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Applicant	Kite Pharma
Established Name	KTE-C19
(Proposed) Trade Name	Yescarta
Pharmacologic Class	CD19-directed genetically-modified autologous T cell
Formulation(s), including Adjuvants, etc	(b) (4) CAR T-cells/kg (to a maximum allowable dose of 2×10^8 CAR T-cells) in 2.5% HSA, (b) (4)
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	A target dose of 2×10^6 anti-CD19 CAR T cells/kg body weight (range: (b) (4) cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T cells
Proposed Indication(s) and Intended Population(s)	Adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant

	(ASCT)
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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
r/r	relapsed/refractory
SCT	stem-cell transplantation

1. EXECUTIVE SUMMARY

KTE-C19 is an engineered autologous T cell immunotherapy. This Biologics Licensure Application (BLA) seeks licensure of KTE-C19 for the treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT).

The primary source of evidence to support this application is a Phase I/II, single-arm, and multicenter study (ZUMA-1). Phase I part of the study enrolled 8 subjects and Phase II enrolled 111 subjects. Of the 111 enrolled subjects in Phase II, 101 subjects received KTE-C19 and data from these subjects therefore constitutes the primary evidence of efficacy for the product. The pre-specified 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) while on study, as assessed by site investigators according to the IWG 2007 response criteria. ORR was also assessed by an independent review committee (IRC) to evaluate the consistency of disease status assessment. Results summarized in this memo are based on a data cut-off date of April 26, 2017.

The ORR as assessed by site investigators was 83% (=84/101) and the lower limit of the 95% exact Clopper-Pearson confidence interval was 74.4%, which is above the pre-set null hypothesis rate of 20%. Fifty-five (54%) subjects had a best response of CR, and 29

subjects (29%) had a best response of PR. The median duration of response (DOR) was 8.2 months (95% CI: 3.5, NE) for all responders with a median follow-up of 4.5 months (range: 0.3, 14.4). The median DOR for the partial responders was 1.9 months (95% CI: 1.4, 2.1) and the median DOR was not reached for complete responders.

The ORR as assessed by the IRC was 72% (=73/101) and the lower limit of the 95% exact Clopper-Pearson confidence interval was 62.5%, which is also above the pre-set null hypothesis rate of 20%. Fifty-two (51%) subjects had a best response of CR, and 21 subjects (21%) had a best response of PR. The median DOR was 9.2 months (95% CI: 5.4, NE) for all responders with a median follow-up of 5 months (range: 0.03, 14.4). The median DOR for the partial responders was 2.1 months (95% CI: 1.3, 5.3) and the median DOR was not reached for complete responders. Results assessed by IRC are consistent with those assessed by site investigators.

Deaths occurred in 3% (= 3/119) of enrolled subjects (Phase I and II combined) before KTE-C19 infusion, and occurred in 39.8% (= 43/108) of infused subjects. Nonfatal Serious Adverse events (SAEs) were reported in 54% (= 58/108) of infused subjects. The most common adverse event of special interest was Cytokine Release Syndrome (CRS) which occurred in 93% (=100/108) of KTE-C19 infused subjects.

Efficacy results in Study ZUMA-1 meet the study objective that ORR was statistically significantly greater than the pre-specified null hypothesis rate of 20%. The statistical analysis results provide evidence to support the Applicant's proposed indication for KTE-C19 in this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

B-cell malignancies are a heterogeneous group of neoplasms that include chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and non-Hodgkin lymphoma (NHL). NHL cancers further can be classified as aggressive NHL diseases and include diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and transformed follicular lymphoma (TFL).

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

The Applicant stated that second-line chemotherapy plus ASCT is the standard of care for the relapsed/refractory aggressive B-cell NHL. The Applicant also stated that those who are refractory to any line of therapy, those who are not eligible to proceed to transplant after relapse, and those who relapse early after transplant have uniformly low survival rates and there are no curative options for these patients. As a combined

population, these patients have an unmet medical need that warrants novel treatment strategies.

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

The Applicant reported that the KTE-C19 manufacturing process used the (b) (4)



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

Table 1 summarizes the major Pre- and post-submission regulatory activities associated with this BLA.

Table 1. Summary of major Pre-and Post-submission regulatory activities

Date	Milestone
12/19/2014	IND 16278 submission
3/27/2014	Orphan Drug Designation granted: DLBCL
12/3 2015	Breakthrough Therapy Designation granted
4/20/2016	Orphan Drug Designation granted: PMBCL
4/25/2016	Orphan Drug Designation granted: FL
10/31/2016	Pre-BLA Meeting
12/02/2016	Rolling BLA 125643 submission: CMC module
3/31/2017	BLA 125643 submission: Clinical module
5/25/2017	BLA filed. Filing Letter issued to Applicant
6/30/2017	BLA 125643 submission: Clinical information (efficacy update)
10/20/2017	PDUFA Action Due Date

(Source: pre-BLA meeting briefing package, BLA 125646/0.1 module 2 introduction to summary, 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-1, 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 includes review of

- Clinical study reports and data sets submitted in module 5 of the rolling BLA submission amendment #1
- Efficacy update submitted in amendment #2
- Efficacy update submitted in amendment #36
- 120-day Safety update submitted in amendment #45

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the three studies included in the BLA submission. Results from study ZUMA-1 form the primary evidence of safety and efficacy of KTE-C19 for the BLA application.

Table 2. Studies supporting the proposed indication in the BLA submission

Study code	Study design	# of subjects treated	Study population
ZUMA-1 (pivotal)	open-label, multicenter, single-arm study phase I/II	108	refractory aggressive B-cell non-Hodgkin lymphoma (NHL)
SCHOLAR-1	retrospective analysis of response and survival data in subjects treated with standard of care therapies	636	refractory aggressive B-cell NHL matched with respect to the refractory disease definition used in ZUMA-1
(b) (4) (subset)	single arm, open-label, Phase I	13	(b) (4)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study ZUMA-1 is the pivotal study that constitutes the primary evidence of safety and efficacy of KTE-C19 in the treatment of relapsed/refractory aggressive B-cell NHL for subjects who are ineligible for ASCT in this BLA submission.

6.1.1 Objectives

The primary objective of phase 1 in Study ZUMA-1 was to evaluate the safety of KTE-C19 regimens.

The primary objective of phase 2 in Study ZUMA-1 was to evaluate the efficacy of KTE-C19, as measured by ORR in subjects with DLBCL, PMBCL, and TFL.

Secondary objectives included assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints.

6.1.2 Design Overview

ZUMA-1 was a Phase I/II single-arm, multi-center study to evaluate the efficacy and safety of KTE-C19 in subjects with relapsed/refractory aggressive B-cell NHL.

In Phase 1, the safety of various conditioning chemotherapy and KTE-C19 regimens was planned to be tested. A safety review team (SRT) monitored the safety results and made recommendations for subsequent action based on the incidence of dose-limiting toxicity (DLT) and overall safety profile.

In phase 2, subjects were enrolled into 3 separate cohorts designated as cohort 1, cohort 2, and cohort 3.

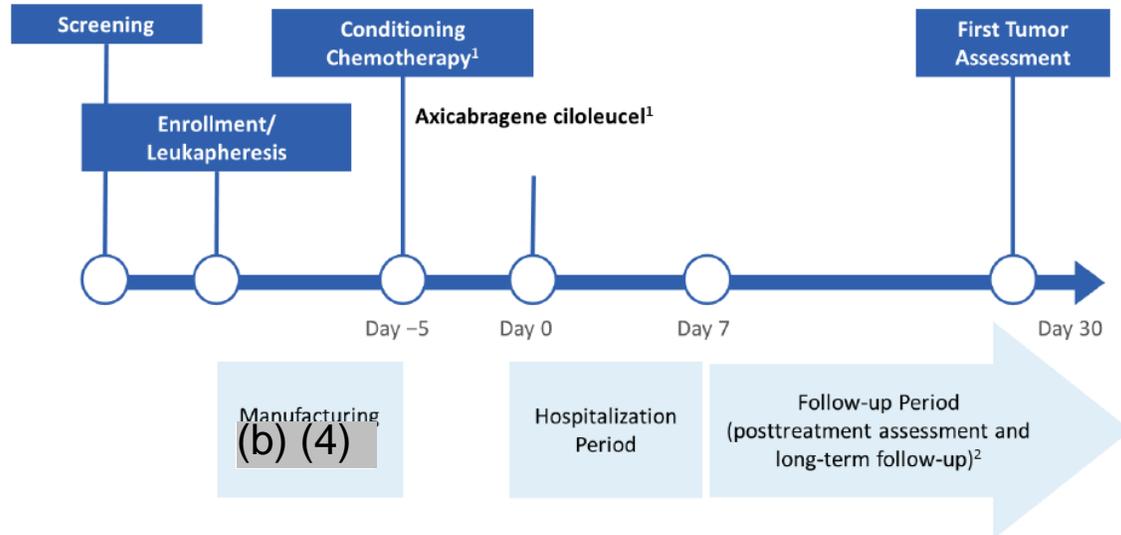
- Cohort 1 enrolled adult subjects with refractory DLBCL
- Cohort 2 enrolled adult subjects with refractory PMBCL and TFL
- Cohort 3 enrolled adult subjects with relapsed / refractory transplant ineligible DLBCL, PMBCL, or TFL

Cohort 3 was added to the study in protocol amendment #5 dated August 12, 2016, to assess the impact of a prophylactic regimen on the rate of CRS and neurotoxicity and to assess the change in EQ-5D scores from baseline to Month 6. The primary evidence of efficacy and safety for the BLA was based on cohorts 1 and 2.

The screening period began on the date the subject signed the IRB/IEC approved Informed Consent Form (ICF) and continued through confirmation of enrollment. In addition to meeting the eligibility criteria, subjects must have had no evidence of a clinically significant infection prior to leukapheresis. Subjects' leukapheresis cells were then shipped to the manufacture site for product manufacture. The conditioning chemotherapy started 5 days before the planned infusion date. All subjects were hospitalized for treatment with KTE-C19 and were to remain in the hospital for a minimum of 7 days following the infusion for the observation and management of treatment-emergent acute AEs. Subsequently, subjects returned to the clinic at Week 2 (± 2 days), Week 4 (± 3 days), Month 2 (± 1 week), and Month 3 (± 1 week). Long-term follow-up (LTFU) for disease status (among subjects remaining in response) and survival continued every 3 months through Month 18, then every 6 months through 5 years, and then annually for a maximum of 15 years.

Figure 1 below gives the overview of design schema.

Figure 1. Study design



¹ Axicabtagene ciloleucel treatment consists of conditioning chemotherapy of 500 mg/m² cyclophosphamide and 30 mg/m² fludarabine on Day -5, Day -4, Day -3 followed by a target of 2×10^6 ($\pm 20\%$) CAR T cells/kg (minimum 1×10^6 CAR T cells/kg) on Day 0.

² Long-term follow-up for disease status and survival continued every 3 months through Month 18, then every 6 months through 5 years, and then annually for a maximum of 15 years.

(Source: Original BLA 125646/0.1; Clinical Study Report Section 9 Figure 2, p.27)

6.1.3 Population

Key elements of the **inclusion criteria** for study ZUMA-1 are listed below.

1. Histologically confirmed DLBCL, PMBCL, or TFL
2. Chemotherapy-refractory disease, defined as one or more of the following:
 - a. No response to first-line therapy (primary refractory disease), defined as progression disease (PD) as best response to first-line therapy or stable disease (SD) as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy. Subjects who are intolerant to first-line chemotherapy were excluded.
 - b. No response to second or greater lines of therapy, defined as PD as best response to most recent therapy regimen, or SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy
 - c. Refractory after ASCT, defined as occurrence of disease progression or relapse ≤ 12 months after ASCT (must have biopsy proven recurrence in relapsed subjects) or, if salvage therapy was given after ASCT, the subject must have had no response to or relapsed after the last line of therapy.
3. Prior therapy including anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen

4. Measurable disease according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (hereafter referred to as IWG 2007 criteria)
5. No evidence of central nervous system (CNS) lymphoma
6. Age 18 or older
7. ECOG performance status of 0 or 1
8. Adequate hematologic, renal, hepatic, pulmonary, and cardiac function

Other main inclusion criteria included:

- Bone marrow with $\geq 5\%$ lymphoblasts by morphologic assessment at screening
- Life expectancy >12 weeks
- Adequate organ function
- Karnofsky (age ≥ 16 years) or Lansky (age <16 years) performance status ≥ 50 at screening
- For each patient, the apheresis product of non-mobilized cells was received and accepted by the manufacturing site

Key elements of the **exclusion criteria** are listed below.

1. History of allogeneic SCT
2. Prior CD19 targeted therapy with the exception of subjects who received KTE-C19 in this study and are eligible for retreatment
3. Prior CAR-T therapy or other genetically modified T-cell therapy
4. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management.
5. History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects underwent leukapheresis and conditioning chemotherapy before they received KTE-C19 cell infusion.

Subjects were dosed with KTE-C19 at a target of 2×10^6 anti-CD19 CAR T cells/kg. The minimum dose to be administered was 1×10^6 anti-CD19 CAR T cells/kg. For subjects weighing greater than 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR T cells was administered.

6.1.6 Sites and Centers

Approximately 148 to 166 subjects were planned to be enrolled at 35 study sites in the US and Europe.

6.1.7 Surveillance/Monitoring

An independent Data Safety Monitoring Board (DSMB) reviewed criteria during the study to pause enrollment after 10, 20, 30, and 50 subjects in Cohorts 1 and 2 had been

treated with KTE-C19 and had the opportunity to be followed for 30 days after the KTE-C19 infusion. Enrollment was to be paused if any of the following criteria were met:

1. Subject incidence > 10% for Grade 5 KTE-C19-related adverse events (AEs) within 30 days
2. Subject incidence > 33% for any of the following Grade 4 KTE-C19-related AEs lasting more than 7 days:
 - Neurologic events
 - CRS
 - Other non-hematological serious adverse event (SAE)
 - Treatment-related infection

Additionally, the DSMB reviewed safety and efficacy data after 20 and 50 subjects in Cohort 1 who had been followed for 3 months after the KTE-C19 infusion and made recommendations based on a risk-benefit analysis of safety and efficacy data from the two pre-specified interim analyses. The DSMB also reviewed SAEs monthly and was to meet more often, as needed.

6.1.8 Endpoints and Criteria for Study Success

For Phase 1, the primary endpoint was the incidence of DLT.

For Phase II, the primary endpoint was ORR as assessed by site investigators according to the IWG 2007 response criteria. ORR was defined as the proportion of subjects with either a CR or PR while on study. All subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered non-responders.

The study protocol also included several secondary endpoints:

- a. Duration of Response (DOR). DOR was defined as the time from the first objective response to disease progression or death due to disease relapse or drug-related toxicity.
- b. Progression free survival (PFS). PFS was defined as the time from the KTE-C19 infusion date to the date of disease progression or death from any cause.
- c. Overall survival (OS). OS was the time from date of first KTE-C19 infusion to the date of death due to any reason.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

Study hypotheses:

The study hypothesis was that the ORR for subjects treated with KTE-C19 in Cohorts 1 and 2 is significantly greater than 20%. i.e.,

$H_0: p \leq 0.2$ vs. $H_a: p > 0.2$.

Analysis populations

Full Analysis Set included all enrolled subjects.

Modified Intent-To-Treat (mITT) analysis set was defined for Phase 2 only and included all subjects treated with KTE-C19 dose at least 1.0×10^6 anti-CD19 CAR T cells/kg.

Safety analysis set included all subjects treated with any dose of KTE-C19.

Statistical methods

Efficacy analyses were to be conducted on the mITT analysis set. For the primary analysis, the investigator assessment of disease status would be used. Sensitivity analyses would be conducted based on IRC's disease assessments.

Primary endpoint

The primary efficacy endpoint, ORR, would be summarized along with the 2-sided exact Clopper-Pearson confidence interval for subjects separately by cohort and for cohorts 1 and 2 combined. 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 measured only for subjects who experienced an objective response (CR or PR). A competing-risk analysis method would be used to estimate the cumulative incidence of relapse/disease-related death in the presence of non-disease related mortality. The cumulative incidence (CIF) for relapse/disease-related death in the presence of non-disease-related mortality was to be estimated and 1-CIF was to be used to estimate the relapse-free rate at 3-month time intervals. In the event that no competing risk events have occurred at the time of any analysis, the Kaplan-Meier (KM) approach would be used to estimate duration of response.

For subjects who received new anticancer therapies, DOR was derived using disease assessments obtained on study prior to initiation of a new anticancer therapy (excluding SCT). In the primary analysis, DOR would not be censored for subjects who underwent SCT. A sensitivity analysis of DOR would be conducted in which the duration of response for subjects underwent SCT was censored at the last evaluable disease assessment prior to SCT.

(Reviewer's comment: As SCT may confound the effect of KTE-C19, FDA had recommended at the IND stage that the Applicant censor DOR at the time of transplantation for subjects who receive SCT in the primary analysis of DOR.)

b. Progression free survival (PFS)

Subjects not meeting the criteria for progression by the analysis data cut-off date would be censored at their last evaluable disease assessment date. For subjects receiving new anti-cancer therapies, PFS was derived using disease assessments obtained on study prior

to initiation of a new anti-cancer therapy (excluding SCT). In the primary analysis, PFS would not be censored for subjects who received SCT. A sensitivity analysis of PFS would be conducted by censoring at the last evaluable disease assessment prior to SCT for subjects who undergo SCT.

(Reviewer's comment: As SCT may confound the effect of KTE-C19, FDA had recommended at the IND stage that the Applicant censor PFS at the time of transplantation for subjects who receive SCT in the primary analysis of PFS.)

The distribution function of PFS would be estimated using Kaplan-Meier method. The median PFS along with 95% confidence intervals would be presented. Estimates of the proportion of subjects alive and progression-free at 3 month intervals would be provided.

c. Overall survival (OS)

The distribution function of OS would be estimated using Kaplan-Meier method. The median OS along with 95% confidence intervals would be presented.

Sample size

The anticipated enrollment in this study was approximately 148 to 166 subjects. Six to 24 subjects would be enrolled into phase 1 of this study.

If the study proceeded to Phase II, approximately 72 subjects would be enrolled into cohort 1 and approximately 20 subjects would be enrolled into cohort 2. The planned total sample size 92 in cohorts 1 and 2 combined had $\geq 90\%$ power to distinguish between KTE-C19 therapy with a 40% true response rate from a pre-specified fixed response rate of 20% or less with a 1-sided alpha of 0.025.

(Reviewer's comment: Ultimately, 7 subjects were treated in Phase I and 101 in Phase II, cohort 1 and 2 combined, in this study. We include all treated subjects in Phase II in the efficacy analyses.)

Interim analyses

The study protocol originally planned dividing the overall 1-sided alpha level of 0.025 between the inference on cohort 1 with an alpha level of 0.022 and the inference in cohorts 1 and 2 combined with an alpha level of 0.0075, using the methodology described in Song, 2007 and Wang, 2007. This alpha adjustment was based on a sample size of 72 in cohort 1 and a total sample size of 92 in cohorts 1 and 2 combined.

Within cohort 1, two interim analyses and one final analysis would be performed.

- Interim analysis #1 would be conducted after 20 subjects in the mITT set of cohort 1 have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis would be for futility purpose only.
- Interim analysis #2 would be conducted after 50 subjects in the mITT set of cohort 1 have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis would assess early demonstration of efficacy.

The final analysis of cohort 1 would occur after 72 subjects in the mITT set of cohort 1 have had the opportunity to be assessed for response 6 months after the KTE-C19 infusion.

Using the Lan-DeMets family of alpha spending functions with a Pocock boundary, the 1-sided alpha level of 0.022 for analysis on cohort 1 would be spent as follows:

- The nominal 1-sided alpha level used to test for efficacy at interim analysis #2 of cohort 1 would be 0.017
- The nominal 1-sided alpha level used to test for efficacy at the final analysis for cohort 1 would be 0.011.

In response to the FDA's information request (dated March 27, 2015), the Applicant made it clear that the trial would not be stopped at the interim, even if the efficacy stopping boundary was crossed at the interim (amendment #21 submitted on July 29, 2015).

(Reviewer's comment: Though the statistical inferences were derived based on a planned sample size of 92 subjects, a total of 101 subjects enrolled in cohorts 1 and 2 were treated in the study. Efficacy analyses in this memo included all 101 treated subjects. We do not consider alpha adjustment in this review memo, because the trial did not stop for efficacy at the 2nd interim analysis though the efficacy stopping boundary was crossed, thus no alpha was spent.)

Subgroup analysis

Subgroup analyses would be performed on the following based on the patient's baseline status:

- ECOG performance status at baseline
- Age at baseline (< 65, ≥ 65)
- Disease type (DLBCL, PMBCL, TFL)
- Refractory subgroup
- Disease stage (I-II, III-IV)
- International prognostic index (IPI) risk category
- Number of prior chemotherapy regimens (1, 2-3, ≥ 4)
- History of bone marrow involvement
- Tumor burden, as measured by the sum of the product of the diameters (SPD) of selected nodes or lesions at baseline (≤ median, > median)
- Expression of CD19 in tumor tissue prior to treatment
- Disease extent as determined by the investigator at screening
 - presence of B symptoms (Y/N)
 - bulky disease (Y/N) (defined in Section 5.1)
 - extranodal disease (Y/N)

Missing data

All subjects who did not meet the criteria for an objective response by the analysis cut-off date would be considered non-responders. For assessment of DOR and PFS, loss to follow-up subjects would be censored at the last disease assessment date.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

For analyses of efficacy and safety in study ZUMA-1, Table 3 summarizes study population and analyses sets. Full analysis set includes a total of 111 subjects. A total of 101 subjects received KTC-C19 that constitutes the mITT set as well as safety analysis set.

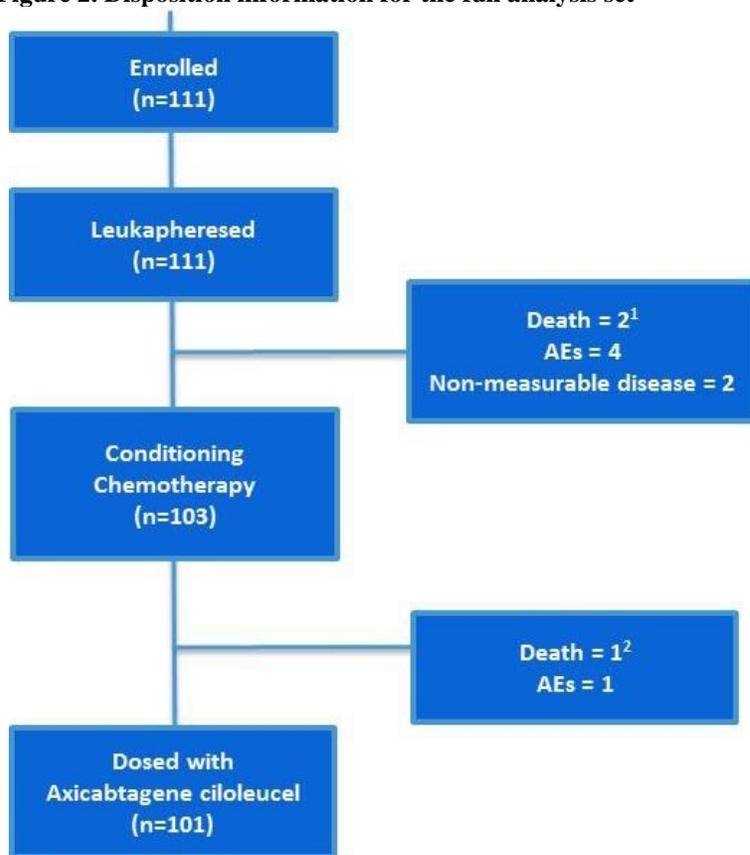
Table 3 Analyses sets

	Phase 1 (N = 8)	Phase 2		Total (N = 111)
		Cohort 1 (N = 81)	Cohort 2 (N = 30)	
Subjects Screened n	11	81 (100)	30 (100)	124
Screen Failures n	3			13
Full Analysis Set n (%)	8 (100)			111 (100)
All Leukapheresed Analysis Set (ALS) n (%)	8 (100)	81 (100)	30 (100)	111 (100)
Subjects Treated with Conditioning Chemotherapy n (%)	7 (88)	77 (95)	26 (87)	103 (93)
Safety Analysis Set n (%)	7 (88)	77 (95)	24 (80)	101 (91)
Modified Intent-to-Treat (mITT) n (%)	NA	77 (95)	24 (80)	101 (91)

(Source: Adapted BLA 125646/0.1; Clinical Study Report Table 10)

Subject disposition information from the full analysis set to mITT set (or safety analysis set) is described in Figure 2.

Figure 2. Disposition information for the full analysis set



¹ Both deaths due to progressive disease

² Death due to tumor lysis syndrome, deemed related to conditioning chemotherapy

(source: original BLA 125646/0.1; CRS report body Figure 5)

6.1.10.1.1 Demographics

Demographics of subjects who received at least one dose of KTE-C19 are summarized in Table 4. All but one subject received treatment in the US. The majority of subjects are White that accounts for 89% of infused subjects. Approximately three-quarters of infused subjects were younger than 65; while two-thirds of participants are male subjects.

Table 4. Subject Demographics (Safety Analysis Set)

	Phase 1 (N = 7)	Phase 2		Total (N = 101)
		Cohort 1 (N = 77)	Cohort 2 (N = 24)	
Age (years)				
n	7	77	24	101
Mean (SD)	52.4 (17.5)	57.4 (10.6)	53.0 (15.5)	56.3 (12.0)
Median	59.0	58.0	57.0	58.0
Min, Max	29, 69	25, 76	23, 76	23, 76
Age Category n(%)				

<65 Years	4 (57)	60 (78)	17 (71)	77 (76)
>=65 Years	3 (43)	17 (22)	7 (29)	24 (24)
Sex n(%)				
Male	5 (71)	50 (65)	18 (75)	68 (67)
Female	2 (29)	27 (35)	6 (25)	33 (33)
Ethnicity n(%)				
Hispanic or Latino	1 (14)	16 (21)	2 (8)	18 (18)
Not Hispanic or Latino	6 (86)	61 (79)	22 (92)	83 (82)
Race n(%)				
Asian	0 (0)	1 (1)	3 (13)	4 (4)
Black or African American	1 (14)	3 (4)	1 (4)	4 (4)
White	6 (86)	71 (92)	19 (79)	90 (89)
Others	0 (0)	2 (3)	1 (4)	3 (3)
Country n(%)				
United States	7 (100)	77 (100)	23 (96)	100 (99)
Israel	0 (0)	0 (0)	1 (4)	1 (1)

(source: original BLA 125646/0.1; CRS report body Table 15)

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-C19 are summarized in Table 5. Three-quarters of infused subjects have DLBCL. Disease stage of III and IV accounts for 85% of infused subjects. Three-quarters of infused subjects had no prior ASCT.

Table 5. Subject Baseline Characteristics (Safety Analysis Set)

	Phase 1 (N = 7)	Phase 2		Total (N = 101)
		Cohort 1 (N = 77)	Cohort 2 (N = 24)	
ECOG Performance Status n(%)				
0	4 (57)	28 (36)	14 (58)	42 (42)
1	3 (43)	49 (64)	10 (42)	59 (58)
Disease Type n(%)				
DLBCL	7 (100)	77(100)	0 (0)	77 (76)
PMBCL	0	0	8 (33)	8(8)
TFL	0	0	16 (67)	16 (16)
Disease stage n(%)				
I	2 (29)	2 (3)	2 (8)	4(4)
II	1 (14)	8 (10)	3 (13)	11 (11)
III	2 (29)	20 (26)	8(33)	28 (28)
IV	2 (29)	47 (61)	11 (46)	58 (57)

Prior Autologous Stem Cell Transplant					
N(%)					
Yes		4 (57)	18 (23)	7(29)	25 (25)
No		3 (43)	59 (77)	17 (71)	76 (75)
Number of Prior Chemotherapy Regimen					
n(%)					
1	0		2 (3)	0	2 (2)
2	1(14)		26 (34)	3 (13)	29 (29)
3	5 (71)		22 (29)	8 (33)	30 (30)
4	1 (14)		20 (26)	8 (33)	28 (28)
5	0		4 (5)	2 (8)	6 (6)
>5	0		3 (4)	3 (13)	6 (6)
Refractory subgroup n (%)					
Primary refractory	0		2 (3)	0	2 (2)
Refractory to 2nd or greater line therapy	3(43)		59 (77)	19(79)	78 (77)
Relapse post ASCT	4 (57)		16 (21)	5 (21)	21 (21)

(source: original BLA 125646/0.1; CRS report body Table 16)

6.1.10.1.3 Subject Disposition

Detailed subject disposition is listed in Table 6 for all enrolled subjects.

Table 6. Subject Disposition (Full Analysis Set)

	Phase 1 (N = 8)	Phase 2		Total (N = 111)
		Cohort 1 (N = 81)	Cohort 2 (N = 30)	
Subjects Enrolled n(%)	8 (100)	81 (100)	30 (100)	111 (100)
Subjects Leukapheresed n(%)	8 (100)	81 (100)	30 (100)	111 (100)
Subjects Treated with Conditioning Chemotherapy n(%)	7 (88)	77 (95)	26 (87)	103 (93)
Subjects Treated with KTE-C19 n(%)	7 (88)	77 (95)	24 (80)	101 (91)
Primary reason for ending treatment n(%)				
Completed treatment	7 (88)	77 (95)	24 (80)	101 (91)
Adverse Event	1 (13)	3 (4)	2 (7)	5 (5)
Death	0	1 (1)	2 (7)	3 (3)
Other	0	0	2 (7)	2 (2)
Primary reason for ending study for subjects treated with KTE-C19 n(%)				
Death	4 (50)	34 (42)	5 (17)	39 (35)
Primary reason for ending study for subjects not treated with KTE-C19 n(%)				
Death	1 (13)	4 (5)	4 (13)	8 (7)
Follow-up Time from KTE-C19 Dose (month) (1)				
N	7	77	24	101

Median (Q1, Q3)	9.0 (2.0, 18.7)	8.8 (6.9, 11.6)	9.1 (8.8, 11.3)	9.1 (7.3, 11.6)
Min, Max	0.6, 19.5	0.3, 15.4	0.5, 15.0	0.3, 15.4

(Source: adapted Summary Report in Response to Agency Request for Additional Efficacy Follow-up on the ZUMA-1 Study to Support BLA STN 125643 Table 1)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Table 7 shows the best response based on investigator assessment for the mITT and full analysis sets.

Table 7. Best Response Based on the Investigator Assessment (mITT Analysis Set and Full Analysis Set)

	Phase 2 Cohort 1 (N=77)	Phase 2 Cohort 2 (N=24)	Phase 2 Overall (N=101)	Full Analysis Set (n=111)
Objective Response (CR+PR), n (%) 95% CI ¹	63 (82%) (71.4, 89.7)	21 (88%) (67.6, 97.3)	84 (83%) (74.4, 89.9)	84 (76%) (66.6, 83.3)
Complete Response, n (%) 95% CI	38 (49%) (37.8, 61.0)	17 (71%) (48.9, 87.4)	55 (54%) (44.2, 64.4)	55 (50%) (39.9, 59.2)
Partial Response, n (%) 95% CI	25 (32%) (22.2, 44.1)	4 (17%) (4.7, 37.4)	29 (29%) (20.2, 38.6)	29 (26.1%) (18.3, 35.3)
Stable Disease	9 (12%)	1 (4%)	10 (10%)	10 (9%)
Progressed Disease	4 (5%)	1 (4%)	5 (5%)	5 (4.5%)
Not evaluable ²	1 (1%)	1 (4%)	2 (2%)	2 (2%)

1. Clopper-Pearson exact confidence interval
2. Two subjects died before first disease response assessment

(Source: FDA statistical reviewer)

In the mITT analysis set of 101 subjects, 84 subjects (83%) had a best disease response of CR or PR, as determined by investigator. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is 74.4%, which is above the null hypothesis rate of 20%. A total of 55 subjects (54%) had the best response of CR, and 29 subjects (29%) had the best response of PR.

For analysis results of the primary endpoint ORR based on the Full Analysis Set, the lower limits of the 95% exact Clopper-Pearson confidence intervals for ORR is 66.6% which is also above the null hypothesis rate of 20%.

Table 8 shows the best response based on IRC assessment for the mITT and full analysis sets. Analysis of ORR assessed by IRC results in the same conclusion as assessed by investigator.

Table 8. Best Response Based on the IRC Assessment (mITT Analysis Set and Full Analysis Set)

	Phase 2 Cohort 1 (N=77)	Phase 2 Cohort 2 (N=24)	Phase 2 Overall (N=101)	Full Analysis Set (n=111)
Objective Response (CR+PR), n (%) 95% CI ¹	52 (68%) (55.9, 77.8)	21(88%) (67.6, 97.3)	73 (72%) (62.5, 80.7)	73 (66%) (56.2, 74.5)
Complete Response, n (%) 95% CI	37 (48%) (36.5, 59.7)	15 (63%) (40.6, 81.2)	52 (51%) (41.3, 61.6)	52 (47%) (37.3, 56.6)
Partial Response, n (%) 95% CI	15 (19%) (11.3, 30.1)	6 (25%) (9.8, 46.7)	21 (21%) (13.4, 30.0)	21 (19%) (12.1, 27.5)
Stable Disease	18 (23%)	1 (4%)	19 (19%)	19 (17%)
Progressed Disease	6 (8%)	1 (4%)	7 (7%)	7 (6%)
Not evaluable ²	1 (1%)	1 (4%)	2 (2%)	2(2%)

1. Clopper-Pearson exact confidence interval
2. Two subjects died before first disease response assessment

(Source: FDA statistical reviewer)

In the mITT analysis set of 101 subjects, 73 subjects (72%) had a best disease response of CR or PR, as determined by IRC. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is 62.5%, which is above the null hypothesis rate of 20%. A total of 52 subjects (51%) had the best response of CR, and 21 subjects (21%) had the best response of PR.

For analysis results of ORR assessed by IRC based on the Full Analysis Set, the lower limits of the 95% exact Clopper-Pearson confidence intervals for ORR is 56.2% which is also above the null hypothesis rate of 20%.

To evaluate the concordance in assessment of disease status, best overall response graded by site investigators and IRC is shown in Table 9.

Table 9. Concordance between investigator and IRC for the best overall response

Frequency	IRC				Total
	PD	SD	PR	CR	
Investigator					
PD	5	0	0	0	5
SD	1	4	3	2	10
PR	0	13	14	2	29
CR	1	2	4	48	55
Total	7	19	21	52	99

(source: FDA statistical reviewer)

Investigator and IRC made the same best overall response call in 72% (=71/99) of the cases. Sixty-two subjects were determined to be responders by both investigator and IRC.

Among responders assessed by site investigators, IRC assessment was in agreement with 74% (=62/84) of cases. Among responders assessed by IRC, investigator assessment was in agreement with 85% (=62/73) of cases.

As a sensitivity analysis based on Full Analysis Set, 62 subjects who were responders assessed by both investigator and IRC result in ORR of 56% (= 62/111) with 95% CI of (46.1%, 65.3%). The lower limit of the 95% exact Clopper-Pearson confidence interval is above the null hypothesis rate of 20%.

6.1.11.2 Analyses of Secondary Endpoints

Duration of remission (DOR)

Table 10 summarizes the DOR results per Investigator assessment. The follow-up time for cohorts 1 and 2 combined ranges from 0.3 months to 14.4 months with a median of 4.5 months. The overall median DOR was 8.2 months with a lower 95% limit of 3.5 months and unattainable upper limit.

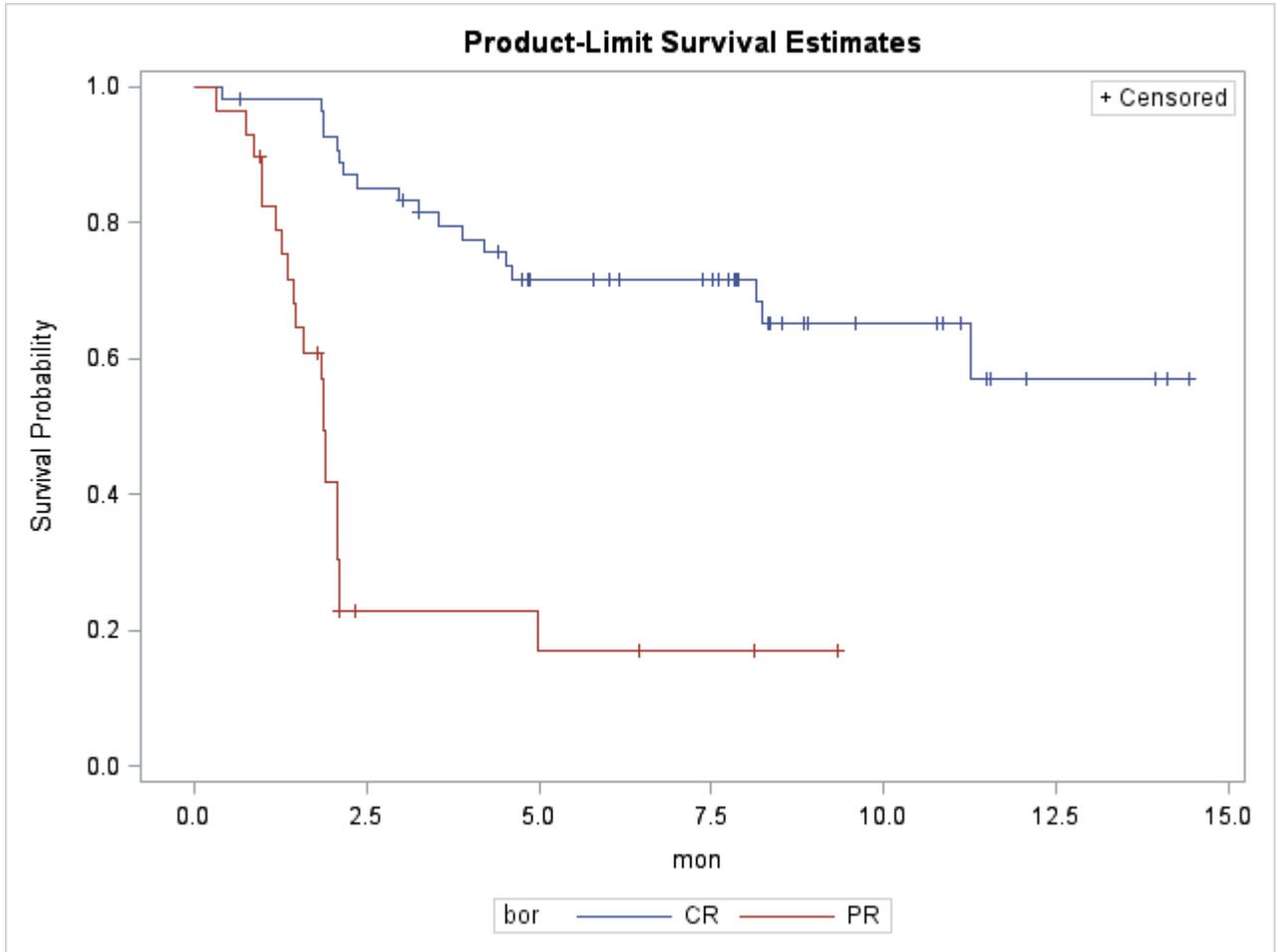
Table 10 DOR results per Investigator assessment

	Cohort 1 (n=63)	Cohort 2 (n=21)	Overall (n=84)
Median follow-up time (months) (min, max)	3.3 (0.4, 14.4)	6.4 (0.3, 14.1)	4.5 (0.3, 14.4)
Number of events	35 (56%)	5 (24%)	40 (47%)
Progressed disease	34 (54%)	4 (19%)	38 (45%)
Death	1 (2%)	1 (5%)	2 (2%)
Percentage censored	28 (44%)	16 (76%)	44 (52%)
Censoring reason			
Response on-going	26 (41%)	14 (67%)	40 (48%)
New cancer therapy	1 (2%)	0	1 (1%)
Stem cell transplant	1 (2%)	2 (10%)	3 (4%)
KM median DOR (months) (95% CI)	4.5 (2.1, NE)	NE (11.3, NE)	8.2 (3.5, NE)

(Source: FDA statistical reviewer)

Figure 3 shows KM curves of DOR by response type. Complete responders had substantially longer DOR than the partial responders. The median DOR was not reached for complete responders, and it was 1.9 months (95% CI: 1.4, 2.1) for the partial responders.

Figure 3 DOR by response type



(Source: FDA statistical reviewer)

In addition, Table 11 summarizes the DOR results per IRC assessment. The overall median DOR was 9.2 months with a lower 95% limit of 5.4 months and unattainable upper limit.

Table 11 DOR results per IRC assessment

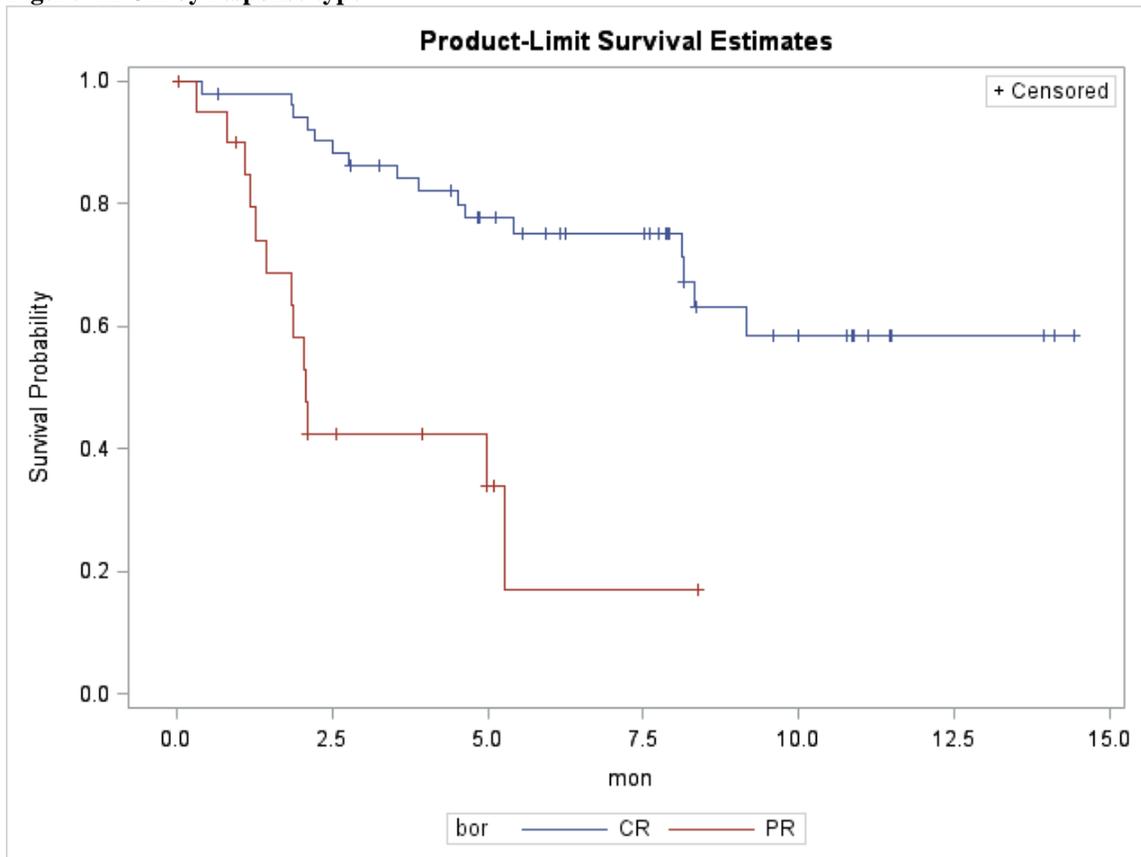
	Cohort 1 (n=52)	Cohort 2 (n=21)	Overall (n=73)
Median follow-up time (months) (min, max)	4.9 (0.4, 14.4)	7.9 (0.03, 14.1)	5.0 (0.03, 14.4)
Number of events	25 (48%)	4 (19%)	29 (40%)
Progressed disease	24 (46%)	3 (14%)	27 (37%)
Death	1 (2%)	1 (5%)	2 (3%)
Percentage censored	27 (52%)	17 (81%)	44 (60%)
Censoring reason			
Response on-going	21 (40%)	14 (67%)	35 (48%)
New cancer therapy	1 (2%)	1 (5%)	2 (3%)

Stem cell transplant	3 (6%)	2 (10%)	5 (7%)
Retreatment	2 (4%)	0	2 (3%)
KM median DOR (months) (95% CI)	8.3 (3.9, NE)	NE (8.1, NE)	9.2 (5.4, NE)

(Source: FDA statistical reviewer)

Figure 4 shows KM curves of DOR by response type. Similar to results of DOR assessed by site investigators, complete responders had substantially longer DOR than the partial responders. The median DOR was not reached for complete responders, and it was 2.1 months (95% CI: 1.3, 5.3) for the partial responders.

Figure 4 DOR by response type



(Source: FDA statistical reviewer)

Two responders died from product-related adverse events. When treating these deaths as competing risk in a competing risk analysis, the Applicant reported similar results as in the KM analysis. The cumulative incidence of relapse and disease related mortality per investigator assessment at 6- and 12-month was 44.2% and 54.9%, respectively. This is in contrast with 46.5% and 57.3%, respectively, based on reverse KM method.

Progression-free survival (PFS)

Table 12 summarizes the PFS results per investigator assessment. The follow-up time for PFS assessment ranges from 0.3 months to 15.3 months with a median of 5.6 months. The overall median PFS was 5.9 months with a 95% CI of (3.4, 12.2) months.

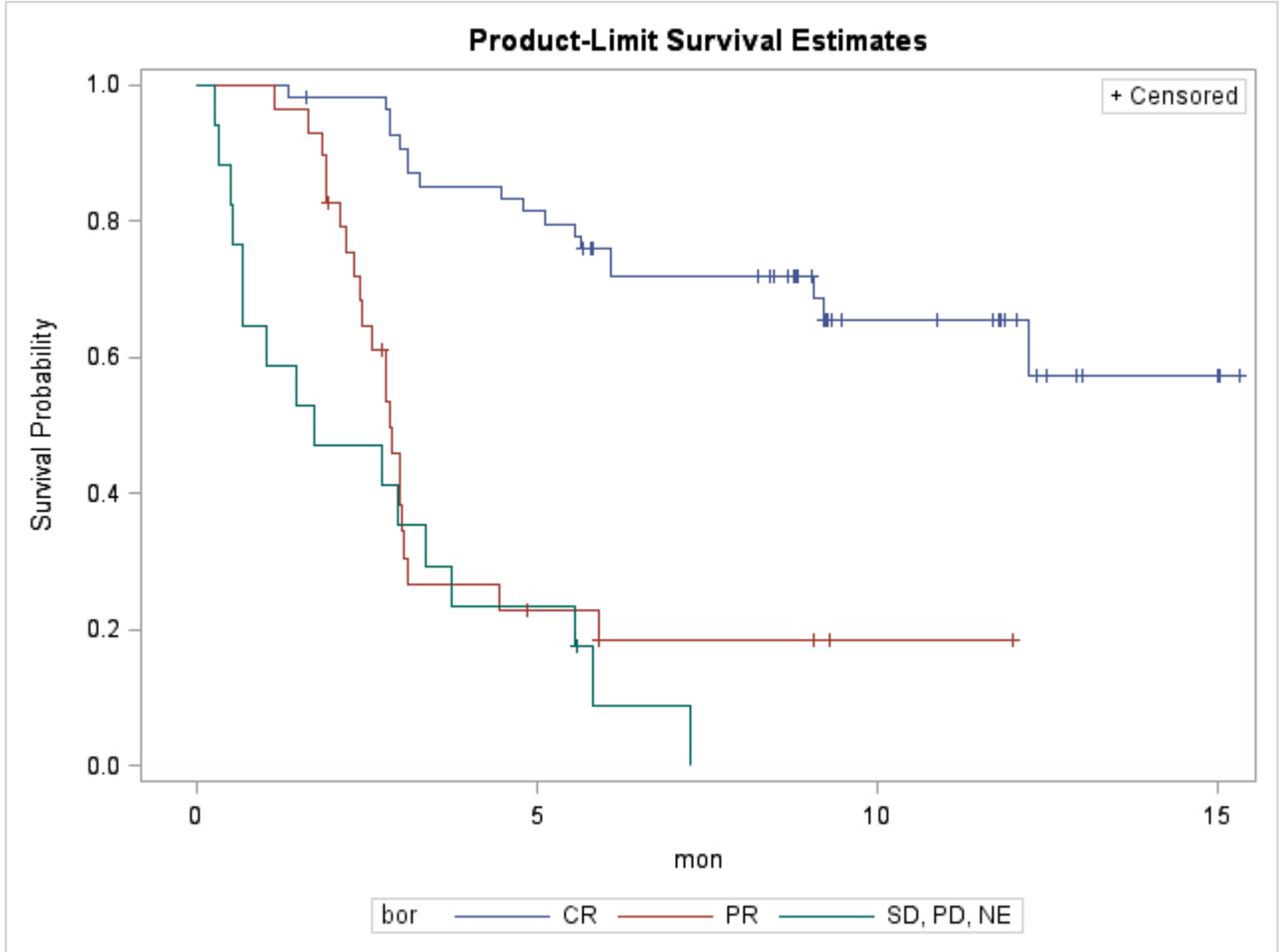
Table 12 PFS results per Investigator assessment

	Cohort 1 (n=77)	Cohort 2 (n=24)	Overall (n=101)
Median follow-up time (months) (min, max)	4.8 (0.3, 15.3)	7.2 (0.5, 15.0)	5.6 (0.3, 15.3)
Number of events	48 (62%)	8 (33%)	56 (55%)
Progressed disease	45 (58%)	6 (25%)	51 (50%)
Death	3 (4%)	2 (8%)	5 (5%)
Percentage censored	29 (38%)	16 (67%)	45 (45%)
Censoring reason			
Response on-going	27 (35%)	14 (58%)	41 (41%)
New cancer therapy	1 (1%)	0	1 (1%)
Stem cell transplant	1 (1%)	2 (8%)	3 (3%)
KM median PFS (months) (95% CI)	5.1 (3.0, 7.3)	NE (6.1, NE)	5.9 (3.4, 12.2)
PFS at			
6 months (95% CI)	41.9% (30.7%, 52.7%)	73.7% (50.4%, 87.3%)	48.9% (38.7%, 58.4%)
12 months (95% CI)	34.2% (23.0%, 45.7%)	68.0% (43.9%, 83.5%)	41.8% (31.4%, 51.9%)

(Source: FDA statistical reviewer)

Figure 5 shows KM curves of PFS by response type. Complete responders had substantially longer PFS than the partial responders and non-responders. The median PFS was not reached for complete responders, and it was 2.8 months (95% CI: 2.4, 3.1) for the partial responders and 1.7 months (95% CI: 0.5, 3.7) for the non-responders.

Figure 5 Progression-free Survival by response type (Investigator assessment)



(Source: FDA statistical reviewer)

Table 13 summarizes the PFS results per IRC assessment. The estimated median PFS for cohort 1 and 2 combined was 6.9 months with a 95% CI of (4.8, 10.0) months.

Table 13 PFS results per IRC assessment

	Cohort 1 (n=77)	Cohort 2 (n=24)	Overall (n=101)
Median follow-up time (months) (min, max)	4.5 (0.3, 15.3)	5.9 (0.5, 15.0)	5.5 (0.3, 15.3)
Number of events	45 (59%)	7 (29%)	52 (52%)
Progressed disease	39 (51%)	5 (21%)	44 (44%)
Death	6 (8%)	2 (8%)	8 (8%)
Percentage censored	32 (42%)	17 (71%)	49 (49%)
Censoring reason			
Response on-going	21 (27%)	14 (58%)	35 (35%)
New cancer therapy	5 (6%)	1 (4%)	6 (6%)

Stem cell transplant	4 (5%)	2 (8%)	6 (6%)
Retreatment	2 (3%)	0	2 (2%)
KM median PFS (months) (95% CI)	5.8 (3.4, 9.1)	NE (6.1, NE)	6.9 (4.8, 10.0)
PFS at 6 months (95% CI)	49.1% (37.0%, 60.1%)	77.6% (54.1%, 90.1%)	55.4% (44.7%, 64.9%)
PFS at 12 months (95% CI)	28.4% (15.6%, 42.7%)	63.2% (36.2%, 81.3%)	36.9% (25.0%, 48.9%)

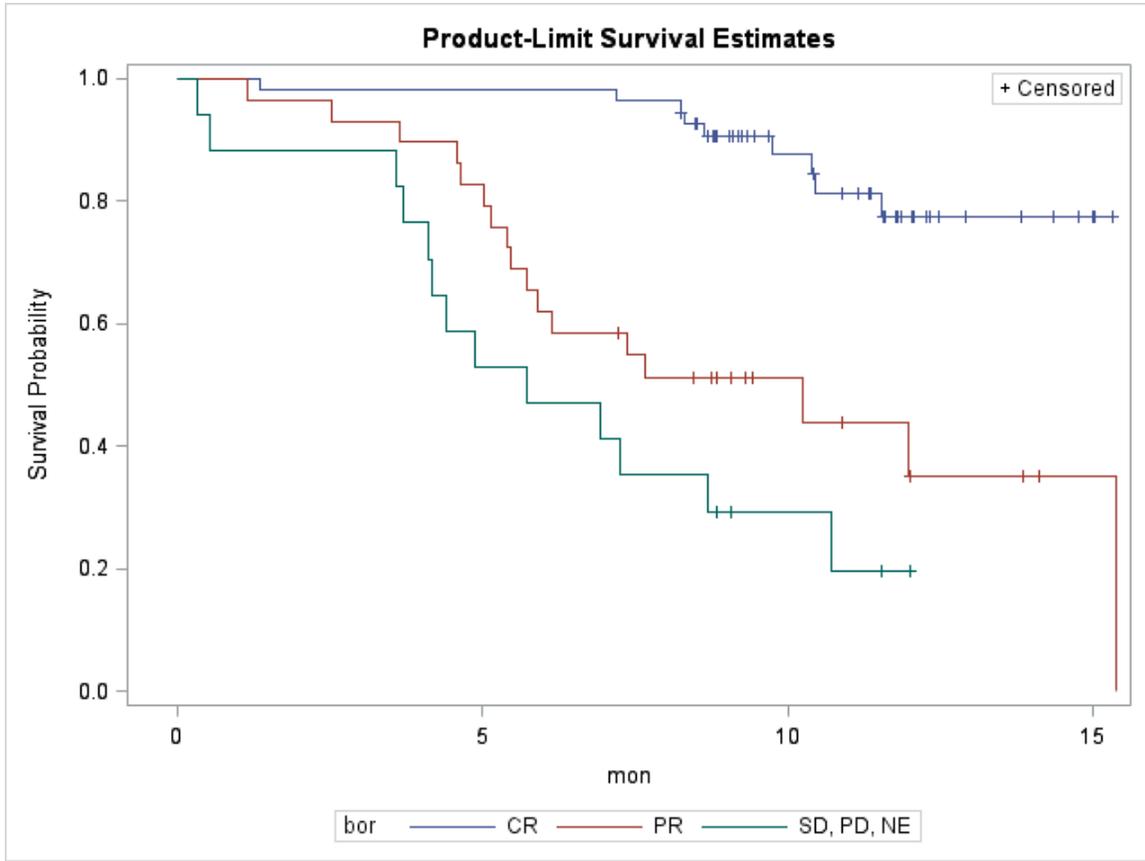
(Source: FDA statistical reviewer)

Overall survival (OS)

A total of 39 subjects (39%) died after KTE-C19 infusion in the mITT population (n = 101). The median follow-up time for OS assessment was 9.1 months (min=0.3, max=15.4). Median OS was 15.4 months (95% CI: 10.7, 15.4). The estimated survival rate at 6- and 12-month was 79.2% (95% CI: 70.0, 85.9) and 54.9% (95% CI: 42.1, 66.0), respectively.

Figure 6 shows KM curves of OS by response type. Complete responders had substantially longer OS than the partial responders and non-responders. The median OS was not reached for complete responders, and it was 10.3 months (95% CI: 5.5, 10.4) for the partial responders and 5.7 months (95% CI: 3.7, 10.7) for the non-responders.

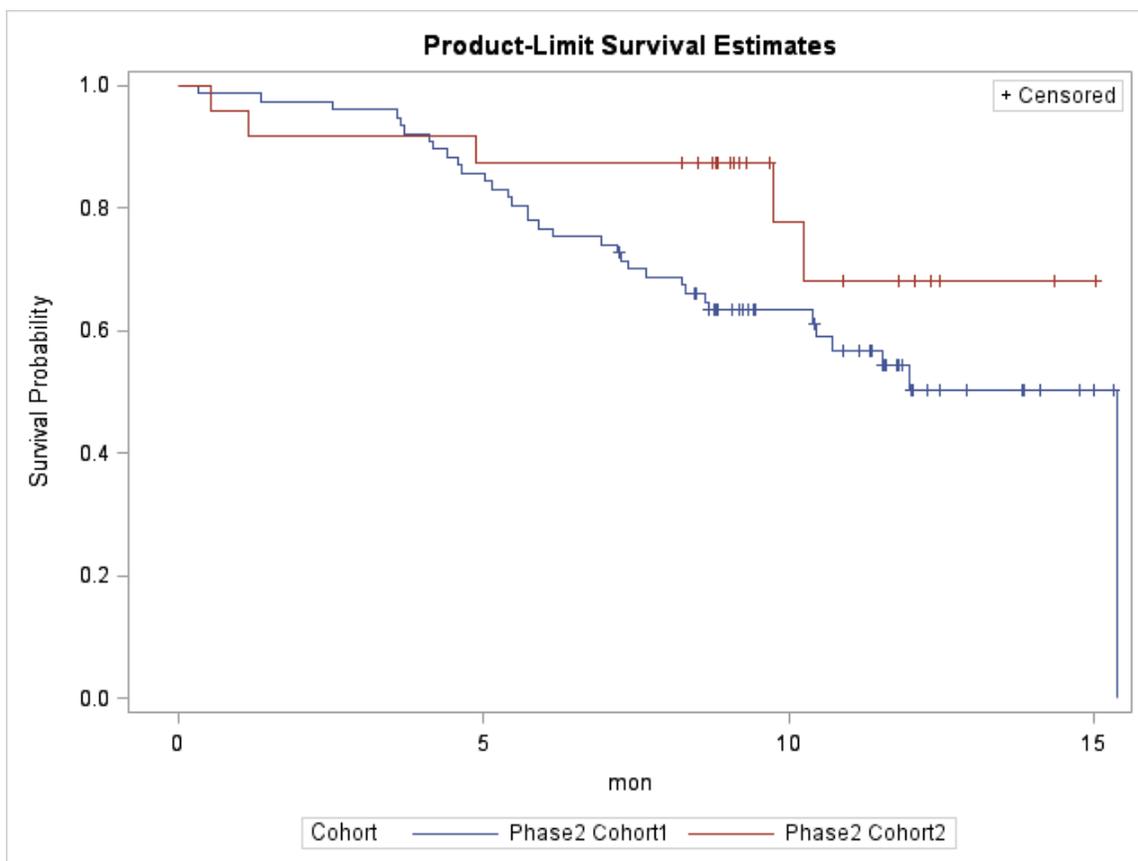
Figure 6 Overall Survival by response type



(Source: FDA statistical reviewer)

Figure 7 shows KM curves of OS by cohort. The survival curve of Cohort 2 is above that of Cohort 1, this may be because Cohort 2 had higher percentage of complete responders than Cohort 1. The median OS was not reached for Cohort 2 and it was 15.4 months (95% CI: 10.4, 15.4) for Cohort 1.

Figure 7 Overall survival by Cohort



(Source: FDA statistical reviewer)

6.1.11.3 Subpopulation Analyses

Table 14 shows ORR per investigator assessment by age group, ethnicity, race and sex. Results of ORR are generally consistent among subgroups.

Table 14 ORR per investigator by age group, ethnicity, race and sex

Subgroup		# of subjects treated (total=101) n (%)	ORR # of responders (%)	95% CI
Age	<=65 years	77	62 (81%)	(70%, 89%)
	>65 years	24	22 (92%)	(73%, 99%)
Sex	Female	33	27 (82%)	(65%, 93%)
	Male	68	57 (84%)	(73%, 92%)
Race	White	90	75 (83%)	(74%, 90%)
	Asian	4	2 (50%)	(7%, 93%)
	Black or African American	4	4 (100%)	(40%, 100%)
	Other	3	3 (100%)	(29%, 100%)

Ethnicity	HISPANIC OR LATINO	18	11 (61%)	(36%, 83%)
	NOT HISPANIC OR LATINO	83	73 (88%)	(79%, 94%)
Overall		101	84 (83%)	(74%, 90%)

(Source: FDA statistical reviewer)

Since only one subject was enrolled in Israel, no subgroup analysis of ORR by country was performed.

Table 15 shows subgroup analysis of ORR by study site. Though some sites had lower ORR than other sites, the number of subjects treated at these sites was too small to make any meaningful conclusion.

Table 15. Subgroup analysis of ORR by study site

Study Site	# of subjects treated (total=101) n (%)	ORR # of responders (%)
001	3 (3%)	3 (100%)
002	17 (17%)	16 (94%)
003	19 (19%)	15 (79%)
004	3 (3%)	3 (100%)
005	4 (4%)	4 (100%)
006	2 (2%)	1 (50%)
007	1 (1%)	1 (100%)
009	10 (10%)	9 (90%)
010	1 (1%)	0
011	1 (1%)	0
012	2 (2%)	2 (100%)
014	2 (2%)	1 (50%)
015	5 (5%)	5 (100%)
017	2 (2%)	1 (50%)
019	8 (8%)	6 (75%)
020	1 (1%)	1 (100%)
021	3 (3%)	3 (100%)
022	6 (6%)	4 (67%)
024	3 (3%)	3 (100%)
025	7 (7%)	6 (86%)
601 (Israel)	1 (1%)	0
Overall	101 (100%)	84 (83%)

(Source: FDA statistical reviewer)

6.1.11.4 Dropouts and/or Discontinuations

Table 16 summarizes subjects' dropouts and discontinuations from the study. The reasons for dropouts and discontinuations included no measurable disease, deaths, and adverse events. Among the 101 infused subjects, 62 subjects have on-going follow-up currently.

Table 16. Subject dropouts and discontinuations

Enrolled in Phase 2	111 (100%)
Leukapheresed	111 (100%)
Discontinued before Conditioning Chemo	8 (7%)
No measurable disease	2 (2%)
Death	2 (2%)
Adverse event	4 (4%)
Conditioning Chemo	103 (93%)
Discontinued before KTE-C19 infusion	2 (2%)
Death	1 (1%)
Adverse event	1 (1%)
KTE-C19 infused	101 (91%)
Follow-up ongoing	62 (65%)
Death	39 (35%)

(source: adapted BLA 125646/0.1; CRS report body Figure 5, FDA statistical reviewer)

6.1.12 Safety Analyses

This section summarizes safety results of Study ZUMA-1.

6.1.12.1 Methods

Descriptive statistic is used to summarize safety data for study ZUMA-1. For data summary, the safety analysis set in this section includes a total of 108 subjects who received at least one dose of KTE-C19, 7 from Phase I and 101 from Phase II.

6.1.12.3 Deaths

No subjects died before KTE-C19 infusion in the Phase I cohort. Three (3) subjects died before KTE-C19 infusion in Phase II.

Deaths reported in the study are listed in Table 17 for the safety analysis set.

Table 17. Deaths reported

	ZUMA-1 N=108 (100%)
Subjects who died	43 (39.8%)
Primary cause of death	
Adverse event	5 (4.6%)
Progressive disease	35 (32.4%)
Other	3 (2.8%)
Death occurred <= 30 days of KTE-C19 infusion	3 (2.8%)
Deaths that occurred > 30 days through 3 months (92 days) of KTE-C19 infusion	4 (3.7%)
Deaths that occurred > 3 months (92 days) after KTE-C19 infusion	36 (33.3%)

(Source: adapted 120-Day Safety Update BLA STN 125643 Table 14.3.24.1)

6.1.12.4 Nonfatal Serious Adverse Events

The Applicant reported 58 (54%) subjects who had at least one treatment-emergent non-fatal Serious Adverse Events in the Safety Analysis Set. Encephalopathy occurred the most among the listed non-fatal SAEs. Table 18 summarizes the treatment-emergent non-fatal SAEs post KTE-C19 infusion.

Table 18. Subject incidence of treatment-emergent non-fatal serious adverse events occurred in more than 1 subject

Preferred Term	All Grades* N (%)	Grade 1-2 N(%)	Grade >=3 N (%)
Subjects with at least one SAE	58 (54)	9 (8)	49 (45)
Encephalopathy	19 (18)	1 (1)	18 (17)
Pyrexia	8 (7)	7 (6)	1(1)
Confusional state	5 (5)	1 (1)	4 (4)
Lung infection	8 (7)	0	8 (7)
Hypotension	3 (3)	0	3 (3)
Neutropenia	3 (3)	0	3 (3)
Acute kidney injury	3 (3)	0	3 (3)
Aphasia	4 (4)	0	4 (4)
Pneumonia	5 (5)	0	5 (5)
B-cell lymphoma	5 (5)	0	5 (5)
Febrile neutropenia	5 (5)	1 (1)	4 (4)
Atrial fibrillation	4 (4)	1 (1)	3 (3)
Ejection fraction decreased	4 (4)	2 (2)	2 (2)
Urinary tract infection	4 (4)	0	4 (4)
Hypoxia	3 (3)	0	3 (3)
Cardiac arrest	3 (3)	0	3 (3)
Somnolence	3 (3)	0	3 (3)
Agitation	2 (2)	0	2 (2)
Lactic acidosis	2 (2)	0	2 (2)
Atrial flutter	2 (2)	1 (1)	1 (1)

*This column includes SAEs from all grades.

(Source: adapted 120-Day Safety Update BLA STN 125643 Table 14.3.2.1.1)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 19 summarizes the AESI post KTE-C19 infusion. CRS occurred the most often in 93% of infused subjects.

Table 19. Adverse events of special interest (AESI)

Group term	All Grades* n=108 (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n(%)
Cytokine release syndrome (CRS)	100 (93)	9 (8)	4 (4)	1 (1)
Neurologic Event	71 (66)	29 (27)	3 (3)	0
Thrombocytopenia	63 (58)	19 (18)	23 (21)	0
Neutropenia	92 (85)	26 (24)	59 (55)	0
Anaemia	72 (67)	46 (43)	3 (3)	0

*This column includes AESI from all grades.

(Source: adapted 120-Day Safety Update BLA STN 125643 Table 14.3.9.1)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support this application is a Phase I/II, single-arm, and multicenter study (ZUMA-1). The Phase I part of the study enrolled 8 subjects and the Phase II part enrolled 111 subjects. Of the 111 enrolled subjects in Phase II, 101 subjects received KTE-C19; data from these 101 subjects therefore constitutes the primary evidence of efficacy for the product. The pre-specified primary efficacy endpoint was ORR, which is defined as the proportion of subjects with either a CR or PR while on study as assessed by site investigators according to the IWG 2007 response criteria. ORR was also assessed by an IRC to evaluate the consistency of disease status assessment.. Efficacy results summarized in this memo are based on a data cut-off date of April 26, 2017.

The ORR as assessed by the investigator was 83% (=84/101) and the lower limit of the 95% exact Clopper-Pearson confidence interval was 74.4%, which is above the pre-set null hypothesis rate of 20%. Fifty-five (54%) subjects had a best response of CR, and 29 subjects (29%) had a best response of PR. The median DOR was 8.2 (95% CI: 3.5, NE) months for all responders with a median follow-up of 4.5 months (range: 0.3, 14.4). The median DOR for the partial responders was 1.9 months (95% CI: 1.4, 2.1) and the median DOR was not reached for complete responders.

The ORR as assessed by the IRC was 72% (=73/101) and the lower limit of the 95% exact Clopper-Pearson confidence interval was 62.5%, which is also above the pre-set null hypothesis rate of 20%. Fifty-two (51%) subjects had a best response of CR, and 21 subjects (21%) had a best response of PR. The median DOR was 9.2 (95% CI: 5.4, NE) months for all responders with a median follow-up of 5 months (range: 0.03, 14.4). The median DOR for the partial responders was 2.1 months (95% CI: 1.3, 5.3) and the median DOR was not reached for complete responders. Results assessed by IRC are consistent with those assessed by site investigators.

Deaths occurred in 3% (= 3/119) of enrolled subjects (Phase I and II combined) before KTE-C19 infusion, and occurred in 39.8% (= 43/108) of infused subjects. Nonfatal Serious Adverse events (SAEs) were reported in 54% (= 58/108) of infused subjects. The most common adverse event of special interest was CRS which occurred in 93% (=100/108) of KTE-C19 infused subjects.

10.2 Conclusions and Recommendations

Efficacy results in Study ZUMA-1 meet the study objective that ORR is statistically significantly greater than the pre-specified null hypothesis rate of 20%. The statistical analysis results provide evidence to support the Applicant's proposed indication for KTE-C19 in this BLA.

References

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