Application Type	Original BLA
STN	125703/0
CBER Received Date	Dec 11, 2019
PDUFA Goal Date	Aug 10, 2020
Division / Office	DB/OBE
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Clinical Reviewer(s)	Helkha Peredo-Pinto Megan Zimmerman
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Priority Review	Yes
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Review Completion Date / Stamped Date	
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	John Scott, Ph.D. Director, FDA/CBER/OBE/DB
Applicant	Kite Pharma
Established Name	KTE-X19
(Proposed) Trade Name	TECARTUS
Pharmacologic Class	CD19-directed genetically-modified autologous T cell
Formulation(s), including Adjuvants, etc.	2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells 5% dimethylsulfoxide (DMSO) and (b) (4) albumin (human)
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	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.
Proposed Indication(s) and Intended Population(s)	adult patients with relapsed or refractory mantle cell lymphoma (MCL)

Table of Contents

Glossary 3

1. Executive Summary 3

2. Clinical and Regulatory Background 4

2.1 Disease or Health-Related Condition(s) Studied 4
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 4
2.4 Previous Human Experience with the Product (Including Foreign Experience) 4
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 4

3. Submission Quality and Good Clinical Practices 5

3.1 Submission Quality and Completeness 5

5. Sources of Clinical Data and Other Information Considered in the Review 5

5.1 Review Strategy 5
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 6
5.3 Table of Studies/Clinical Trials 6

6. Discussion of Individual Studies/Clinical Trials 6

6.1 Trial #1 6
6.1.1 Objectives 6
6.1.2 Design Overview 6
6.1.3 Population 7
6.1.4 Study Treatments or Agents Mandated by the Protocol 7
6.1.6 Sites and Centers 7
6.1.7 Surveillance/Monitoring 7
6.1.9 Statistical Considerations & Statistical Analysis Plan 8
6.1.11 Efficacy Analyses 13
6.1.12 Safety Analyses 17

10. Conclusions 18

10.1 Statistical Issues and Collective Evidence 18
10.2 Conclusions and Recommendations 18

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 Biologics Licensure Application (BLA) seeks licensure of KTE-X19 for the treatment of adult patients with relapsed/refractory Mantle Cell Lymphoma (r/r MCL). KTE-X19 is an engineered autologous T cell immunotherapy.

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study (ZUMA-2). The primary efficacy endpoint was overall remission rate (ORR), which is defined as the proportion of subjects with either a complete response (CR) or partial response (PR), as assessed by an independent review committee (IRC). The primary evidence of efficacy for KTE-X19 is based on the inferential analysis set (IAS), which was the first 60 subjects treated with KTE-X19 at a target dose of 2×10^6 anti-CD19 CAR T cells/kg. The FDA clinical review team re-adjudicated the response assessments for IAS, based on which the ORR was 86.7% (95% CI: 75.4%, 94.1%) and the CR rate was 61.7% (95% CI: 48.2%, 73.9%).

Duration of response (DOR) was based on July 24, 2019 data cutoff. The follow-up time for DOR ranged from 0 to 888 days with a median of 240 days for the inferential analysis set. The overall median DOR was not estimable, due to 69% censoring. The median DOR was not estimable for subjects whose best response was CR, due to 84% censoring. The

median DOR was 129 days (95% CI: 48, 358) for subjects whose best response was partial response.

The safety analysis set included 82 subjects treated at any dose of KTE-X19. Deaths occurred in 24% of subjects. Treatment-emergent Serious Adverse Events (SAE) were reported in 66% of subjects. The most common adverse event of special interest was Cytokine Release Syndrome (CRS) which was reported in 91% of KTE-X19 infused subjects.

Study ZUMA-2 met its primary efficacy endpoint: The pre-specified null hypothesis of 25% ORR was rejected. The statistical analysis results provide evidence to support the applicant's proposed indication for KTE-X19 in this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) with distinctive clinical, biological, and molecular characteristics. Based on information submitted by the applicant, MCL accounts for approximately 6% of all new cases of NHL in the United States (US). The estimated annual incidence of MCL is 1 to 2 per 100,000 persons in the US. MCL is more likely to affect men than women, and the median age at diagnosis is 68 years.

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

According to the applicant, the frontline therapy for MCL leads to ORRs of up to 94% and CR rates of up to 53%. However, the majority of patients with MCL relapse and often progress to a clinically aggressive phenotype that is challenging to treat. For patients in the relapsed or refractory (r/r) setting, there is no recognized standard of care.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

NA.

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. The major pre-submission regulatory activities

Meeting Topic (Type)	Discussion Points	Format	Timeframe	FDA Responses
Initial multidisciplinary BTD meeting (Type B)	Planned regulatory interactions; key aspects of the planned registration package; ZUMA-2 Cohort 1	Face-to-face	21 September 2018 – Meeting canceled after preliminary meeting responses	CRMTS #11366 (m1.6.3)
Format/content of the BLA (Type B)	Format and content of the planned BLA for r/r MCL	Written responses	23 April 2019	CRMTS #11721 (m1.6.3)
REMS meeting (Type B)	Format and content of the planned KTE-X19 REMS	Teleconference	24 September 2019 – Meeting canceled after preliminary meeting responses	CRMTS #11945 (m1.6.3)
Pre-BLA meeting (Type B)	Discussion of the topline data from ZUMA-2 Cohort 1	Face-to-face	15 November 2019	DRMTS #12027 (m1.6.3)

Abbreviations: BLA, Biologics License Agreement; BTD, Breakthrough Therapy Designation; FDA, Food and Drug Administration; MCL, mantle cell lymphoma; REMS, Risk Evaluation and Mitigation Strategy; r/r, relapsed or refractory.

(Source: original Table 2 Section 2.5 clinical overview BLA 125703/0.0)

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

Table 2. The major post-submission regulatory activities

Milestone	Date
DCC Receipt Date	December 11, 2019
Filling Letter issued	February 7, 2020
Mid-Cycle Communication with Applicant	March 26, 2020
External Late-Cycle meeting	May 28, 2020
PUDUFA Action Due Date	August 10, 2020

(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-2, 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

Study ID	Phase	Study Design	Population Details	Status
KTE-C19-102 (ZUMA-2)[a]	2	Open label; safety and efficacy; multicenter	Pathologically confirmed r/r MCL, with documentation of either overexpression of cyclin D1 or presence of t(11;14)	Primary Analysis: Data cutoff date of 24 July 2019 Ongoing: 15-year Safety Follow-up
KTE-C19-103 (ZUMA-3)	1/2	Open label; safety and efficacy; multicenter	Adult r/r B-precursor acute lymphoblastic leukemia	Ongoing
KTE-C19-104 (ZUMA-4)	1/2	Open label; safety and efficacy; multicenter	Pediatric r/r B-precursor acute lymphoblastic leukemia or r/r B-cell non-Hodgkins lymphoma	Ongoing
KTE-C19-108 (ZUMA-8)	1/2	Open label; safety and efficacy; multicenter	r/r chronic lymphocytic leukemia	Ongoing
KT-US-472-0118 (ZUMA-18)	Expanded Access	Open label; expanded access; multicenter	Pathologically confirmed r/r MCL, with documentation of either overexpression of cyclin D1 or presence of t(11;14)	Planned

(Source: Original Table 1 Section 2.7.3 summary of clinical efficacy BLA 125703/0.0)

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (Study ZUMA-2)

6.1.1 Objectives

The primary objective was to evaluate the efficacy of KTE-X19, as measured by ORR, in subjects with r/r MCL.

The secondary objectives included assessing the safety and tolerability of KTE-X19 and additional efficacy endpoints.

6.1.2 Design Overview

ZUMA-2 was a Phase 2, multicenter, open-label study evaluating the safety and efficacy of
KTE-X19 in subjects with r/r MCL. Up to approximately 130 subjects were to be enrolled into 2 separate cohorts. Cohort 1 was to enroll and treat up to approximately 90

subjects with a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, with up to approximately 80 of these subjects receiving KTE-X19 (10 subjects enrolled in Cohort 1 received axicabtagene ciloleucel). Cohort 2 was to enroll and treat up to 40 subjects with KTE-X19 at a target dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg. Each subject was to proceed through the following study periods:

- Screening
- Enrollment/leukapheresis
- Bridging therapy, if applicable
- Conditioning chemotherapy
- Investigational product treatment
- Post-treatment assessment
- Long-term follow-up

6.1.3 Population

Eligible subjects were 18 years of age or older with pathologically confirmed MCL that had progressed after or was refractory to anthracycline or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and ibrutinib or acalabrutinib. Subjects must have had an Eastern Cooperative Oncology Group performance status of 0 or 1, at least 1 measurable lesion, and no evidence of central nervous system lymphoma. Detailed inclusion and exclusion criteria are in Section 7.2 of the clinical study report.

6.1.4 Study Treatments or Agents Mandated by the Protocol

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

6.1.6 Sites and Centers

This study was to be conducted at up to 33 study centers in the US, France, Germany, and the Netherlands.

6.1.7 Surveillance/Monitoring
An independent Data Safety Monitoring Board (DSMB) reviewed safety data after 10, 20, 38, and 44 subjects in Cohort 1 had been treated with KTE-X19. The DSMB also reviewed safety data after 10 subjects in Cohort 2 had been treated with KTE-X19.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: ORR (complete response [CR] + partial response [PR]) using an Independent Radiology Review Committee (central assessment) per the Lugano Classification

The study protocol also included several secondary efficacy endpoints:

- Best objective response using central assessment
- ORR and best objective response using the investigator assessment
- Duration of response (DOR)
- PFS

- OS

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypotheses:
H_0: *ORR* $\leqslant$ 0.25 vs. H*a*: *ORR* >0.25

Analysis populations

a. Full Analysis Set: all enrolled subjects
b. Modified Intent-To-Treat (mITT) analysis set: all subjects treated with KTE-X19
c. Inferential Analysis Set: the first 60 subjects treated with KTE-X19 in Cohort 1 and have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment since KTE-X19 infusion
d. Safety analysis set: all subjects treated with KTE-X19

Statistical methods

Primary endpoint

ORR was summarized along with the 2-sided exact Clopper-Pearson confidence interval. In the event any subject underwent a stem cell transplant (SCT) or any additional anti-cancer therapy while on study, the subject's best response would be derived only based on disease outcomes assessed prior to SCT or initiation of a new therapy, whichever was earlier.

Other secondary endpoints

a. Duration of response (DOR)

DOR was defined as the time from the first objective response to disease progression or death and applied only to subjects who experienced an objective response (CR or PR). Data from retreatment period will not be included for analysis.
The Kaplan-Meier approach was be used to estimate DOR. For subjects who initiated new anti-cancer therapy (including SCT) DOR would be censored at the last evaluable disease assessment date prior to initiation of a new therapy in the primary analysis.

b. Progression free survival (PFS)

PFS was defined as the time from the date of anti-CD19 CAR T cells infusion to that of disease progression or death from any cause.
Kaplan-Meier plots and estimates of survival probability along with its 2-sided 95% confidence intervals were generated for PFS. The same censoring rule applies to PFS for subjects who initiated new anti-cancer therapy (including SCT) as to DOR.

c. Overall survival (OS)

OS was defined as the time from the date of anti-CD19 CAR T cells infusion to that of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at the last date known to be alive or the data cutoff date, whichever was earlier. The distribution function of OS was estimated using the Kaplan-Meier method. The median OS estimate was presented along with 95% confidence intervals.

Sample size
Up to approximately 130 subjects with r/r MCL were to be enrolled and treated with anti-CD19 CAR T cells, including 10 axicabtagene ciloleucel subjects and up to approximately 80 KTE-X19 subjects in Cohort 1 and up to approximately 40 KTE-X19 subjects in Cohort 2. A sample size of 60 KTE-X19 subjects in Cohort 1 provided at least 96% power to distinguish an active therapy with a 50% true response rate from a therapy with a response rate of 25% or less, with a 1-sided alpha level of 0.025.

Interim analyses
Four interim analyses in Cohort 1 and one interim analysis in Cohort 2 were to be performed for safety and/or futility.

Subgroup analysis
Subgroup analyses were planned based on age, sex, race, and a variety of 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
The target dose in Cohort 1 was 2 x 10^6 anti-CD19 CAR T cells/kg. The first 10 subjects in Cohort 1 were treated with axicabtagene ciloleucel, all other subjects in ZUMA-2 were treated with KTE-X19. The main difference between the two products is that the manufacture of KTE-X19 includes a (b) (4) T-cell enrichment step.

The target dose in Cohort 2 (0.5 x 10^6 anti-CD19 CAR T cells/kg) is one fourth of the target dose in Cohort 2.
Because the target dose in Cohort 1 is the proposed labeled dose for KTE-X19 treatment, efficacy analysis will be primarily based on Cohort 1 (excluding the 10 subjects treated with axicabtagene ciloleucel).

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 are summarized in Table 4. Most subjects (93%) received treatment in the US. Seventy-five infused subjects (91%) were white. Approximately half of infused subjects were younger than 65, and 83% of participants were male.

Table 4. Subject Demographics (Safety Analysis Set)

	Cohort 1 (N=68)	Cohort 2 (N=14)	Overall (N=82)
Age (years)			
n	68	14	82
Mean (StD)	63.2 (7.9)	61.8 (5.4)	62.9 (7.5)
Median	65.0	61.5	65.0
Min, max	38, 79	52, 73	38, 79
Age Category, n (%)			
< 65 Years	29 (43)	11 (79)	40 (49)
≥ 65 Years	39 (57)	3 (21)	42 (51)
Sex, n (%)			
Male	57 (84)	11 (79)	68 (83)
Female	11 (16)	3 (21)	14 (17)
Ethnicity, n (%)			
Hispanic or Latino	11 (16)	2 (14)	13 (16)
Not Hispanic or Latino	55 (81)	12 (86)	67 (82)
Race, n (%)			
Black or African American	1 (1)	0	1 (1)
White	62 (91)	13 (93)	75 (91)
Native Hawaiian or other Pacific Islander	1 (1)	0	1 (1)
Others	4 (6)	1 (7)	5 (6)
Country, n (%)			
United States	62 (91)	14 (100)	76 (93)
France	3 (4)	0	3 (4)
Netherlands	2 (3)	0	2 (2)
Germany	1 (1)	0	1 (1)

(Source: original Table 9 CSR report body BLA 125703/0.0)

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 are summarized in Table 5. Eighty-seven percent (87%) of infused subjects had stage IV disease. The median number of prior therapies was 3, and 43% of subjects in Cohort 1 had prior ASCT.

Table 5. Subject Baseline Characteristics (Safety Analysis Set)

	Cohort 1 (N=68)	**Cohort 2 (N=14)**	**Overall (N=82)**
ECOG Performance Status, n (%)			
0	44 (65)	7 (50)	51 (62)
1	24 (35)	7 (50)	31 (38)
Disease Type, n (%)			
Classical MCL	40(59)	7 (50)	47(57)
Diffuse	20 (29)	4 (29)	24(29)
Nodular	10 (15)	1(7)	11 (13)
Pleomorphic	4 (6)	2 (14)	6 (7)
Other	6 (9)	0	6 (7)
Blastoid MCL	17 (25)	6 (43)	23 (28)
Other	1(1)	1(7)	2 (2)
Unknown	10 (15)	0	10 (12)
Disease stage, n (%)			
II	2 (3)	0	3 (4)
III	8 (12)	1(7)	8 (10)
IV	58 (85)	13 (93)	71 (87)
Prior Autologous Stem Cell Transplant n(%)			
Yes	29 (43)	6(43)	35 (43)
No	39 (57)	8 (57)	47 (57)
Number of Prior Regimens, n (%)			
Median (Min, Max)	3 (1, 5)	3 (2,5)	3 (1,5)
4	14 (21)	2 (14)	16 (20)
5	11 (16)	2 (14)	13 (16)
Simplified Mantel Cell Lymphoma International Prognostic Index (s-MIPI) Risk Category			
Low risk	28 (41)	6 (43)	34 (41)
Intermediate risk	29 (43)	4 (29)	33 (40)
High risk	9 (13)	3 (21)	12 (15)
Missing	2 (3)	1 (7)	3 (4)

Refractory/Relapsed subgroup, n (%)			
Relapsed after last MCL therapy	12 (18)	1 (7)	13 (16)
Refractory to last MCL therapy	27 (40)	7(50)	34 (41)
Relapsed post auto-SCT	29 (43)	6 (43)	35 (43)

(source: abbreviated Table 10 CSR report body BLA 125703/0.0)

6.1.10.1.3 Subject Disposition

Detailed subject disposition is listed in Table 6 for the full analysis set. Cohort 1 and 2 combined, 91 subjects were enrolled and 82 (90%) were treated with KTE-X19.

Table 6. Subject Disposition (Full Analysis Set)

	Cohort 1 (N = 74)	**Cohort 2 (N = 17)**	**Total (N = 91)**
Subjects Enrolled, n (%)	74	17	91
Subjects received bridging therapy, n (%)	28 (38)	8 (47)	36 (40)
Subjects Treated with Conditioning Chemotherapy, n (%)	69 (93)	15 (88)	84 (92)
Subjects not treated with conditioning chemotherapy nor with KTE-X19, n (%)	5 (7)	2 (12)	7 (8)
Death[a]	3 (4)	1 (6)	4 (4)
Full consent withdrawal[b]	1 (1)	0	1 (1)
Adverse event[c]	1 (1)	1 (6)	2 (2)
Subjects did not initiate KTE-X19 infusion after conditioning chemotherapy, n (%)	1 (1)	1 (6)	2 (2)
Adverse event	0	1 (6)	1 (1)
Other[d]	1 (1)	0	1 (1)
Subjects Treated with KTE-X19, n (%)	68 (92)	14 (82)	82 (90)
Primary reason for ending study for subjects Not treated with KTE-X19 n (%)			
Full consent withdrawal	1 (1)	0	1 (1)
Death	4 (5)	3 (18)	7 (8)
Other	1 (1)	0	1 (1)
Primary reason for ending study for subjects treated with KTE-X19, n (%)			
Death	16 (22)	4 (24)	20 (22)
Actual Follow-up Time from KTE-X19 Dose (month)			
N	68	14	82
Median (Q1, Q3)	10.3 (6.5,25.5)	15.0 (14.1,16.1)	11.4 (7.5,19.9)
Min, Max	1.2, 32.3	0.6, 18.0	0.6, 32.3

a KTE-X19 was not successfully manufactured for 1 of the subjects in Cohort 1 who died due to disease progression before having the opportunity to be leukapheresed a second time

b KTE-X19 was not successfully manufactured for this subject after 2 leukapheresis attempts

c KTE-X19 was not successfully manufactured from these subjects' initial leukapheresis material; both subjects had AEs that preclude treatment before having the opportunity to be leukapheresed a second time

d One subject in Cohort 1 did not meet criteria for infusion due to history of cardia issues (atrial fibrillation)

(source: abbreviated Table 7 report body, Clinical Study Report, BLA 125703/0.0)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Table 7 presents ORR based on IRC adjudication after one dose of KTE-X19 in Cohort 1. The FDA clinical review team re-adjudicated the response assessment for the inferential analysis set, and based on the re-adjudication, the ORR was 86.7% (95% CI: 75.4%, 94.1%) and the CR rate was 61.7% (95% CI: 48.2%, 73.9%). In the mITT analysis set, which has not been re-adjudicated, the ORR was 92.6% (95% CI: 83.7%, 97.6%) and the CR rate was 64.7% (95% CI: 52.2%, 75.9%). Table 7 also shows a supportive analysis, using as the denominator all subjects who were enrolled, regardless of exposure to KTE-X19. In this analysis, the ORR was 85.1% (95% CI: 75.0%, 92.3%), with a CR rate of 59.5% (95% CI: 47.4%, 70.7%). In all three analyses the null hypothesis of 25% response rate was rejected, supporting the robustness of the results.

Table 7. Best Response per IRC (Inferential Analysis Set, mITT Analysis Set and Full Analysis Set)

	Inferential Analysis set (N=60)	**Cohort 1 mITT (N=68)**	**Cohort 1 Full Analysis set (N=74)**
Objective Response, n (%) (95% CI*)	52 (**86.7%**) (75.4%, 94.1%)	63 (92.6%) (83.7%, 97.6%)	63 (85.1%) (75.0%, 92.3%)
Best response, n (%)			
Complete Response (95% CI*)	37 (**61.7%**) (48.2%, 73.9%)	44 (64.7%) (52.2%, 75.9%)	44 (59.5%) (47.4%, 70.7%)
Partial Response (95%CI*)	15 (25%) (14.7%, 37.9%)	19 (27.9%) (17.7%, 40.2%)	19 (25.7%) (16.2%, 37.2%)

*Clopper-Pearson exact confidence interval

(Source: FDA statistical reviewer)

ORR and CR observed in Cohort 2 were 93% (=13/14) and 64% (=9/14) respectively, consistent with those in Cohort 1. ORR based on the investigator assessment were consistent with that based on the central assessment.

6.1.11.2 Analyses of Secondary Endpoints

Duration of remission (DOR)

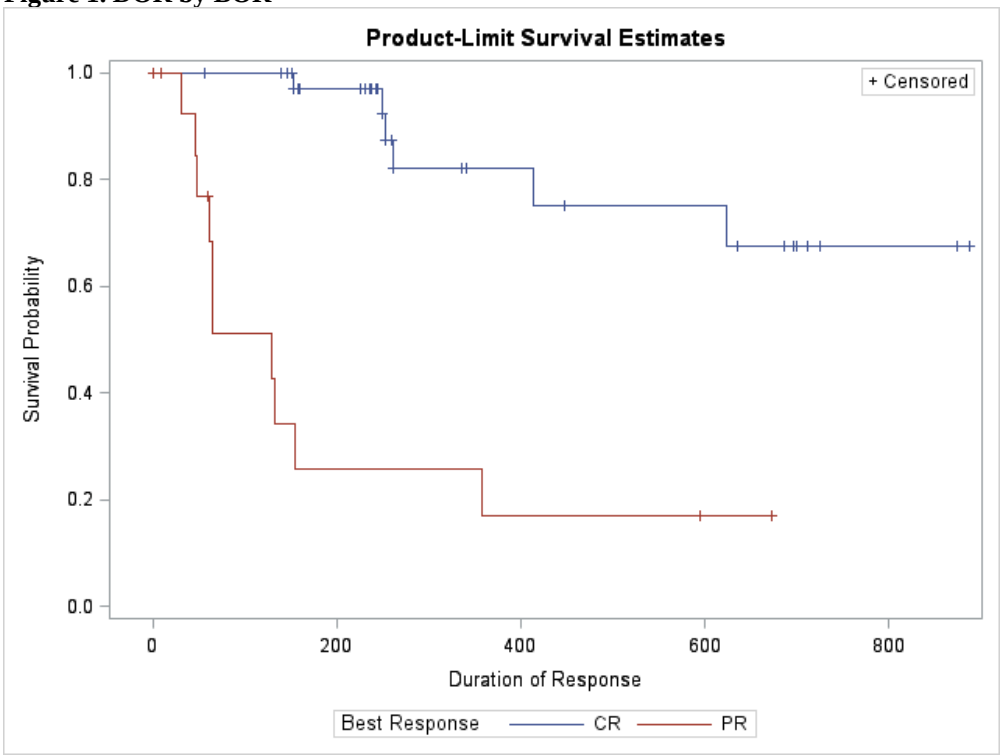
Table 8 summarizes the DOR results based on IRC adjudication in the IAS. The follow-up time ranges from 0 days (new cancer therapy after initial response) to 888 days with a median of 240 days. The median DOR was not estimable, due to the high percentage of censoring (69%). The duration of response was longer in patients who achieved CR, as compared to patients with a best response of PR (Figure 1). The median DOR was not reached for subjects who achieved CR, due to 84% censoring, and it was 129 days (95% CI: 48, 358) for those whose best response was PR.

Table 8. DOR results per IRC (IAS)

	Inferential Analysis Set (N=60)
Number of responders	52
Duration of response (days) Estimated median (95% CI)	NE (358, NE)
Median follow-up time (min, max)	240 (0, 888)
Percentage censored	69%
DOR if BOR is CR (days)	
Estimated median (95% CI)	NE (413, NE)
Median follow-up time (min, max)	252 (56, 888)
Percentage censored	84%
DOR if BOR is PR (days)	
Estimated median (95% CI)	129 (48, 358)
Median follow-up time (min, max)	65 (0, 672)
Percentage censored	33%

(Source: FDA statistical reviewer)

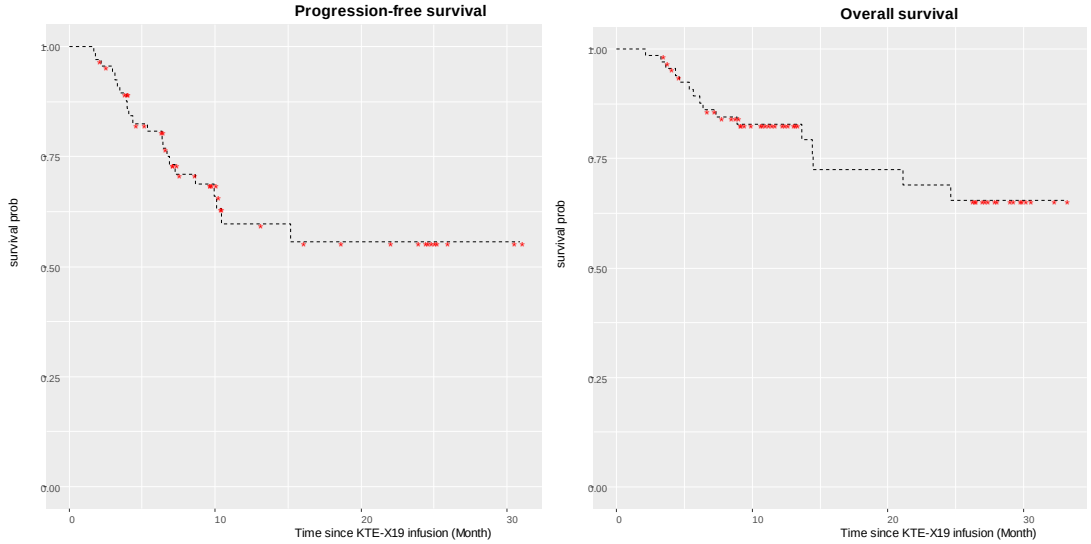
Figure 1. DOR by BOR



(Source: FDA statistical reviewer)

Progression-free survival and Overall survival
Fewer than 50% of subjects experienced death or progression prior to being censored, so median PFS and OS were not estimated. See Figure 2 for Kaplan-Meier curves of PFS and OS for the mITT population. 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 PFS and OS (mITT)

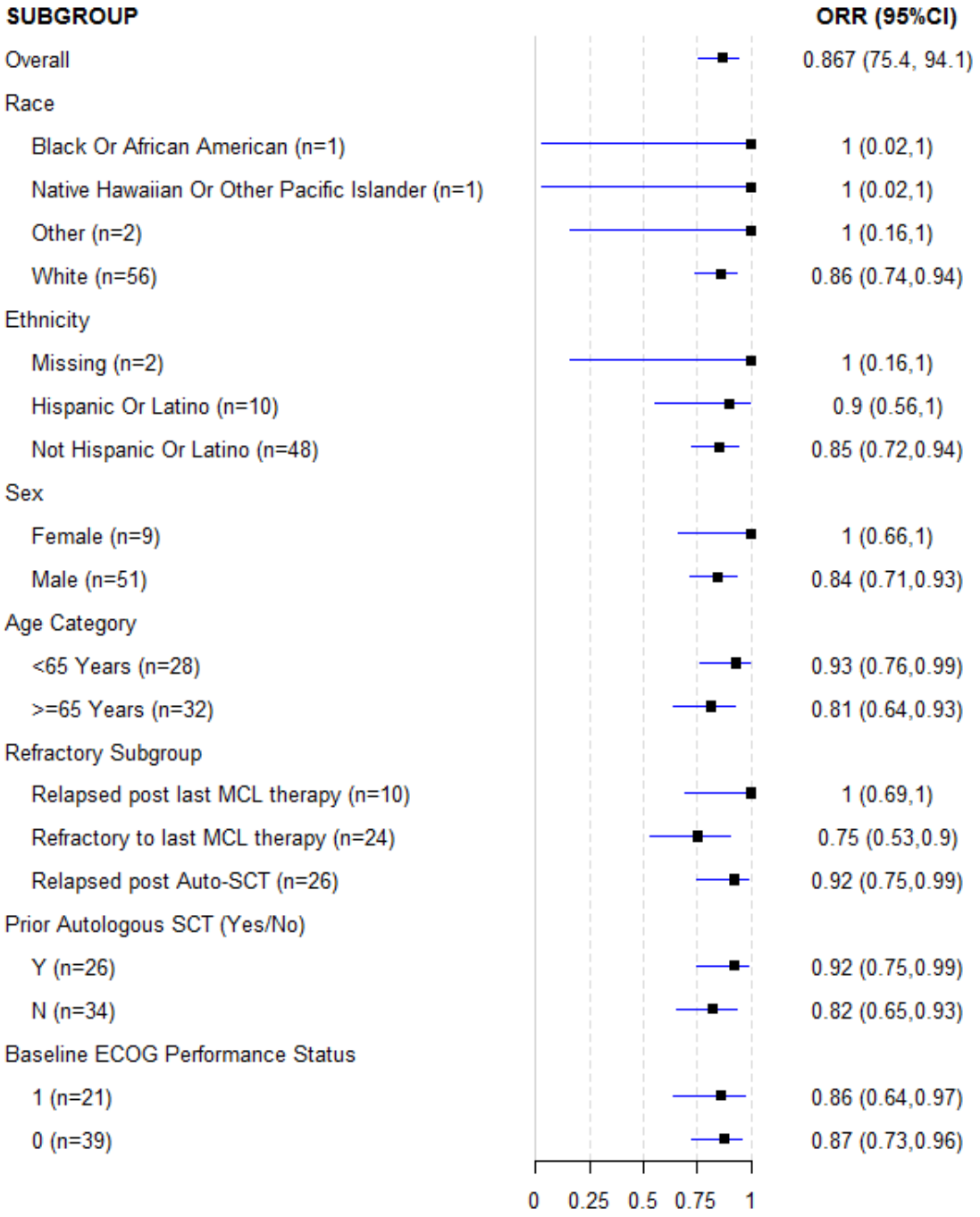


(Source: FDA statistical reviewer)

6.1.11.3 Subpopulation Analyses

A forest plot of ORR by key demographics and baseline disease characteristics is shown in Figure 3. Baseline disease characteristics were selected so that each subgroup has at least 10 subjects. ORR appears to be consistent across race, ethnicity, age category, sex, refractory subgroups, prior autologous SCT (Y/N) and ECOG performance status.

Figure 3. Forest plot of ORR per IRC (IAS)



Only one subject was treated outside of the United States in the IAS, therefore, no subgroup analysis by country was performed.

Fourteen out of 16 sites treated no more than 4 subjects. The remaining two sites treated 17 and 6 subjects, respectively, and both sites had 100% response rate.

6.1.11.4 Dropouts and/or Discontinuations

Ninety-one (91) subjects were enrolled, 7 (8%) did not receive conditioning chemo, 2 (2%) did not receive KTE-X19. Twenty (22%) subjects died during follow-up. The details of the dropouts/discontinuations are provided in Table 6.

6.1.12 Safety Analyses

This section summarizes safety results of Study ZUMA-2.

6.1.12.1 Methods

Descriptive statistics are used to summarize safety data for study ZUMA-2. For data summary, the safety analysis set in this section includes a total of 82 subjects who received at least one dose of KTE-X19.

6.1.12.3 Deaths

The applicant reported that 20 subjects (24%) had died as of the data cutoff: 16 subjects (24%) in Cohort 1 and 4 subjects (29%) in Cohort 2. Sixteen subjects died due to PD (14 subjects in Cohort 1 and 2 subjects in Cohort 2).

Five subjects died within 3 months of the KTE-X19 infusion, and 15 subjects died > 3 months after the KTE X19 infusion. Three subjects died due to AEs.

Table 9. Deaths reported (Safety Analysis Set)

	Cohort 1 (N=68)	Cohort 2 (N=14)	Overall (N=82)
Subjects who died, n (%)	16 (24)	4 (29)	20 (24)
Primary cause of death, n (%)			
Adverse event	2 (3)	1 (7)	3 (4)
Progressive disease	14 (21)	2 (14)	16 (20)
Other	0	1 (7)	1 (1)
Death occurred <= 30 days of KTE-X19 infusion, n (%)	0	1 (7)	1 (1)
Deaths that occurred > 30 days through 3 months (92 days) of KTE-X19 infusion, n (%)	4 (6)	0	4 (5)
Deaths that occurred > 3 months (92 days) after KTE-X19 infusion, n (%)	12 (18)	3 (21)	15 (18)

Data cutoff date=24JUL2019
(Source: adapted Table 69 Report Body BLA 12703/0.0, correcting for one subject who died because of progressive disease but reported as “other” (cause unknown) at data cutoff)

6.1.12.4 Nonfatal Serious Adverse Events

The applicant reported 54 (66%) subjects in the safety analysis set had at least one treatment-emergent Serious Adverse Events. The most common SAEs were pyrexia (17 subjects, 21%), followed by encephalopathy (16 subjects, 20%). The most common worst Grade 3 or higher SAEs were hypotension (9 subjects, 11%) and encephalopathy (7 subjects, 9%).

6.1.12.5 Adverse Events of Special Interest (AESI)

The applicant reported 75 (91%) subjects in the safety analysis set experienced cytokine release syndrome (CRS). The most common CRS symptoms were pyrexia and hypotension. Fifty-six (68%) had neurologic events, with the most common manifestations being tremor and encephalopathy. Fifty-seven (70%) subjects had thrombocytopenia, 70 (85%) had neutropenia, and 53 (65%) had anemia. Forty-six (56%) had infections and infestations, with upper respiratory tract infection and pneumonia being the most common examples.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This Biologics Licensure Application (BLA) seeks licensure of KTE-X19 for the treatment of adult patients with relapsed/refractory Mantle Cell Lymphoma (r/r MCL). KTE-X19 is an engineered autologous T cell immunotherapy.

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study (ZUMA-2). The primary efficacy endpoint is overall remission rate (ORR), which is defined as the proportion of subjects with either a complete response (CR) or partial response (PR), as assessed by an independent review committee (IRC). The primary evidence of efficacy for KTE-X19 is based on the inferential analysis set (IAS), which includes the first 60 subjects treated with KTE-X19 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. The FDA clinical review team re-adjudicated the response assessment for IAS, and based on the re-adjudication, the ORR was 86.7% (95% CI: 75.4%, 94.1%) and the CR rate was 61.7% (95% CI: 48.2%, 73.9%).

Duration of response (DOR) was based on July 24, 2019 data cutoff. The follow-up time for DOR ranged from 0 to 888 days with a median of 240 days for the inferential analysis set. The overall median DOR was not estimable, due to 69% censoring. Specifically, the median DOR was not estimable for subjects whose best response was CR, due to 84% censoring; the median DOR was 129 days (95% CI: 48, 358) for subjects whose best response was partial response.

The safety analysis set included 82 subjects treated at any dose of KTE-X19. Twenty subjects (24%) died. Fifty-four subjects (66%) experienced at least one treatment-emergent Serious Adverse Events (SAE). The most common adverse event of special interest was Cytokine Release Syndrome (CRS) which was reported in 91% of KTE-X19 infused subjects.

10.2 Conclusions and Recommendations

Study ZUMA-2 met its primary efficacy objective, with the pre-specified null hypothesis of ≤25% ORR was rejected. The statistical analysis results provide substantial evidence of effectiveness to support the approval of KTE-X19 for the applicant's proposed indication.