Clinical Pharmacology BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology

Office of Tissues and Advanced Therapy

BLA	125703/0
Product	TECARTUS (brexucabtagene autoleucel, KTE-X19), Cell suspension for intravenous infusion
Sponsor	Kite Pharma, Inc.
Indication	Treatment of adult patients with relapsed or refractory mantle cell lymphoma (r/r MCL)
Date Received	December 11, 2019
Reviewer	Xiaofei Wang, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation and Pharmacology/Toxicology
RPM	Adriane Fisher
Through	Tejashri Purohit-Sheth, M.D., FACAAI, CQIA Director Division of Clinical Evaluation and Pharmacology/Toxicology

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1 EXECUTIVE SUMMARY

Kite Pharma Inc. seeks approval of KTE-X19 (brexucabtagene autoleucel, anti-CD19 CAR T cells, TECARTUS®) for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (r/r MCL). KTE-X19 comprises autologous T cells transduced with retroviral vector containing an anti-CD19 chimeric antigen receptor (CAR). The proposed KTE-X19 dosing regimen is a single target dose of 2 x 10^6 cells/kg body weight, with a maximum of 2 x 10^8 anti-CD19 CAR T cells. KTE-X19 is to be administered via intravenous (IV) infusion.

The clinical pharmacology section of this biologics license application (BLA) is supported by one Phase 2 clinical study that evaluated the efficacy, safety, pharmacokinetic (PK) and pharmacodynamics (PD) of KTE-X19 in adult subjects with relapsed or refractory mantle cell lymphoma (r/r MCL).

The proposed dosing regimen of KTE-X19 administered by intravenous (IV) infusion has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable. From a clinical pharmacology standpoint, the BLA is acceptable to support approval.

2 INTRODUCTION

KTE-X19 is an autologous chimeric antigen receptor (CAR) T-cell product that is genetically modified ex vivo to express a chimeric antigen receptor (CAR) to target CD19 on the cell surface of malignant B cells. The CAR consists of a single-chain antibody fragment against CD19 linked to CD3ζ and CD28 T-cell activating domains that result in elimination of CD19-expressing cells. Following CAR engagement with CD19+ target cells, the CD3ζ domain activates the downstream signaling cascade that leads to T cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. The intracellular signaling domain of CD28 provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T cell- function, including interleuking-2 (IL-2) production. In addition, activated T cells secrete cytokines and other molecules that can recruit and activate additional anti-tumor immune cells.

KTE-X19 is produced from leukapheresis material obtained from the individual patient and is unique to each patient. The manufacturing process contains a (b) (4) T-cell enrichment step, which is intended to reduce the likelihood of circulating CD19-expressing tumor cells in patients' leukapheresis material driving the activation, expansion, and exhaustion of the anti-CD19 CAR T cell during the ex vivo manufacturing process. The T cells are then activated and transduced with the anti-CD19 CAR containing γ (b) (4) retrovirus. Transduced cells are expanded in the presence of recombinant human IL-2, washed, and cryopreserved.

KTE-X19 is to be administered by intravenous infusion at a single target dose of 2 x 10^6 CAR T cells/kg body weight, with a maximum of 2 x 10^8 CAR T cells.

This application is supported by a phase 2 clinical study (Study No. KTE-X19-102, ZUMA-2) that evaluated the efficacy and safety of KTE-X19 in adult subjects with relapsed or refractory mantle cell lymphoma (r/r MCL). MCL is an aggressive subtype of non-Hodgkin lymphoma (NHL) with distinctive clinical, biological and molecular characteristics.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Following are key clinical pharmacology findings of KTE-X19 in adult subjects with r/r MCL:

- General pharmacokinetics/cellular kinetics of KTE-X19:
    - Following infusion, KTE-X19 exhibited an initial rapid expansion phase followed by a rapid decline and then a gradual decrease. The median time to reach peak levels of KTE-X19 in blood was 15 days post-infusion.
    - At the dose of 2 x 10^6 anti-CD19 CAR T cells/kg, KTE-X19 levels decreased to near baseline at Month 3 post-infusion. KTE-X19 was detectable in some adult subjects with r/r MCL up to 24 months in peripheral blood at the time of the data cutoff date.
    - At the dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg, the peak levels and $AUC_{0\text{-}28d}$ of KTE-X19 were approximately 60% of that in subjects treated at the dose of 2 x 10^6 anti-CD19 CAR T cells/kg. KTE-X19 levels decreased to undetectable levels in majority of the evaluable subjects by 15 months post-dose.

- KTE-X19 pharmacokinetics/cellular kinetics in specific populations:
    - KTE-X19 exposure (Cmax and $AUC_{0\text{-}28d}$) was numerically higher in subjects < 65 years of age compared to subjects ≥ 65 years of age. However, with limitations imposed by high inter-subject variability of KTE-X19 exposure, small sample size, and other factors such as tumor burden, the impact of age on KTE-X19 exposure should be interpreted with caution.
    - KTE-X19 exposure was similar between male and female subjects.
    - Baseline tumor burden did not show a monotonic association with KTE-X19 expansion.
    - Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with KTE-X19. Subjects who received both tocilizumab and corticosteroids had higher KTE-X19 exposure than subjects who received either medication alone or neither medication. These observations are

confounded by the fact that the need for tocilizumab and/or corticosteroids was triggered by toxicity, which was associated with higher KTE-X19 exposures.

- After infusion, substantially higher median values of Cmax and $AUC_{0\text{-}28d}$ of KTE-X19 were reported in responders [complete response (CR) and partial response (PR)] compared to non-responders.

- Higher KTE-X19 exposures (Cmax and $AUC_{0\text{-}28d}$) were reported in subjects with higher grades of CRS or neurologic event (Grade 3 or higher versus Grade 2, Grade 1, or no events).

- After KTE-X19 infusion, substantial elevation in peak levels and $AUC_{0\text{-}28d}$ were observed in subjects with Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following biomarkers: ferritin, granzyme B, IL-2Rα, IL-6, IL-8, IL-10, IL-15, perforin, and TNF-α.

- After KTE-X19 infusion, substantial elevation in peak levels and $AUC_{0\text{-}28d}$ were observed in subjects with Grade 3 or higher neurologic event compared to subjects with Grade 2, Grade 1 or no neurologic event for following biomarkers: granzyme B, IFN-γ, IL-1RA, IL-2, IL-6, IL-10, IL-15, and TNF-α.

- Cytokines and immune effector molecules were evaluated in available CSF samples (n=17):
    - Levels of three pro-inflammatory cytokines (CRP, CXCL-10, and IL-6) were at least 5-fold higher than the median baseline values.
    - Median levels of following analytes were substantially elevated in the CSF of subjects with Grade 3 or higher neurologic events compared to levels in subjects who had Grade 2, Grade 1, or no neurologic events: CRP, ferritin, ICAM-1, IL-2Rα, IL-6, IL-8, and VCAM-1.

  Due to high inter-subject variability and small sample size, the data should be interpreted with caution.

- KTE-X19 induced B-cell aplasia in majority of the treated subjects. Median B-cell levels were recovered to 10.62% (range: 3.97-15.99%) by Month 18 in evaluable subjects.

- There was no reported presence of replication-competent retrovirus (RCR) in the blood of KTE-X19 treated subjects.

4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125703 and finds it acceptable pending the following revisions shown below.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

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

12.2. Pharmacodynamics

After ~~[TRADENAME]~~ TECARTUS infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was generally observed between ~~4~~ four and eight ~~8~~ days after infusion and levels generally returned to baseline within 28 days.

Due to the on-target effect of ~~[TRADENAME]~~ TECARTUS, a period of B-cell aplasia is expected.

12.3. Pharmacokinetics

Following infusion (target dose of 2×10^6 anti-CD19 CAR T cells/kg) of ~~[TRADENAME]~~ TECARTUS, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by three~~3~~ months. Peak levels of anti-CD19 CAR T cells occurred within the first seven~~7~~ to 15 days after ~~[TRADENAME]~~ TECARTUS infusion.

The number of anti-CD19 CAR T cells in blood was associated with objective response [complete remission (CR) or partial remission (PR)]. The median peak anti-CD19 CAR T-cell level in responders vs nonresponders was 102.4~~97.52~~ cells/µL (range: 0.2~~4~~ to 2589.5~~47~~ cells/µL; n = 52~~62~~), and 12.0~~0.39~~ cells/µL (range: 0.2~~16~~ to 1364.0 ~~22.02~~ cells/µL, n = 8~~5; Wilcoxon rank rank-sum test p = 0.0020~~), respectively. The median $AUC_{0\text{-}28d}$ in patients with an objective response was 1487.0~~1386.28~~ cells/µL•days (range: 3.8~~3~~ to 2.77E+04 cells/µL•days; n = 62) vs

169.55.51 cells/µL•days in nonresponders (range: 1.81 to 1.17E+04293.86 cells/µL•days; Wilcoxon rank-sum p = 0.0013; n = 85).

To Applicant: please add a paragraph describing PK information for tocilizumab and corticosteroids use.

Median peak anti-CD19 CAR T-cell values were 74.108 cells/µL in patients ≥ 65 years of age (n = 39) and 112.45 cells/µL in patients < 65 years of age (n = 28). Median anti-CD19 CAR T-cell AUC values were 876.548 cells/µL·day in patients ≥ 65 years of age and 1640.21 cells/µL·day in patients < 65 years of age.

Gender had no significant impact on $AUC_{Day\ 0\text{-}28}$ and C_{max} of [TRADENAME] TECARTUS.

Hepatic and renal impairment studies of [TRADENAME] TECARTUS were not conducted.

5 RECOMMENDATIONS

The clinical pharmacology information in this BLA is acceptable, provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in Section 12 of the package insert. Please refer to section 4 for detailed Labeling Recommendations.

6 APPENDIX - INDIVIDUAL STUDY

6.1 Study #1

6.1.1 Study Design

Study Title: A Phase 2 multicenter study evaluating the efficacy of KTE-X19 in subjects with relapsed/refractory mantle cell lymphoma (Study No.: ZUMA-2)

Objectives

Primary Objectives

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

Secondary Objectives

The secondary objectives included assessing the safety and tolerability of KTE-X19, additional efficacy endpoints, and the change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.

Study Pharmacokinetics and Pharmacodynamics Objectives

To assess levels of anti-CD19 CAR T cells in blood and levels of cytokines in serum and association with clinical outcomes.

Study Design

This is an ongoing, single arm, open-label, multi-center, Phase 2 study to evaluate the safety and efficacy of KTE-X19 in adult subjects with r/r MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTK inhibitor (ibrutinib and or acalabrutinib).

Subjects were enrolled into 2 separate dose cohorts and treated to evaluate the efficacy of KTE-X19.

- Cohort 1: Pivotal Cohort was expected to enroll and treat up to approximately 90 subjects with a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum dose of 2×10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg), with up to approximately 80 of these subjects receiving KTE-X19 (10 subjects in this cohort received axicabtagene ciloleucel).

- Cohort 2: Cohort 2 was expected to enroll and treat up to 40 subjects with KTE-X19 at a target dose of 0.5×10^6 anti-CD19 CAR T cells/kg (maximum dose of 0.5×10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg).

Subjects received a single intravenous (IV) infusion of KTE-X19 on Day 0 after receiving the 3-day conditioning chemotherapy (fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day) on Day -5 through Day -3.

The dose used in Cohort 1 was selected based on the results of a clinical study of another Kite anti-CD19 CAR T-cell product, axicabtagene ciloleucel in subjects with refractory aggressive large B-cell lymphoma (ZUMA-1). The dose for Cohort 2 was based on results from an interim analysis of 28 subjects in Cohort 1 (9 subjects treated with axicabtagene ciloleucel and 19 subjects treated with KTE-X19). Three months after administration, subjects in Cohort 1 had approximately 3- to 5-fold higher peak expansion and cumulative exposure (area under the curve $AUC_{0\text{-}28d}$) values of anti-CD19 CAR T cells relative to the peak and $AUC_{0\text{-}28d}$ observed in subjects in ZUMA-1. However, additional data collected from both cohorts indicated that 1) the expansion of anti-CD19 CAR T cells in subjects in Cohort 2 was less robust than anticipated; and 2) subjects in Cohort 1 with 6-month follow-up data demonstrated durable responses and a manageable safety profile. Therefore, the KTE-19 dose of 2 x 10^6 anti-CD19 CAR T cells/kg was deemed the optimal dose for treatment of MCL. Cohort 1 was re-opened and additional subjects were enrolled and treated at the dose of 2 x 10^6 anti-CD19 CAR T cells/kg.

At the time of the data cutoff date of July 24, 2019, 74 subjects were enrolled in Cohort 1, and 68 subjects received KTE-X19. The primary endpoint analysis was conducted with the first 60 subjects in Cohort 1 who were treated with KTE-X19. All subjects in Cohort 1 received KTE-X19 at doses ranging from 1.6 to 2 x 10^6 anti-CD19 CAR T cells/kg, except for 2 subjects: one subjects received dose at 0.6 x 10^6 anti-CD19 CAR T cells/kg, and one received KTE-X19 at the dose of 1 x 10^6 anti-CD19 CAR T cells/kg. The subject with the dose of 0.6 x 10^6 anti-CD19 CAR T cells/kg was not included in primary efficacy analysis (inferential analysis). In Cohort 2, 17 subjects were enrolled, and 14 subjects received KTE-X19.

For pharmacokinetic analysis, blood samples were collected at enrollment/leukapheresis (prior to conditional chemotherapy), pre-dose (prior to infusion on Day 0), and on Days 7, 14, 28, Month 3, then every 3 months though Month 24 and annually thereafter post-infusion.

Blood levels of KTE-X19 were monitored by a validated (b) (4) assay, which is specifically designed for measuring (b) (4)

Blood samples were also obtained for pharmacodynamics biomarker analysis at following time points: baseline (prior to conditioning chemotherapy), pre-dose (prior to infusion on Day 0), and on Days 3, 7, 14, and 28 post-infusion.

A panel of 40 pro-inflammatory, and immune-modulating cytokines, chemokines, and effector-molecules were measured for pharmacodynamics assessment. Levels of following 17 key analytes were presented:

- Homeostatic/proliferative: interleukin (IL)-2, IL-7, and IL-15
- Inflammatory/immune modulating: C-reactive protein (CRP), interferon-gamma (IFN-γ), IL-1 receptor antagonist (IL-1RA), IL-2 receptor alpha (IL-2Rα), IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α)
- Chemokine: C-X-C chemokine (CXCL)10, and IL-8
- Immune effector: granzyme B and perforin
- Other analytes: ferritin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)

6.1.2 Results

6.1.2.1 Pharmacokinetics/Cellular Kinetics

General Pharmacokinetic/Cellular Kinetic Characteristics of KTE-X19

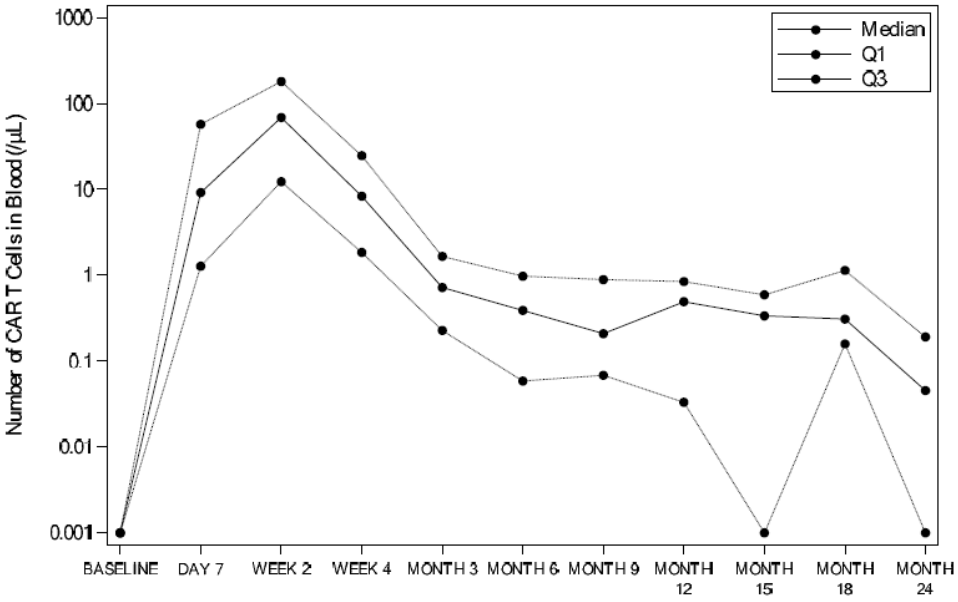
The exposure of KTE-X19 increased with dose increased from 0.5 x 10^6 anti-CD19 CAR T cells/kg to 2 x 10^6 anti-CD19 CAR T cells/kg. Substantial inter-subject variabilities were observed for KTE-X19 pharmacokinetic (PK) profiles.

In Cohort 1, after single dose infusion, KTE-X19 exhibited a rapid exponential increase followed by a rapid decline and then a gradual decrease (Figure 1a). The median time to reach peak levels of KTE-X19 in blood was 15 days (range: 8 – 31 days) after infusion. The median peak level of KTE-X19 in the blood (Cmax) were 88.6 cells/µL (range: 0.16 – 2589.5 cells/µL). The median area under the blood concentration vs. time curve from Day 0 to Day 28 ($AUC_{0\text{-}28d}$) was 1136.6 days*cells/µL (range 1.8 – 2.77E+04 days*cells/µL). At 1 month after KTE-X19 infusion, the median blood level of KTE-X19 was 8.3 cells/µL (range: 1.8 – 24.6 cells/µL), and by 3 months, levels of KTE-X19 decreased to near baseline: median of 0.7 cells/µL (range: 0.2 – 1.7 cells/µL).

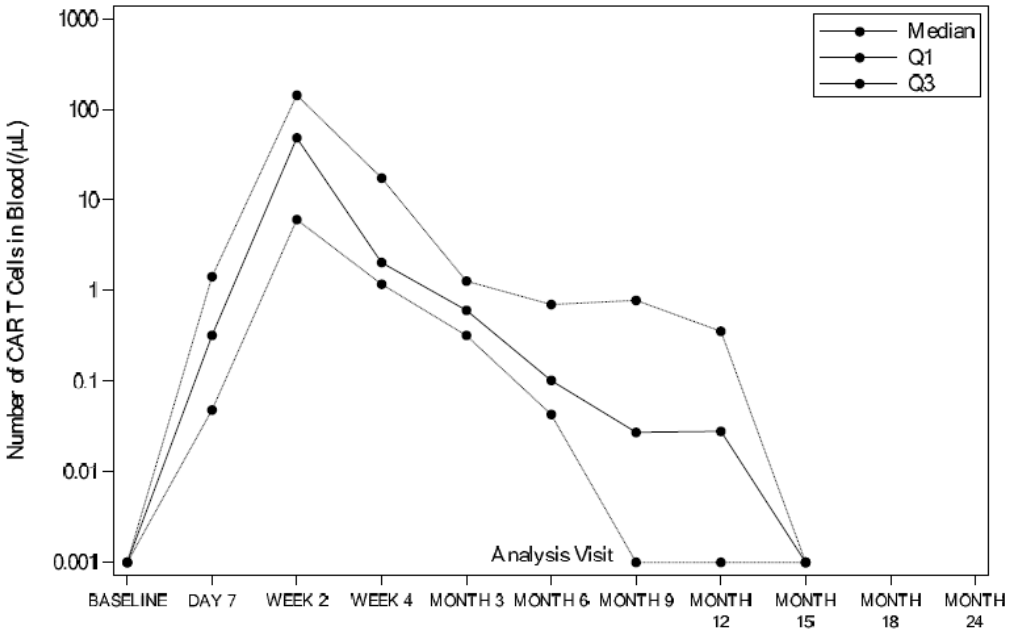
KTE-X19 was detectable (median: 0.1 cells/µL; range: <LLOQ to 0.2 cells/µL) in some adult subjects with r/r MCL (6 of 10 subjects) up to 24 months in peripheral blood at the time of the data cutoff date.

Figure 1. Median KTE-X19 (Q1, Q3) blood levels (cells/ µL) versus time profile in adult subjects with r/r MCL (ZUMA-2, Cohort 1 & 2)

a. Cohort 1



b. Cohort 2



Source: applicant submission: Figure 14.5.4.1.2.1 & Figure 14.5.4.1.2.2 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 819-810.

The peak levels and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects treated in Cohort 2 with 0.5 x 10^6 anti-CD19 CAR T cells/kg were approximately 60% of that of subjects treated in Cohort 1 with 2 x 10^6 anti-CD19 CAR T cells/kg. Median peak level of KTE-19 was 56.1 cells/µL (range: 0.3 – 393.7 cells/µL). The median time to reach peak levels of KTE-X19 in blood was 15 days (range: 15 – 92 days) after infusion. The median $AUC_{0\text{-}28d}$ was 688.4 days*cells/µL (range <LLOQ – 4265.8 days*cells/µL). KTE-X19 levels in Cohort 2 decreased toward background levels by Month 3 post-infusion in all subjects (median: 0.6 cells/ µL, range: <LLOQ to 14.2 cells/µL) and decreased to undetectable levels in 4 of 5 subjects by 15 months post-dose (Figure 1b).

Pharmacokinetics/Cellular Kinetics in Special Population or Subgroups (Cohort 1)

Age, Sex and Race

Table 1 shows KTE-X19 exposure in different subgroups of subjects.

Table 1. KTE-X19 Exposure in Subgroups (Cohort 1, N=68)

		$AUC_{0\text{-}28d}$ (days* cells/µL)	**Cmax (cells/µL)**	**Tmax (days)**
Age	< 65 years (N=29)	1640.2 (5.5, 2.72E+04)	112.5 (0.4, 2589.5)	15 (8, 31)
	≥ 65 years (N=39)	876.5 (1.8, 2.77E+04)	74.1 (0.2, 2565.8)	15 (8, 30)
Sex	Female (N=11)	1377.6 (35.7, 1.4E+04)	88.6 (2.5, 1753.6)	15 (8, 30)
	Male (N=57)	1112.9 (1.8, 2.77E+04)	86.8 (0.2, 2589.5)	15 (8, 31)
Race	Black or African American (N=1)	2569.3 (2569.3, 2569.3)	182.4 (182.4, 182.4)	8 (8, 8)
	Native Hawaiian or Other Pacific Islander (N=1)	281.5 (281.5, 281.5)	22.1 (22.1, 22.1)	31 (31, 31)
	White (N=62)	1241.2 (1.8, 2.77E+04)	95.9 (0.2, 2589.5)	15 (8, 31)
	Other (N=4)	331.3 (140.4, 1.06E+04)	27.9 (10.0, 1369.5)	15 (8, 29)

In ZUMA-2, Cohort 1, 39 (57.4%) of 68 subjects were ≥ 65 years of age. The median KTE-X19 peak levels were 74.1 anti-CD19 CAR T positive cells/µL (range: 0.2 to 2565.8 cells/µL) vs. 112.5 anti-CD19 CAR T positive cells/µL (range: 0.4 to 2589.5 cells/µL) for subjects ≥ 65 years and < 65 years, respectively. The median of $AUC_{0\text{-}28d}$ were 876.5 day*cells/µL (range: 0.8 to 2.77E+04 day*cells/µL) vs. 1640.2 day*cells/µL (range: 5.5 to 2.72E+04 day*cells/µL) for elderly subjects ≥ 65 years of age) and less than 65 years old subjects, respectively. The median value for the time to reach peak levels of KTE-X19 (Tmax) was around 15 days for both subject groups. With limitations imposed by high inter-subject variability of KTE-X19 exposure, small

sample size, and other factors such as tumor burden, the impact of age on KTE-X19 exposure should be interpreted with caution.

Of 68 subjects in ZUMA-2, Cohort 1, 57 (84%) were male and 11 subjects (16%) were female. KTE-X19 exposure was similar between male and female subjects. This suggests that sex is not a factor affecting KTE-X19 expansion.

The populations studied in ZUMA-2 were primarily white subjects. Therefore, the impact of race on KTE-X19 expansion cannot be clearly elucidated.

Baseline Tumor Burden

Impact of baseline tumor burden on KTE-X19 pharmacokinetics was evaluated. Tumor burden was measured as the sum of the cross-products of target lesions, i.e., the sum of the product of the longest perpendicular diameters of lesions. As shown in Table 2, there's no apparent monotonic association between baseline tumor burden and KTE-19 exposure.

Table 2. KTE-X19 exposure and baseline tumor burden (ZUMA-2, Cohort 1)

	Q1: [Min=260.2, Q1=709.7] (N = 16)	Q2: (Q1=709.7, Median=1818.0] (N = 16)	Q3: (Median=1818.0, Q3=5059.9] (N = 16)	Q4: (Q3=5059.9, Max=16877.8] (N = 15)	Total (N = 63)
Area Under Curve (From Day 0 To Day 28)					
n	16	15	16	15	62
Mean (StD)	1384.03 (1744.22)	4061.41 (5282.18)	4219.07 (7045.56)	2727.84 (6864.12)	3088.52 (5615.50)
Median (Q1, Q3)	458.99 (119.22, 2387.58)	1486.96 (281.50, 7933.81)	2168.29 (850.80, 3646.78)	566.27 (144.38, 1996.00)	1188.93 (218.99, 2960.77)
Min, Max	1.81, 4728.86	19.03, 1.67E+04	45.10, 2.77E+04	43.81, 2.72E+04	1.81, 2.77E+04
Peak					
n	16	15	16	15	62
Mean (StD)	118.62 (153.15)	461.25 (688.56)	362.52 (658.50)	250.14 (653.72)	296.28 (579.60)
Median (Q1, Q3)	42.18 (7.96, 189.47)	135.82 (22.02, 775.02)	133.00 (55.46, 282.45)	48.11 (12.04, 167.23)	83.12 (17.18, 264.33)
Min, Max	0.16, 431.33	1.60, 2241.62	1.92, 2565.84	2.88, 2589.47	0.16, 2589.47
Time to Peak (Days)					
n	16	15	16	15	62
Mean (StD)	11.50 (3.63)	13.73 (5.90)	14.38 (5.04)	18.40 (6.85)	14.45 (5.87)
Median (Q1, Q3)	11 (8, 15)	15 (8, 15)	15 (12, 15)	15 (15, 25)	15 (8, 15)
Min, Max	8, 16	8, 31	8, 29	8, 31	8, 31

Source: applicant submission: Table 14.5.4.5.13 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 186.

<u>Tocilizumab and Corticosteroids</u>

Tocilizumab and systemic corticosteroids were used for management of cytokine release syndrome (CRS) and neurologic events after KTE-X19 infusion in study ZUMA-2. In Cohort 1, 38 subjects received both tocilizumab and corticosteroids, 10 subjects only received tocilizumab

and 2 subjects received corticosteroids alone. As shown in Table 3, KTE-X19 exposure levels were the highest in subjects who received both tocilizumab and corticosteroids, followed by subjects who received tocilizumab alone. These results are in line with the fact that higher KTE-X19 exposure levels are associated to more severe adverse events that require management with both tocilizumab and corticosteroids or tocilizumab alone.

Table 3. KTE-X19 exposure and tocilizumab and corticosteroids (ZUMA-2, Cohort 1)

	Steroids alone (N = 2)	Tocilizumab alone (N = 10)	Both Steroids and Tocilizumab (N = 38)	Neither Steroids nor Tocilizumab (N = 18)
Area Under Curve (From Day 0 To Day 28)				
n	2	10	37	18
Mean (StD)	367.84 (177.23)	2086.08 (3128.27)	4586.54 (6966.71)	1329.35 (2117.82)
Median (Q1, Q3)	367.84 (242.52, 493.16)	1188.93 (341.70, 2090.42)	1996.00 (460.37, 4728.86)	360.35 (35.67, 1725.29)
Min, Max	242.52, 493.16	102.83, 1.06E+04	5.51, 2.77E+04	1.81, 8571.46
Peak				
n	2	10	37	18
Mean (StD)	24.21 (15.24)	219.81 (411.30)	461.49 (726.00)	106.14 (190.35)
Median (Q1, Q3)	24.21 (13.43, 34.98)	86.47 (33.18, 144.38)	167.23 (33.33, 425.21)	24.72 (2.48, 129.29)
Min, Max	13.43, 34.98	6.61, 1369.47	0.39, 2589.47	0.16, 789.41
Time to Peak (Days)				
n	2	10	37	18
Mean (StD)	15.00 (0.00)	15.50 (7.03)	13.78 (5.91)	13.78 (5.61)
Median (Q1, Q3)	15 (15, 15)	15 (8, 17)	15 (8, 15)	15 (8, 16)
Min, Max	15, 15	8, 29	8, 31	8, 31
Baseline				
n	2	10	37	18
Mean (StD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Min, Max	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00

Data cutoff date = 24JUL2019
Peak is defined as the maximum number of CAR T measured post infusion.
Area under curve (AUC) is defined as the area under curve in a plot of CAR T cells against scheduled visit from Day 0 to Day 28.
Time to peak is defined as number of days from KTE-X19 infusion to the date when the CAR T cells in blood firstly reached the maximum post-baseline level.

Data Source: ADCART, ADCM Program Name: t_pk_summ_by_ster_toci_sec4_5.sas Output Generated: 20191010T15:03

Source: applicant submission: Table 14.5.4.5.2.11.1. in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 153.

Product Characteristics and KTE-X19 Pharmacokinetics/Cellular Kinetics

An exploratory analysis was conducted to assess the association of product characteristics with KTE-X19 PK profiles. Results indicated that (b) (4) may have potential impact on KTE-X19 expansion (Table 4).

Table 4. Potential Associations of post-infusion peak KTE-X19 levels in blood with product characteristics (Cohort 1)

Analyte	N[a]	Regression Coefficient (95% CI)	Nominal p Value
(b) (4)			

Source: applicant submission: Table 13 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 60.

As shown in Table 5, the association between product characteristics (b) (4) with KTE-X19 PK profiles were not monotonic. KTE-X19 with (b) (4) may potentially be associated with better benefit-risk profiles. However, due to small sample size, the results need to be interpreted with caution.

Table 5. Quartile analysis of impact of KTE-X19 product characteristics (b) (4)) on pharmacokinetics/cellular kinetics, efficacy and safety (ZUMA-2, Cohort 1)

	Pharmacokinetic Parameters		Response Groups		Toxicity Groups	
Product Characteristics	**Cmax Cells/ µL Median (Min, Max)**	**AUC_{0-28d} Day*Cells/µL Median (Min, Max)**	**Responder N (%)**	**Nonresponder N (%)**	**Grade 3 or higher neurologic event N (%)**	**Grade 3 or higher cytokine release syndrome N (%)**
(b) (4)						

6.1.2.2 Exposure-Response Relationship

6.1.2.2.1. Exposure-Efficacy Relationship

The relationship between KTE-X19 exposure and efficacy was based on the clinical reviewer's assessment of best overall response (BOR) for ZUMA-1 Cohort 1 subjects.

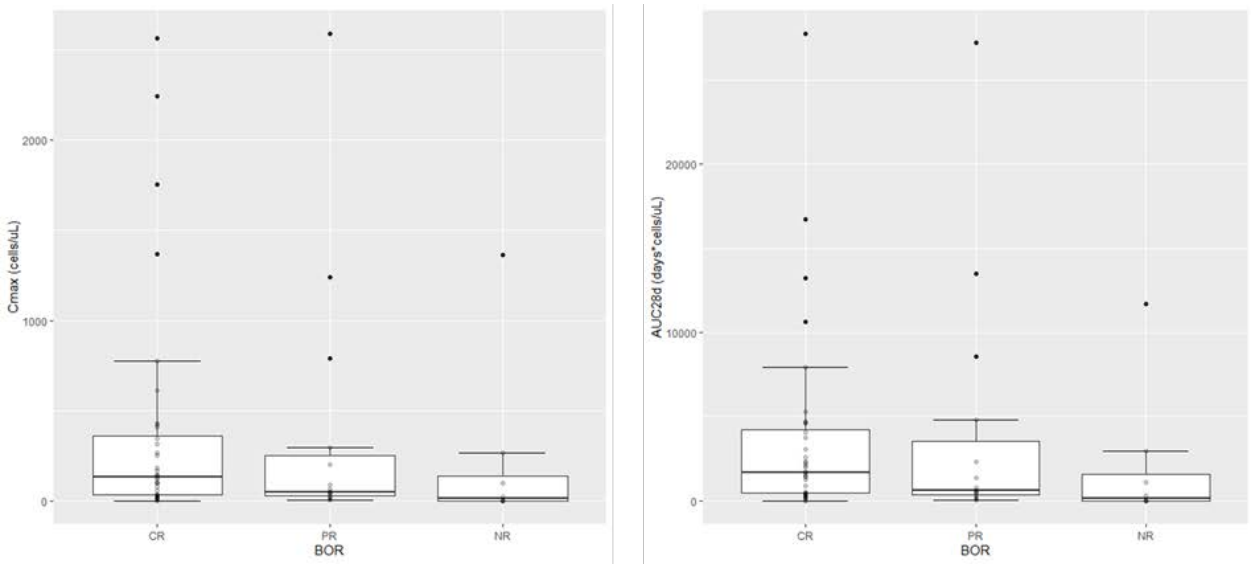
A summary of the comparison of KTE-X19 pharmacokinetic parameters between responding and non-responding subjects is provided in Table 6 below. As shown in Figure 2, the median values of Cmax and AUC_{0-28d} of KTE-X19 were higher in responding (R) subjects [complete response (CR) or partial response (PR)] than that in non-responding (NR) [stable disease (SD),

progressive disease (PD)] subjects (Wilcoxon rank-sum test for Cmax: p=0.057; Wilcoxon rank-sum test for $AUC_{0\text{-}28d}$: p=0.054).

Table 6. Comparison of KTE-X19 (anti-CD19 CAR+ viable T cells) pharmacokinetic parameters between responding and non-responding subjects

Parameters (Unit)	Unit	Responding Subjects N=52	Non-Responding Subjects N=8
Cmax [median (min, max)]	cells/µL	102.4 (0.2, 2589.5)	12.0 (0.2, 1364.0)
Tmax [median, (min, max)]	days	15 (8, 31)	11.5 (8, 16)
$AUC_{(0\text{-}28d)}$ [median, (min, max)]	days*cells/µL	1487.0 (3.8, 27743.6)	169.5 (1.8, 11691.1)

Figure 2. Boxplot of KTE-X19 exposure by best overall response (BOR)



6.1.2.2.2. Exposure-Safety Relationship

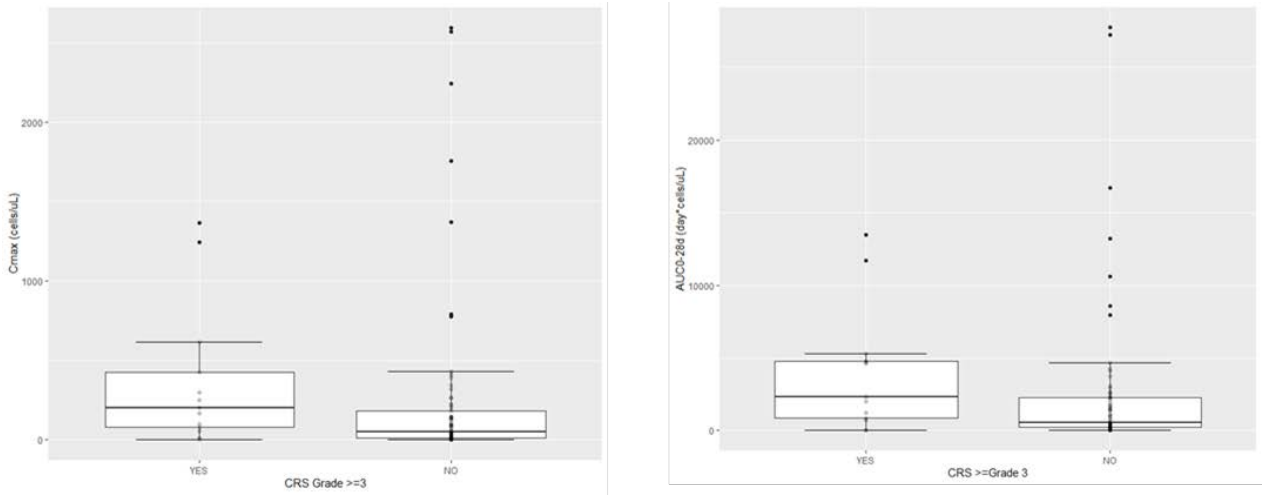
Exposure and Cytokine Release Syndrome (CRS)

The impact of KTE-X19 exposure on cytokine release syndrome (CRS) was evaluated using data from both Cohort 1 & Cohort 2. As shown in Table 7 & Figure 3, the median peak levels and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects with Grade 3 or higher CRS were higher compared to subjects with Grade 2, Grade 1 or no CRS (Wilcoxon rank-sum test p value: 0.050 for Cmax, p values: 0.040 for $AUC_{0\text{-}28d}$).

Table 7. Summary of KTE-X19 (anti-CD19 CAR+ viable T cells) exposure and cytokine release syndrome (ZUMA-2, Cohort 1 &2)

Parameters	Cytokine Release Syndrome	
Median (Min, Max)	Grade ≥ 3	Grade ≤ 2
Cmax (cells/µL)	202.6 (1.9, 1364.0)	53.4 (0.16, 2589.5)
$AUC_{0\text{-}28d}$ (days*cells/µL)	2312.3 (43.8, 1.35E+04)	583.4 (1.8, 2.77E+04)
Tmax (days)	15 (8, 17)	15 (8, 31)

Figure 3. Boxplot of CTL019 exposure and cytokine release syndrome (CRS) (ZUMA-2, Cohort 1 & 2)



Exposure and Neurological Events

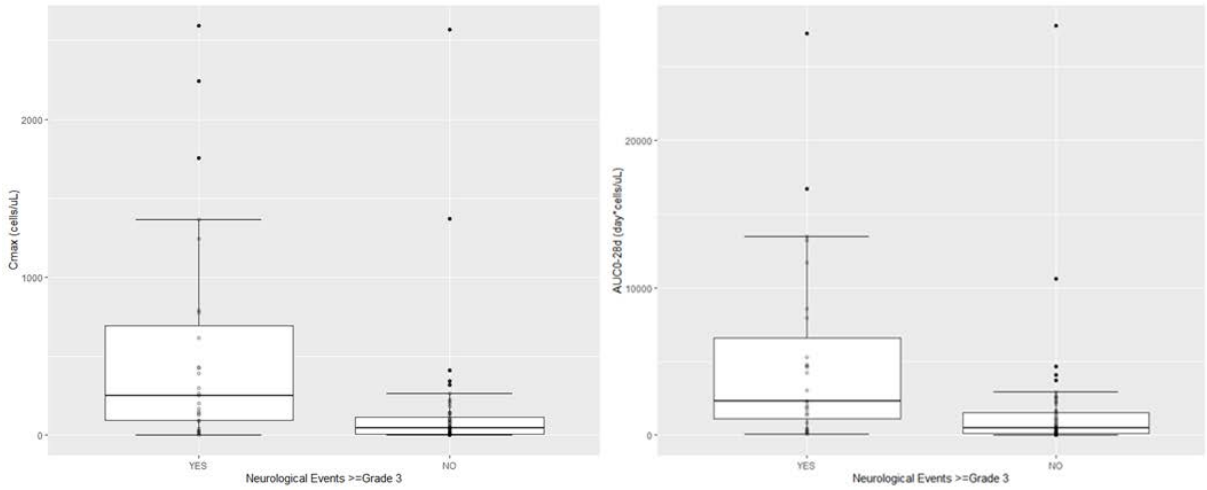
The impact of KTE-X19 exposure on cytokine release syndrome (CRS) was also evaluated. Subjects with Grade 3 or higher neurologic events had substantial higher KTE-X19 exposure than subjects with Grade 2, Grade 1 or no CRS (Wilcoxon rank-sum test p value: 0.00004 for Cmax, p values: 0.00008 for $AUC_{0\text{-}28d}$).

Table 8. Summary of KTE-X19 (anti-CD19 CAR+ viable T cells) exposure and neurological events (ZUMA-2, Cohort 1 &2)

Parameters	Neurological Events	
Median (Min, Max)	Grade ≥ 3	Grade ≤ 2
Cmax (cells/µL)	249.6 (2.9, 2589.5)	44.4 (0.16, 2565.8)
$AUC_{0\text{-}28d}$	2312.3	492.3

(days*cells/µL)	(64.6, 2.73E+04)	(1.8, 2.77E+04)
Tmax (days) [median, range]	15 (8, 30)	15 (8, 31)

Figure 4. Boxplot of KTE-X19 exposure and neurologic events (ZUMA-2, Cohort 1 & Cohort 2)



6.1.2.3 Pharmacodynamics

Conditioning chemotherapy (lymphodepletion) and CAR-T cells infusion followed by CAR-T cell activation are associated with serum level changes of pro-inflammatory cytokines, modulating cytokines, chemokines, and effector molecules. To assess pharmacodynamic (PD) effects of KTE-X19, a panel of 40 biomarker analytes were measured. A subset of 17 analytes that were associated previously anti-CD19 CAR T-cell therapy were preselected for evaluation.

As shown in Tables 9 and 10, in cohort 1, after conditioning chemotherapy and prior to infusion (Day0) of KTE-19, median serum levels of CRP, ferritin, and IL-7 increased by ~ 2-3 folds compared to baseline levels (prior to conditioning chemotherapy). On Day 0, prior to KTE-X19, median serum levels of IL-15 had ~ 10-fold increase compared to baseline levels. Median serum perforin levels decreased during the same time period.

After KTE-X19 infusion, majority of these 17 key analytes serum levels increased except for TNF-α and VCAM-1). The median time to peak for all key analytes ranged from 4 to 8 days post-infusion. Four weeks after KTE-X19 infusion, the majority of the key analytes returned to near- or below baseline levels except 6 analytes (CXCL10, ferritin, IFN-γ, IL-6, IL-8, and IL-15) remained elevated by 2-fold or more in ≥ 20% of subjects.

The PD biomarker serum level changes in Cohort 2 were similar to Cohort 1, except for CRP, granzyme B and IL-6. The values of median peak levels and median AUC (baseline to Day 28 post-dose) of these 3 analytes in Cohort 1 were about 150-200% of that in Cohort 2.

Table 9. Number of Subjects with a 2-fold or Higher Change from Baseline at Peak in Key Analytes (Cohort 1, N=68)

Cytokine[a]	Baseline Median (n, Min, Max)	Day 0 Median (n, Min, Max)	Week 4 Median (n, Min, Max)	Peak Median (n, Min, Max)	AUC Median (n, Min, Max)	Time to Peak Median (n, Min, Max)
CRP (mg/L)	13.47 (66, 0.50, 496.00[b])	30.33 (66, 1.41, 496.00[b])	0.65 (65, 2.76E-05[b], 496.00[b])	113.95 (68, 4.33, 496.00[b])	869.87 (67, 33.25, 1.50E+04)	4 (68, 1, 17)
CXCL10 (pg/mL)	468.75 (66, 103.20, 2000.00[b])	529.75 (66, 114.30, 2000.00[b])	546.60 (65, 75.60, 2000.00[b])	2000.00[b] (68, 256.60, 2000.00[b])	2.52E+04 (67, 6935.75, 5.97E+04)	8 (68, 1, 31)
Ferritin (ng/mL)	189.05 (66, 0.78[b,c], 4003.70)	504.62 (66, 0.78[b,c], 3022.70)	597.10 (65, 0.78[b,c], 1.24E+04)	1302.41 (68, 0.80[b,c], 2.50E+04[b,c])	2.77E+04 (67, 25.60, 3.68E+05)	8 (68, 1, 30)
Granzyme B (pg/mL)	1.00[b] (66, 1.00[b], 76.60)	1.00[b] (66, 1.00[b], 77.90)	1.00[b] (65, 1.00[b], 430.60)	40.60 (68, 1.00[b], 6024.40)	347.95 (67, 32.00, 3.37E+04)	8 (68, 1, 31)
ICAM-1 (ng/mL)	649.67 (66, 120.30, 4.31E+04)	682.39 (66, 136.55, 3.62E+04)	564.44 (65, 105.07, 3.32E+04)	1252.07 (68, 230.12, 6.06E+04)	2.54E+04 (67, 4179.33, 1.17E+06)	8 (68, 1, 31)
IFN-γ (pg/mL)	7.50[b] (66, 7.50[b], 165.40)	7.50[b] (66, 7.50[b], 144.80)	24.00 (65, 7.50[b], 800.00)	410.25 (68, 7.50[b], 1876.00[b])	3402.55 (67, 135.00, 2.66E+04)	8 (68, 1, 29)
IL-1RA (pg/mL)	565.80 (66, 140.50, 2233.62)	518.95 (66, 105.00, 4000.00[b,c])	399.70 (65, 31.20[b], 3080.50)	1782.65 (68, 158.40, 9000.00[b,c])	2.71E+04 (67, 4471.05, 1.10E+05)	8 (68, 1, 31)
IL-2 (pg/mL)	0.90[b] (66, 0.90[b], 3.00)	0.90[b] (66, 0.90[b], 3.50)	0.90[b] (65, 0.90[b], 2.20)	5.85 (68, 0.90[b], 77.60)	57.85 (67, 16.20, 306.35)	4 (68, 1, 17)
IL-2Rα (ng/mL)	5.02 (66, 0.08[b,c], 29.62)	5.79 (66, 0.08[b,c], 43.79)	3.49 (65, 0.08[b,c], 66.80)	18.72 (68, 2.20, 100.00[b])	295.47 (67, 27.63, 2188.00)	8 (68, 1, 24)
IL-6 (pg/mL)	1.60[b] (66, 1.60[b], 27.00)	1.60[b] (66, 1.60[b], 31.40)	21.20 (65, 1.60[b], 976.00[b])	86.00 (68, 1.60[b], 976.00[b])	1071.00 (67, 51.20, 2.30E+04)	8 (68, 1, 31)
IL-7 (pg/mL)	15.61 (66, 4.00, 42.50)	27.95 (66, 13.40, 63.20)	18.20 (65, 1.40[b], 44.90)	32.20 (68, 16.30, 72.80)	741.20 (67, 143.95, 1599.05)	4 (68, 1, 32)
IL-8 (pg/mL)	10.91 (66, 3.50, 148.60)	11.80 (66, 1.10[b], 446.90)	14.30 (65, 3.30, 653.60)	41.19 (68, 9.60, 750.00[b])	588.05 (67, 163.85, 1.00E+04)	8 (68, 1, 32)

Cytokine[a]	Baseline Median (n, Min, Max)	Day 0 Median (n, Min, Max)	Week 4 Median (n, Min, Max)	Peak Median (n, Min, Max)	AUC Median (n, Min, Max)	Time to Peak Median (n, Min, Max)
IL-10 (pg/mL)	0.70[b] (66, 0.70[b], 14.10)	0.70[b] (66, 0.70[b], 132.60)	0.70[b] (65, 0.70[b], 35.90)	16.55 (68, 0.70[b], 246.10)	155.40 (67, 22.40, 2364.00)	8 (68, 1, 30)
IL-15 (pg/mL)	3.30 (66, 1.40[b], 7.60)	32.70 (66, 13.10, 79.10)	6.10 (65, 1.40[b], 98.00)	40.30 (68, 13.70, 188.70)	548.30 (67, 228.25, 2383.95)	4 (68, 1, 29)
Perforin (ng/mL)	15.82 (66, 2.21, 100.00[b])	3.54 (66, 0.01[b], 74.52)	13.50 (65, 1.76, 45.21)	18.71 (68, 0.69, 100.00[b])	394.80 (67, 47.88, 1372.14)	22 (68, 1, 32)
TNF-α (pg/mL)	8.00 (66, 0.70[b], 174.60)	5.70 (66, 0.70[b], 79.10)	3.10 (65, 0.70[b], 27.70)	9.50 (68, 2.00, 116.57)	169.15 (67, 44.60, 1230.90)	8 (68, 1, 32)
VCAM-1 (ng/mL)	1162.89 (66, 0.04[b], 1.57E+05)	1143.15 (66, 0.04[b], 9.79E+04)	1003.94 (65, 0.04[b], 8.58E+04)	1843.57 (68, 503.80, 1.56E+05)	3.87E+04 (67, 4772.41, 3.51E+06)	8 (68, 1, 32)

Data cutoff date = 24JUL2019

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; CXCL, C-X-C motif chemokine; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IL-2Rα, interleukin-2 receptor alpha; LLOQ, lower limit of quantification; Max, maximum; Min, minimum; TNF, tumor necrosis factor; ULOQ, upper limit of quantification; VCAM, vascular cell adhesion molecule.

Notes: Peak is defined as the maximum post-baseline level of the cytokine from baseline to Week 4. AUC measures the total levels of cytokine over time, and is defined as the AUC in a plot of levels of cytokine against scheduled visit from baseline (Day -4) to Day 28. Time to peak is defined as number of days from KTE-X19 infusion to the date when the cytokine first reached the maximum post-baseline level. Due to the timing of samples collected immediately after infusion (Day 3, Day 7, Day 14, Day 28), the calculated values for peak, AUC¬, and time to peak are considered estimates.

Source: applicant submission: Table 4 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 19-20.

Table 10. Summary of levels of key analytes in serum and time to peak serum levels (Cohort 1, N=68)

Cytokine	At Peak (N = 68) n (%)	At Day 0 (N = 66) n (%)	At Day 3 (N = 63) n (%)	At Day 7 (N = 62) n (%)	At Week 2 (N = 61) n (%)	At Week 4 (N = 65) n (%)
CRP	51 (75.0)	33 (50.0)	39 (61.9)	36 (58.1)	10 (16.4)	3 (4.6)
CXCL10	43 (63.2)	7 (10.6)	23 (36.5)	38 (61.3)	13 (21.3)	17 (26.2)
Ferritin	56 (82.4)	27 (40.9)	34 (54.0)	42 (67.7)	43 (70.5)	29 (44.6)
Granzyme B[a]	43 (63.2)	2 (3.0)	25 (39.7)	35 (56.5)	9 (14.8)	8 (12.3)
ICAM-1	16 (23.5)	0 (0)	5 (7.9)	13 (21.0)	4 (6.6)	1 (1.5)
IFN-γ [a]	59 (86.8)	12 (18.2)	45 (71.4)	47 (75.8)	21 (34.4)	33 (50.8)
IL-1RA	42 (61.8)	12 (18.2)	15 (23.8)	29 (46.8)	3 (4.9)	7 (10.8)
IL-10[a]	59 (86.8)	9 (13.6)	39 (61.9)	50 (80.6)	18 (29.5)	11 (16.9)
IL-15	66 (97.1)	65 (98.5)	61 (96.8)	58 (93.5)	48 (78.7)	32 (49.2)
IL-2[a]	59 (86.8)	3 (4.5)	49 (77.8)	23 (37.1)	3 (4.9)	1 (1.5)
IL-2Rα	50 (73.5)	10 (15.2)	27 (42.9)	41 (66.1)	33 (54.1)	9 (13.8)
IL-6[a]	61 (89.7)	12 (18.2)	38 (60.3)	48 (77.4)	45 (73.8)	50 (76.9)
IL-7	38 (55.9)	33 (50.0)	20 (31.7)	18 (29.0)	14 (23.0)	8 (12.3)
IL-8	52 (76.5)	12 (18.2)	35 (55.6)	35 (56.5)	16 (26.2)	16 (24.6)
Perforin	12 (17.6)	0 (0)	0 (0)	8 (12.9)	2 (3.3)	4 (6.2)
TNF-α	20 (29.4)	2 (3.0)	8 (12.7)	12 (19.4)	2 (3.3)	3 (4.6)
VCAM-1	9 (13.2)	2 (3.0)	1 (1.6)	6 (9.7)	0 (0)	2 (3.1)

Data cutoff date = 24JUL2019

Abbreviations: CRP, C-reactive protein; CXCL, C-X-C motif chemokine; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IL-2Rα, interleukin-2 receptor alpha; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Notes: Peak is defined as the maximum post-baseline level of the cytokine from baseline to Week 4. The fold change is defined as the concentration at each visit divided by the concentration at baseline, for each subject. The number and percentage of subjects with a 2-fold or greater change from baseline is presented.

a Because the median baseline levels of these cytokines were below the lower limit of quantification, the true fold change over baseline at peak and later time points is not determinable.

Source: applicant submission: Table 5 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 21.

PD Biomarkers and Safety Analysis

An exploratory correlative analysis was conducted to evaluate associations between PD biomarkers levels and safety endpoints (cytokines release syndrome (CRS) and neurologic events) for Cohort 1 subjects.

PD Biomarkers and CRS

Of 17 key analytes, the median peak serum levels of following 9 analytes in subjects with Grade 3 or higher CRS were higher (nominal Wilcoxon rank-sum p values ≤ 0.05) than in subjects with Grade 2, Grade 1, or no CRS: ferritin, granzyme B, IL-2Rα, IL-6, IL-8, IL-10, IL-15, perforin, and TNF-α.

PD Biomarkers and Neurologic Events

Of the 17 key analytes, the median peak serum levels of following 8 analytes were higher (norminal Wilcoxon rank-sum p values ≤ 0.05) among subjects who experienced Grade 3 or higher neurologic events versus Grade 2, Grade 1, or no neurologic events: granzyme B, IFN-γ, IL-1RA, IL-2, IL-6, IL-10, IL-15, and TNF-α.

PD Biomarkers in Cerebrospinal Fluid (CSF)

To elucidate the pathophysiology of neurologic events following KTE-X19 treatment, CSF samples were collected from subjects optionally prior to KTE-X19 infusion, after infusion, or after a Grade 2 or higher neurologic event. Cytokines and immune effector molecules were analyzed. The applicant also planned an exploratory phenotypic analysis of immune cell subsets in CSF using (b) (4) . However, due to very low subject numbers and low cell counts, the Applicant concluded that the data could not be interpreted, and as such, these data were not submitted.

Compared to the median baseline levels, the median baseline levels, the medians of 3 pro-inflammatory cytokines (CRP, CXCL-10, and IL6) were at least 5-fold higher. However, due to high inter-subject variability and small sample size, the data should be interpreted with caution (Table 11).

As shown in Table 12, median CSF levels of 7 analytes were elevated in subjects with Grade 3 or higher neurologic event compared to levels in subjects with Grade 2, Grade 1, or no neurologic event: CRP, ferritin, ICAM-1, IL-2Rα, IL-6, IL-8, and VCAM-1. Due to low sample size, the result should be interpreted with caution.

Table 11. Changes in CSF Analytes Following Infusion of KTE-X19 (Cohort 1)

Cytokine	Baseline Median (n, Min, Max)	Post-baseline Median (n, Min, Max)
CRP (mg/L)	0.03 (4, 5.62E-03, 0.17)	0.15 (15, 0.01, 4.96[a])
CXCL10 (pg/mL)	444.85 (4, 40.50, 2102.40)	6578.30 (14, 1493.30, 5.00E+04[a])
Ferritin (ng/mL)	8.24 (2, 5.92, 10.57)	12.33 (10, 4.54, 632.40[a])
Granzyme B (pg/mL)	0.75 (4, 0.50[a,b], 1.00[a,b])	1.00 (14, 0.50[a,b], 7.10)
ICAM-1 (ng/mL)	3.31 (4, 1.85, 4.23)	9.82 (15, 3.17, 86.00)
IFN-γ (pg/mL)	7.50[a] (4, 7.50[a], 7.50[a])	7.50[a] (14, 7.50[a], 1259.90)
IL-1RA (pg/mL)	25.10 (4, 15.60[a], 53.50)	65.50 (14, 15.60[a], 5740.70)
IL-2 (pg/mL)	0.90[a] (4, 0.90[a], 0.90[a])	0.90[a] (14, 0.90[a], 0.90[a])
IL-2Rα (ng/mL)	0.08 (4, 3.90E-03[a,c], 0.13)	0.21 (14, 0.04, 6.09)
IL-6 (pg/mL)	1.60[a] (4, 1.60[a], 1.60[a])	19.80 (14, 1.60[a], 570.10)
IL-7 (pg/mL)	1.40[a] (4, 1.40[a], 1.40[a])	1.40[a] (14, 1.40[a], 4.10)
IL-8 (pg/mL)	48.10 (4, 30.20, 54.20)	60.95 (14, 19.90, 750.00[a])
IL-10 (pg/mL)	0.70[a] (4, 0.70[a], 0.70[a])	0.70[a] (14, 0.70[a], 19.90[a])
IL-15 (pg/mL)	2.80 (4, 1.40[a], 5.40)	7.80 (14, 1.40[a], 67.10)
Perforin (ng/mL)	7.50E-03[a] (4, 5.00E-03[a], 0.01[a])	0.01[a] (14, 5.00E-03[a], 0.01[a])
TNF-α (pg/mL)	0.70[a] (4, 0.70[a], 0.70[a])	0.70[a] (14, 0.70[a], 3.80)
VCAM-1 (ng/mL)	10.32 (4, 4.71, 12.32)	16.39 (15, 6.18, 46.77)

Data cutoff date = 24JUL2019

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; CXCL10, C-X-C motif chemokine ligand 10; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-gamma; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IL-2Rα, interleukin-2 receptor alpha; LLOQ, lower limit of quantification; Max, maximum; Min, minimum; TNF-α, tumor necrosis factor; ULOQ, upper limit of quantification; VCAM-1, vascular cell adhesion molecule-1.

Notes: Because of the limited sample size, any data arising from a lumbar puncture performed after KTE-X19 infusion is combined into a "post-baseline" analysis set. Sampling times ranged from Day 7 to Day 109 after KTE-X19 infusion.

a Reported values represent an assigned numerical value given to results that fell outside the dilution-corrected limit of quantification.

b For some cytokines, 2 imputed below-LLOQ values were assigned; therefore, either may be reported and both represent a result below the LLOQ in this table.

c For 3 of the cytokines presented here (ferritin, IL-1RA, and IL-2Rα), 2 assays were used during the course of the study as more sensitive methods of quantification became available; assigned, imputed values for LLOQ and ULOQ for all assays used in the study are provided in Appendix 7.2. As a consequence of the use of 2 different assays for some cytokines, imputed LLOQ and ULOQ values reported in this table may vary depending on which assay was used for a particular data point.

Source: applicant submission: Table 15 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 65.

Table 12. Potential Associations of CSF cytokines with neurologic event (Cohort 1)

Cytokine	Grade 3 or Higher (N = 12) Median (n, Min, Max)[a]	Grade 2, Grade 1, or None (N = 5) Median (n, Min, Max)[a]	Median Ratio
CRP (mg/L)	0.16 (10, 0.02, 4.96[a])	0.09 (5, 0.01, 0.47)	1.80
CXCL10 (pg/mL)	5519.20 (9, 1493.30, 5.00E+04[a])	2.01E+04 (5, 1711.20, 2.49E+04)	0.28
Ferritin (ng/mL)	18.39 (6, 10.01, 632.40[a])	7.42 (4, 4.54, 8.57)	2.48
Granzyme B (pg/mL)	1.00[a,b] (9, 0.50[a,b], 7.10)	1.00[a,b] (5, 0.50[a,b], 1.00[a,b])	1.00
ICAM-1 (ng/mL)	11.00 (10, 3.17, 86.00)	4.34 (5, 3.23, 9.65)	2.54
IFN-γ (pg/mL)	7.50[a] (9, 7.50[a], 1259.90)	15.70 (5, 7.50[a], 140.70)	0.48
IL-1RA (pg/mL)	63.30 (9, 28.20, 5740.70)	67.70 (5, 15.60[a,c], 184.50)	0.94
IL-2 (pg/mL)	0.90[a] (9, 0.90[a], 0.90[a])	0.90[a] (5, 0.90[a], 0.90[a])	1.00
IL-2Rα (ng/mL)	0.36 (9, 0.04, 6.09)	0.16 (5, 0.04, 0.28)	2.21
IL-6 (pg/mL)	23.70 (9, 1.60[a], 570.10)	5.80 (5, 1.60[a], 32.20)	4.09
IL-7 (pg/mL)	1.40[a] (9, 1.40[a], 4.10)	1.40[a] (5, 1.40[a], 3.10)	1.00
IL-8 (pg/mL)	85.30 (9, 19.90, 750.00[a])	38.80 (5, 38.30, 131.00)	2.20
IL-10 (pg/mL)	0.70[a] (9, 0.70[a], 19.90)	0.70[a] (5, 0.70[a], 0.70[a])	1.00
IL-15 (pg/mL)	6.40 (9, 1.40[a], 67.10)	9.90 (5, 3.30, 15.90)	0.65
Perforin (ng/mL)	0.01[a,b] (9, 5.00E-03[a,b], 0.01[a,b])	0.01 (5, 5.00E-03[a,b], 0.01[a,b])	1.00
TNF-α (pg/mL)	0.70[a] (9, 0.70[a], 3.80)	0.70[a] (5, 0.70[a], 0.70[a])	1.00
VCAM-1 (ng/mL)	17.93 (10, 7.69, 46.77)	9.20 (5, 6.18, 15.35)	1.95

Data cutoff date = 24JUL2019
Abbreviations: CSF, cerebrospinal fluid; CRP, C-reactive protein; CXCL10, C-X-C motif chemokine ligand 10; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-gamma; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IL-2R alpha, interleukin-2 receptor alpha; Max, maximum; Min, minimum; VCAM-1, vascular cell adhesion molecule-1.
Notes: The median ratio is defined as the ratio of median value for Grade 3 or higher events divided by median value for Grade 2, Grade 1, or no events. Multiplicity adjustment was not performed; therefore, p values should be considered a signal but are exploratory only and do not indicate statistical significance.

a Reported values represent an assigned numerical value given to results that fell outside the dilution-corrected limit of quantification.

b For some cytokines, 2 imputed below-LLOQ values were assigned; therefore, either may be reported and both represent a result below the LLOQ in this table.

c For 3 of the cytokines presented here (ferritin, IL-1RA, and IL-2Rα), 2 assays were used during the course of the study as more sensitive methods of quantification became available; assigned, imputed values for LLOQ and ULOQ for all assays used in the study are provided in Appendix 7.2. As a consequence of the use of 2 different assays for some cytokines, imputed LLOQ and ULOQ values reported in this table may vary depending on which assay was used for a particular data point.

Source: applicant submission: Table 16 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 67.

6.1.2.4 Immunogenicity

For immunogenicity assessment, the applicant monitored presence of binding antibodies against FMC63. FMC63 is the parental murine anti-human CD19 antibody used for development of the anti-CD19 variable regions of the CAR construct. The immunogenicity testing included an initial screening testing with an enzyme-linked immunosorbent assay (ELISA). Positive samples underwent further confirmatory testing using a cell-based assay to confirm whether the positive

signal observed in the screening assay was due to binding of a properly folded scFv expressed on an anti-CD19 CAR.

Results from the initial screening assay showed 17 subjects had positive test results (14 subjects in Cohort 1 and 3 subjects in Cohort 2). Further confirmatory assay testing demonstrated that all 17 subjects were antibody negative at all time points tested.

6.1.2.5 B-cell Aplasia

Treatment of KTE-X19 may induce B-cell aplasia. The incidence of B-cell aplasia was assessed using a (b) (4) assay.

Treatment of KTE-X19 induced B-cell aplasia in majority of subjects. At baseline, after conditioning chemotherapy but before KTE-X19 infusion, median B-cell levels in all subjects in Cohort 1 were 8.73% of viable leukocytes (range: 0.02-95.24%). At Month 3, median B-cell levels declined to 0.09% (range: 0.02-96.15%). Median B-cell levels was recovered to 10.62% (range: 3.97-15.99%) by Month 18 in evaluable subjects.

B-cell levels, and KTE-X19 levels were analyzed by objective response (Table 13). At Month 24, 6 of 8 subjects in ongoing response had B-cell recovery and detectable KTE-X19 cells. This indicated that ongoing B-cell aplasia at Month 24 was not required for maintaining disease response. The CAR T-cells detected in these subjects may be non-functional anti-CD19 CAR T cells. In non-responding subjects, the percentage of B-cell levels increased from baseline at Month 3 and 6 post-infusion. This observation suggested there may be non-functional CAR T-cells in nonresponders.

Table 13. B-cell recovery following KTE-X19 infusion in subjects with ongoing response (ZUMA-2, Cohort1)

	Ongoing Response (N = 34)			Relapsed (N = 17)			Nonresponder (N = 4)		
	n (%)	B cell (%)[a] Median (Min, Max)	CAR T cells Median (Min, Max)	n (%)	B cell (%)[a] Median (Min, Max)	CAR T cells Median (Min, Max)	n (%)	B cell (%)[a] Median (Min, Max)	CAR T cells Median (Min, Max)
Baseline – all subjects	32 (94.1)	10.58 (0.08, 88.10)	<LLOQ	16 (94.1)	7.07 (0.03, 90.03)	<LLOQ	4 (100.0)	35.72 (6.12, 95.24)	< LLOQ
B cells below LLOQ	8 (25.0)		<LLOQ	1 (6.3)		<LLOQ			
B cells detectable	24 (75.0)	10.58 (0.08, 88.10)	<LLOQ	15 (93.8)	7.07 (0.03, 90.03)	<LLOQ	4 (100.0)	35.72 (6.12, 95.24)	< LLOQ
Month 3 – all subjects	29 (85.3)	0.04 (0.02, 0.27)	1.04 (0.04, 7.50)	10 (58.8)	0.17 (0.02, 39.81)	0.74 (< LLOQ, 6.06)	2 (50.0)	57.21 (18.27, 96.15)	< LLOQ
B cells below LLOQ	17 (58.6)		0.70 (0.04, 4.06)	2 (20.0)		2.32 (1.34, 3.30)			
B cells detectable	12 (41.4)	0.04 (0.02, 0.27)	1.14 (0.10, 7.50)	8 (80.0)	0.17 (0.02, 39.81)	0.22 (< LLOQ, 6.06)	2 (100.0)	57.21 (18.27, 96.15)	< LLOQ
Month 6 – all subjects	34 (100.0)	0.07 (0.02, 25.72)	0.55 (< LLOQ, 2.98)	9 (52.9)	8.90 (0.23, 86.58)	0.10 (< LLOQ, 0.83)	1 (25.0)	64.47 (64.47, 64.47)	< LLOQ
B cells below LLOQ	13 (38.2)		0.89 (< LLOQ, 2.53)	1 (11.1)		0.83 (0.83, 0.83)			
B cells detectable	21 (61.8)	0.07 (0.02, 25.72)	0.24 (< LLOQ, 2.98)	7 (77.8)	8.90 (0.23, 86.58)	0.06 (< LLOQ, 0.33)	1 (100.0)	64.47 (64.47, 64.47)	< LLOQ
Month 12 – all subjects	11 (32.4)	1.54 (0.07, 29.43)	0.54 (< LLOQ, 5.40)	2 (11.8)	18.71 (18.71, 18.71)	0.26 (0.03, 0.49)		NA	NA
B cells below LLOQ	6 (54.5)		0.77 (< LLOQ, 5.40)	1 (50.0)		0.49 (0.49, 0.49)		NA	NA
B cells detectable	5 (45.5)	1.54 (0.07, 29.43)	0.06 (< LLOQ, 0.72)	1 (50.0)	18.71 (18.71, 18.71)	0.03 (0.03, 0.03)		NA	NA

	Ongoing Response (N = 34)			Relapsed (N = 17)			Nonresponder (N = 4)		
	n (%)	B cell (%)[a] Median (Min, Max)	CAR T cells Median (Min, Max)	n (%)	B cell (%)[a] Median (Min, Max)	CAR T cells Median (Min, Max)	n (%)	B cell (%)[a] Median (Min, Max)	CAR T cells Median (Min, Max)
Month 15 – all subjects	10 (29.4)	4.43 (0.02, 42.10)	0.44 (< LLOQ, 4.36)	3 (17.6)	20.46 (19.36, 21.56)	0.34 (< LLOQ, 0.54)		NA	NA
B cells below LLOQ	3 (30.0)		0.90 (0.09, 4.36)	1 (33.3)		0.54 (0.54, 0.54)		NA	NA
B cells detectable	7 (70.0)	4.43 (0.02, 42.10)	0.34 (< LLOQ, 0.62)	2 (66.7)	20.46 (19.36, 21.56)	0.17 (< LLOQ, 0.34)		NA	NA
Month 18 – all subjects	11 (32.4)	7.94 (0.04, 31.89)	0.24 (< LLOQ, 3.17)	1 (5.9)	15.99 (15.99, 15.99)	0.31 (0.31, 0.31)		NA	NA
B cells below LLOQ	6 (54.5)		1.19 (0.21, 3.17)					NA	NA
B cells detectable	5 (45.5)	7.94 (0.04, 31.89)	0.02 (< LLOQ, 0.24)	1 (100.0)	15.99 (15.99, 15.99)	0.31 (0.31, 0.31)		NA	NA
Month 24 – all subjects	8 (23.5)	9.07 (0.03, 45.38)	0.05 (< LLOQ, 0.62)	1 (5.9)	13.37 (13.37, 13.37)			NA	NA
B cells below LLOQ	2 (25.0)		0.35 (0.08, 0.62)					NA	NA
B cells detectable	6 (75.0)	9.07 (0.03, 45.38)	0.02 (< LLOQ, 0.54)	1 (100.0)	13.37 (13.37, 13.37)			NA	NA

Data cutoff date = 24JUL2019

Abbreviations: CAR, chimeric antigen receptor; LLOQ, lower limit of quantification; Max, maximum; Min, minimum; NA, not applicable.

Notes: Ongoing response data for ZUMA-2 are based on the first 60 subjects who received KTE-X19 in ZUMA-2 Cohort 1, and had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment (inferential analysis set). Nonresponders are defined as subjects experiencing best response of stable or progressive disease. Blank cells indicate a value that below the lower limit of quantification or was not measured. 'NA' indicates time points for which no data are available. Four subjects were censored and excluded from this analysis because they had a new anti-cancer therapy, and 1 subject was excluded because of consent withdrawal.

a B-cell levels are given as a percentage representing the number of $CD19^+$, $CD20^+$ or $CD19^+CD20^+$ B cells relative to viable CD45 lymphocytes.

Source: applicant submission: Table 12 in section 5.3.4.2. ZUMA-2 Pharmacokinetics/ Pharmacodynamics Report, page 59-60.

6.1.2.6 Replication-competent Retrovirus (RCR)

KTE-X19 comprises retroviral vector transduced T cells, the presence of replication-competent retrovirus (RCR) in the blood of treated subjects were monitored during the study. No subjects were found to be RCR positive at any time.

6.1.3 Conclusions

- General pharmacokinetics/cellular kinetics of KTE-X19:
  - Following infusion, KTE-X19 exhibited an initial rapid expansion phase followed by a rapid decline and then a gradual decrease. The median time to reach peak levels of KTE-X19 in blood was 15 days post-infusion.
  - At the dose of 2×10^6 anti-CD19 CAR T cells/kg, KTE-X19 levels decreased to near baseline at Month 3 post-infusion. KTE-X19 was detectable in some adult subjects with r/r MCL up to 24 months in peripheral blood at the time of the data cutoff date.
  - At the dose of 0.5×10^6 anti-CD19 CAR T cells/kg, the peak levels and $AUC_{0\text{-}28d}$ of KTE-X19 were approximately 60% of that in subjects treated at the dose of 2×10^6 anti-CD19 CAR T cells/kg. KTE-X19 levels decreased to undetectable levels in majority of the evaluable subjects by 15 months post-dose.

- KTE-X19 pharmacokinetics/cellular kinetics in specific populations:
  - KTE-X19 exposure (Cmax and $AUC_{0\text{-}28d}$) was numerically higher in subjects < 65 years of age compared to subjects ≥ 65 years of age. However, with limitations imposed by high inter-subject variability of KTE-X19 exposure, small sample size, and other factors such as tumor burden, the impact of age on KTE-X19 exposure should be interpreted with caution.
  - KTE-X19 exposure were similar between male and female subjects.
  - Baseline tumor burden did not show a monotonic association with KTE-X19 expansion.
  - Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with KTE-X19. Subjects who received both tocilizumab and corticosteroids higher KTE-X19 exposure than subjects who received either medication alone or neither medication. These observations are confounded by the fact that the need for tocilizumab and/or corticosteroids was triggered by toxicity, which was associated with higher KTE-X19 exposures.

- After infusion, substantially higher median values of Cmax and $AUC_{0\text{-}28d}$ of KTE-X19 were reported in responders [complete response (CR) and partial response (PR)] compared to non-responders.

- Higher KTE-X19 exposure (Cmax and $AUC_{0\text{-}28d}$) were reported in subjects with higher grades of CRS or neurologic event (Grade 3 or higher versus Grade 2, Grade 1, or no events).

- After KTE-X19 infusion, substantial elevation in peak levels and $AUC_{0\text{-}28d}$ were observed in subjects with Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1 or no CRS for following biomarkers: ferritin, granzyme B, IL-2Rα, IL-6, IL-8, IL-10, IL-15, perforin, and TNF-α.

- After KTE-X19 infusion, substantial elevation in peak levels and $AUC_{0\text{-}28d}$ were observed in subjects with Grade 3 or higher neurologic event compared to subjects with Grade 2, Grade 1 or no neurologic event for following biomarkers: granzyme B, IFN-γ, IL-1RA, IL-2, IL-6, IL-10, IL-15, and TNF-α.

- Cytokines and immune effector molecules were evaluated in available CSF samples (n=17):
    - Levels of three pro-inflammatory cytokines (CRP, CXCL-10, and IL-6) were at least 5-fold higher than the median baseline values.
    - Median levels of following analytes were substantially elevated in the CSF of subjects with Grade 3 or higher neurologic events compared to levels in subjects who had Grade 2, Grade 1, or no neurologic events: CRP, ferritin, ICAM-1, IL-2Rα, IL-6, IL-8, and VCAM-1.

  Due to high inter-subject variability and small sample size, the data should be interpreted with caution.

- KTE-X19 induced B-cell aplasia in majority of the treated subjects. Median B-cell levels were recovered to 10.62% (range: 3.97-15.99%) by Month 18 in evaluable subjects.

- There was no reported presence of replication-competent retrovirus (RCR) in the blood of KTE-X19 treated subjects.