%)	35 (65%)	(51%, 77%)

a. Clopper-Pearson exact confidence interval

(Source: FDA statistical reviewer)

OCR appears to be consistent across baseline characteristics including ECOG, Prior allogeneic SCT (Y/N), number of prior regimen, prior Blinatumomab (Y/N), prior Inotuzumab (Y/N) and disease status at enrollment (Table 10).

Table 10. ORR by age group, ethnicity, race and sex (efficacy evaluable set)

Subgroup		Subgroup size (N=54) n (%)	Responders n (%)	95% CI[a] (%)
ECOG	0	16 (30%)	13 (81%)	(54%, 96%)
	1	38 (70%)	22 (58%)	(41%, 74%)
Prior Allogeneic SCT	N	31 (57%)	19 (61%)	(42%, 78%)
	Y	23 (43%)	16 (70%)	(47%, 87%)
No. of Prior Regimen	1	9 (17%)	6 (67%)	(30%, 93%)
	2	19 (35%)	11 (58%)	(34%, 80%)
	3	14 (26%)	9 (64%)	(35%, 87%)
	4	10 (19%)	7 (70%)	(35%, 93%)
	5	1 (2%)	1 (100%)	(3%, 100%)
	8	1 (2%)	1 (100%)	(3%, 100%)
Prior Blinatumomab	N	29 (54%)	21 (72%)	(53%, 87%)
	Y	25 (46%)	14 (56%)	(35%, 76%)
Prior Inotuzumab	N	42 (78%)	27 (64%)	(48%, 78%)
	Y	12 (22%)	8 (67%)	(35%, 90%)
Disease status at Enrollment	First untreated relapse	4 (7%)	2 (50%)	(7%, 93%)
	Primary refractory disease	14 (26%)	9 (64%)	(35%, 87%)
	Refractory relapse	25 (46%)	17 (68%)	(47%, 85%)
	Second or later untreated relapse	11 (20%)	7 (64%)	(31%, 89%)
Overall	54 (100%)	54 (100%)	35 (65%)	(51%, 77%)

a. Clopper-Pearson exact confidence interval

(Source: FDA statistical reviewer)

76% of subjects in the efficacy evaluable set were treated in the United states and the OCR was 61%, which was consistent with the overall OCR.

The maximum number of subjects treated at a given site was 7 subjects, 18 sites treated 1 or 2 subjects, the rest of sites treated 3, or 4 subjects. Due to the small number of subjects treated at each site, no subgroup by site was performed.

6.1.11.4 Dropouts and/or Discontinuations

In Phase 2, seventy-one (71) subjects were enrolled, 14 (20%) did not receive KTE-X19. Twenty (28%) subjects died during follow-up as of the 09Sept2020 cutoff. The details of the dropouts/discontinuations are provided in Table 6.

6.1.12 Safety Analyses

This section summarizes safety results of Study ZUMA-3.

6.1.12.1 Methods

Descriptive statistics are used to summarize safety data for study ZUMA-3. For data summary, the safety analysis set in this section includes a total of 55 subjects who received at least one dose of KTE-X19 in Phase 2.

6.1.12.3 Deaths

The applicant reported that 23 subjects (42%) had died as of the data cutoff March 19, 2021. Fourteen subjects (25%) died due to PD.

Four subjects (7%) died within 3 months of the KTE-X19 infusion, and 14 subjects (25%) died > 3 months after the KTE X19 infusion.

Table 9. Deaths reported (Phase 2, Safety Analysis Set)

	Phase 2 (N=55)
Subjects who died, n (%)	23 (42)
Primary cause of death, n (%) Adverse event Progressive disease Other	 8 (15) 14 (25) 1 (2)
Death occurred <= 30 days of KTE-X19 infusion, n (%)	4 (7)
Deaths that occurred > 30 days through 3 months (92 days) of KTE-X19 infusion, n (%)	5 (9)
Deaths that occurred > 3 months (92 days) after KTE-X19 infusion, n (%)	14 (25)

Data cutoff date=19Mar2021
(Source: Table 15. 120-day safety update)

6.1.12.4 Nonfatal Serious Adverse Events

The applicant reported 42 (76%) subjects in the Phase 2 safety analysis set had at least one treatment-emergent Serious Adverse Events. The most common SAEs were hypotension (16 subjects, 29%), followed by pyrexia (15 subjects, 27%), and hypoxia (7 subjects, 13%). The most common worst Grade 3 or higher SAEs were hypotension (13 subjects, 24%), hypoxia (7 subjects, 13%), and pyrexia (6 subjects, 11%).

6.1.12.5 Adverse Events of Special Interest (AESI)

The applicant reported 49 (89%) subjects in the Phase 2 safety analysis set experienced cytokine release syndrome (CRS). The most common CRS symptoms were pyrexia (46 subjects, 94%), hypotension (33 subjects, 67%) and sinus tachycardia (18 subjects, 37%).

Thirty-three (60%) had neurologic adverse events, including 14 subjects (25%) with worst Grade 3 or higher neurologic AEs. One subject had a Grade 5 neurologic AE of brain herniation. The most common neurologic AEs were tremor (15 subjects, 27%), confused state (14 subjects, 25%) and encephalopathy (12 subjects, 22%).

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This efficacy supplement Biologics Licensure Application (sBLA) seeks licensure of KTE-X19 for the treatment of adult patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia (r/r B-ALL). KTE-X19 is an engineered autologous T cell immunotherapy. KTE-X19 received FDA BLA approval in July 2020 for the indication of adult patients with relapsed/refractory mantle cell lymphoma (r/r MCL)

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study, ZUMA-3. The primary efficacy endpoint was overall complete remission (OCR) rate, which is defined as the proportion of subjects with either a complete remission (CR) or a complete remission with an incomplete hematologic recovery (CRi), as assessed by an independent review committee (IRC).

The primary evidence of efficacy is based on the ZUMA-3 efficacy evaluable set, which were subjects who received at least one dose of KTE-X19 in Phase 2 and had measurable disease post bridging therapy. The FDA clinical review team re-adjudicated the disease response, based on which the OCR rate was 65% (95% CI: 50.6%, 77.3%) for the efficacy evaluable set and the lower limit of the 95% confidence interval was above the pre-set null hypothesis rate of 40%. The CR rate were 54% (95% CI: 39.6%, 67.4%). The follow-up time for DOR ranged from 1 day (no adequate disease assessment beyond initial response) to 16 months with a median of 5 months. The estimated median DOR was 13.6 months (95% CI: 9.4, NE). Seventy-seven percent (95% CI: 55.7%, 89.2%) of responders were estimated to remain in remission 6 months after initial response.

The safety analysis set included 55 subjects who received at least one dose of KTE-X19 in Phase 2. Deaths occurred in 42% of subjects. Treatment-emergent Serious Adverse Events (SAE) were reported in 76% of subjects. The most common adverse event of special interest was Cytokine Release Syndrome (CRS) which was reported in 89% of KTE-X19 infused subjects in Phase 2.

10.2 Conclusions and Recommendations

Study ZUMA-3 met its primary efficacy endpoint: the pre-specified null hypothesis of 40% OCR rate was rejected. The statistical analysis results provide sufficient evidence to support the applicant’s proposed indication for KTE-X19 in this BLA supplement.