



**Tecartus<sup>®</sup>**  
(autologous anti-CD19-transduced CD3+ cells)

**Authorization Number: 67884**  
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**Clinical Study Results**

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Gilead Sciences Switzerland Sàrl  
General-Guisan-Strasse 8  
6300 Zug  
Switzerland

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## **1. INTRODUCTION**

As of 2020, Gilead discloses clinical study results of newly authorized products in Switzerland by Swissmedic according to the requirements laid out in Art. 71-73 TPO (Ordinance on Therapeutic Products).

Below you will find the information for clinical studies relevant for the marketing authorization for Tecartus® (autologous anti-CD19-transduced CD3+ cells) in Switzerland.

## 2. OVERVIEW ON CLINICAL STUDIES

Study number	Study title:	Indication:	EudraCT-Number:
KTE-C19-102	A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)	Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton tyrosine kinase (BTK) inhibitor.	2015-005008-27

### 3. STUDY SYNOPSIS KTE-C19-102

#### STUDY SYNOPSIS

##### Study KTE-CC19-102

**Kite Pharma, Inc.**  
**2400 Broadway**  
**Santa Monica, CA**  
**90404 USA**

<b>Title of Study:</b> A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)
<b>Investigators:</b> Multicenter study
<b>Study Centers:</b> This study was conducted at a total of 33 study centers in the US, France, Germany, and The Netherlands.
<b>Publications:</b>  Citations for publications based upon this study are provided below.  Locke F, Wang M, Siddiqi T, Castro J, Shah B, Lee H, et al. ZUMA-2: A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-C19 (Anti-CD19 CAR T cells) in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (r/r MCL). American Society Of Clinical Oncology(ASCO) Annual Meeting 2016.  Wang M, Locke F, Siddiqi T, Castro J, Shah B, Lee H, et al. ZUMA-2: A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-C19 (Anti-CD19 CAR T cells) in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (r/r MCL). European Society for Medical Oncology (ESMO) Congress 2016; Abstract 3305.  Wang M, Locke FL, Munoz J, Goy A, Holmes HE, Siddiqi T, et al. ZUMA-2: Phase 2 Multicenter Study Evaluating Efficacy of Kte-C19 in Patients with Relapsed/Refractory Mantle Cell Lymphoma [Abstract]. J Clin Oncol 2018;36 (Suppl 15):TPS3102.
<b>Study Period:</b>  16 May 2016 (First Subject Screened)  23 July 2019 (Last Observation for the Primary Endpoint)  24 July 2019 (Last Observation for this Report)
<b>Phase of Development:</b> Phase 2
<b>Objectives:</b>  The primary objective was to evaluate the efficacy of KTE-X19, as measured by objective response rate (ORR), in subjects with relapsed/refractory (r/r) mantle cell lymphoma (MCL).  The secondary objectives of this study 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.

**Methodology:** ZUMA-2 is a Phase 2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in subjects with r/r MCL whose disease had progressed on anthracycline-or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib and/or acalabrutinib). The study was designed to evaluate the ORR and durability of response after treatment with KTE-X19.

Up to approximately 130 subjects were to be enrolled into 2 separate cohorts and treated to evaluate the efficacy of KTE-X19. Cohort 1, the pivotal cohort, was to enroll and treat up to approximately 90 subjects with a target dose of  $2 \times 10^6$  anti-CD19 CAR T cells/kg, with up to approximately 80 of these subjects receiving KTE-X19 (10 subjects enrolled in Cohort 1 received axicabtagene ciloleucel; data from these subjects are described in a separate report). Cohort 2 was to enroll and treat up to 40 subjects with KTE-X19 at a target dose of  $0.5 \times 10^6$  anti-CD19 CAR T cells/kg. The first 60 subjects in Cohort 1 who were treated with KTE-X19 were to form the basis for statistical hypothesis testing of the primary endpoint. Data from Cohort 2 were to be descriptive only.

Each subject was to proceed through the following study periods:

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

**Number of Subjects (Planned and Analyzed):**

**Cohort 1:** target dose of  $2 \times 10^6$  anti-CD19 CAR T cells/kg

- Planned: Up to approximately 80 subjects treated with KTE-X19
- Enrolled/leukapheresed: 74 subjects

**Cohort 2:** target dose of  $0.5 \times 10^6$  anti-CD19 CAR T cells/kg

- Planned: Up to 40 subjects treated with KTE-X19
- Enrolled/leukapheresed: 17 subjects

**Diagnosis and Main Criteria for Inclusion:**

Eligible subjects were to be 18 years of age or older with pathologically confirmed MCL that had progressed after or was refractory to anthracycline or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and ibrutinib or acalabrutinib; subjects must have had an Eastern Cooperative Oncology Group performance status of 0 or 1, at least 1 measurable lesion, and no evidence of central nervous system lymphoma

**Duration of Treatment:** Subjects were considered to be enrolled in the study when they commenced leukapheresis to obtain leukocytes (white blood cells) for the manufacturing of KTE-X19. Subjects were to receive a single infusion of KTE-X19. Under circumstances where subjects initially responded and subsequently relapsed, subjects may have been eligible for a second course of conditioning chemotherapy and KTE-X19.

All enrolled subjects were to be followed for survival and disease status (if applicable) for up to approximately 15 years after the last subject had been treated with KTE-X19.

**Test Product, Dose, and Mode of Administration:** KTE-X19 is an autologous chimeric antigen receptor (CAR) T-cell product in which a subject's T cells are engineered to express receptors that result in elimination of CD19-expressing cells. Subjects were to receive a single infusion of KTE-X19 administered intravenously at a target dose of  $2 \times 10^6$  anti-CD19 CAR T cells/kg (Cohort 1) or  $0.5 \times 10^6$  anti-CD19 CAR T cells/kg (Cohort 2). Under circumstances where subjects initially responded and subsequently relapsed, subjects may have been eligible for a second course of conditioning chemotherapy and KTE-X19. KTE-X19 is a subject-specific product, and the intended subject was to be identified by a unique subject ID number.

KTE-X19 was to be administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m<sup>2</sup>/day and cyclophosphamide 500 mg/m<sup>2</sup>/day administered for 3 days. At the discretion of the investigator and after discussion with the medical monitor, bridging therapy could be considered for any subject. Bridging therapy was to be administered after leukapheresis and was to be completed at least 5 days prior to the initiation of conditioning chemotherapy.

After bridging therapy (if applicable), subjects were to receive a 3-day conditioning chemotherapy regimen followed by a 2-day rest period and then were to receive a single infusion of KTE-X19. Subjects who received bridging therapy were required to undergo another PET-CT scan to establish a new baseline prior to receiving conditioning chemotherapy and the subsequent infusion of KTE-X19.

**Reference Therapy, Dose, Mode of Administration, and Batch No.:** None

**Criteria for Evaluation:**

- Primary endpoint: ORR (complete response [CR] + partial response [PR]) using an Independent Radiology Review Committee (central assessment) per the Lugano Classification {Cheson 2014}.
- Secondary endpoints:
  - Efficacy
    - Best objective response using central assessment
    - ORR and best objective response using the investigator assessment
    - Progression-free survival (PFS)
    - Overall survival (OS)
  - Pharmacokinetics/Pharmacodynamics: Evaluation criteria are described in m5.3.4.2.
  - Safety:
    - Incidence of adverse events (AEs) and clinically significant changes in laboratory values
    - Incidence of antibodies to KTE-X19
  - Other:
    - Changes over time in the European Quality of Life-5 Dimension and visual analogue scale scores
- Exploratory endpoints:
  - ORR and duration of second response among subjects retreated with KTE-X19

### **Statistical Methods:**

#### **Efficacy:**

In Cohort 1, efficacy analyses were to be conducted using the inferential analysis set (the first 60 subjects who were treated with KTE-X19 at a dose of  $2 \times 10^6$  anti-CD19 CAR T cells/kg) and the full analysis set (all subjects enrolled/leukapheresed). In Cohort 2, efficacy analyses were to be conducted in the modified-intent-to-treat analysis set (all subjects who received KTE-X19 at a dose of  $0.5 \times 10^6$  anti-CD19 CAR T cells/kg).

**ORR using central assessment:** The primary efficacy endpoint was the ORR, defined as the incidence of CR or PR using central assessment per the Lugano Classification {Cheson 2014}. Confidence intervals (CIs) for the ORR were to be calculated using the following methods:

- Clopper-Pearson (an exact interval)
- Wilson's method (sensitivity analysis)
- Agresti-Coull method (sensitivity analysis)
- Modified Jeffrey's method (sensitivity analysis)

The hypothesis was that the ORR to KTE-X19 using central assessment would be significantly higher than the prespecified historical control rate of 25%. This hypothesis was to be tested in the inferential analysis set of Cohort 1 at the 1-sided significance level of 0.025 using an exact binomial test (data from Cohort 2 were to be descriptive only).

**Best objective response using central assessment:** The subject incidence of best response (CR, PR, stable disease [SD], PD, and not evaluable) was to be calculated using central assessment per the Lugano Classification {Cheson 2014}. CIs for the best objective response were to be calculated using the same methods used to calculate CIs for the ORR.

**ORR and Best Objective Response Using the Investigator Assessment:** The ORR and subject incidence of best response was also to be calculated using the investigator assessment (subjects in Cohort 1 were to be evaluated per IWG 2007 Criteria {Cheson 2007}, and subjects in Cohort 2 were to be evaluated per the Lugano Classification {Cheson 2014}). The concordance of objective response and best response as determined by central and investigator assessment was to be evaluated in Cohort 1 using concordance, concordance rate, a kappa statistic, and a 2-sided 95% CI for the kappa statistic.

**DOR:** DOR was defined only for subjects who had an objective response (CR or PR) and was the time from the first objective response to disease progression or death. DOR estimates were to be determined using the Kaplan-Meier (KM) approach and derived using disease assessments (per central and investigator assessment) obtained on study prior to initiation of new anticancer therapy (including stem cell transplant [SCT]). The follow-up time for DOR was to be estimated using the reverse KM approach.

**PFS:** PFS was defined as the time from the KTE-X19 infusion date to the date of disease progression or death from any cause. In the full analysis set, PFS was defined as the time from the enrollment date to the date of disease progression or death from any cause. Progression was to be defined using both central assessment and investigator assessment. Subjects alive and not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. PFS will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (including stem cell transplant).

**OS:** OS was defined as the time from the KTE-X19 infusion to the date of death from any cause. In the full analysis set, OS was defined as the time from enrollment to the date of death from any cause. Subjects who had not died by the data cutoff date were to be censored at the last date they were known to be alive or at the data cutoff date, whichever was earlier.

**Pharmacokinetics/Pharmacodynamics:** Statistical methods are described in m5.3.4.2.



### **Safety:**

**AEs:** AEs were to be coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0, and the severity of AEs was to be graded using CTCAE version 4.03. The subject incidence of AEs and SAEs were to be summarized or listed by preferred term and toxicity grade. Additional summaries were to be provided for KTE-X19-related AEs and SAEs, Grade 3 or higher AEs, Grade 3 or higher KTE-X19-related AEs, and fatal AEs. A subgroup analysis of AEs was to be performed by age and sex. The subject incidence of deaths was also to be provided.

**AEs of special interest:** AEs of special interest were to include important identified risks (CRS, neurologic events [including cerebral edema], cytopenias, infections, and hypogammaglobulinemia) and important potential risks (secondary malignancies, immunogenicity, tumor lysis syndrome, and presence of replication competent retrovirus). Cardiac arrhythmia, cardiac failure, and autoimmune disorders were also to be examined. The subject incidence of each AE of special interest was to be summarized by preferred term and toxicity grade.

CRS was to be identified as a syndrome, and its severity was to be graded according to Kite's modification of the grading system proposed by Lee and colleagues {Lee 2014}. In the modified grading scale, neurologic AEs were not to be reported as part of CRS. Individual symptoms of CRS were to be graded for severity using CTCAE version 4.03 and linked to the corresponding CRS episode.

Neurologic AEs were to be identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy, which focused on CNS toxicity without regard to temporal relationship or concomitant medications. Events were to be identified with a prespecified search list of MedDRA preferred terms.

Immunogenicity was to be identified by the development of antibodies that tested positive for reactivity against the murine monoclonal antibody FMC63 (parent antibody for the single-chain variable region fragment used for production of the anti-CD19 CAR in KTE-X19) as measured by a traditional sandwich-based enzyme-linked immunosorbent assay. Positive samples underwent further testing with a confirmatory cell-based assay to determine whether the signal observed in the screening assay was due to the antibody binding to a properly folded scFv expressed on the surface of an anti-CD19 CAR.

The incidence of subjects with detectable RCR in blood samples was to be summarized. For subjects with detectable RCR, the persistence of RCR over time was also to be summarized.

For other AEs of interest, specific AEs were to be categorized using the dictionary-coded event term and standardized MedDRA queries or other search strategies. Cytopenias were to be summarized by categories of thrombocytopenia, neutropenia, and anemia, and a summary of cytopenias present on or after Day 30 was to be provided. Infections were to be summarized by categories of bacterial, viral, opportunistic, and other infections.

### **SUMMARY OF RESULTS:**

#### **Subject Disposition and Demographics:**

**Cohort 1:** Seventy-four subjects were enrolled (ie, leukapheresed). Sixty-nine subjects received conditioning chemotherapy, and 68 subjects received KTE-X19. Of the 68 subjects who received KTE-X19, 25 subjects received bridging therapy. The median potential follow-up time from the KTE-X19 infusion was 11.6 months (range: 1.9 to 32.3 months). The median age was 65.0 years (range: 38 to 79 years), and 57% were ≥ 65 years of age. Eighty-four percent of subjects were male, and the majority were white (91%). At enrollment, 85% of subjects had Stage IV disease, and 54% of subjects had bone marrow involvement. Based on the s-MIPI, 41% of subjects were classified as low risk, 43% of subjects were classified as intermediate risk, and 13% of subjects were classified as high risk. Eighty-one percent of subjects received ≥ 3 prior regimens, and 43% of subjects had relapsed following prior autologous SCT.

**Cohort 2:** Seventeen subjects were enrolled, 15 subjects received conditioning chemotherapy, and 14 subjects received KTE-X19. Of the 14 subjects who received KTE-X19, 7 subjects received bridging therapy. The median potential follow-up time from the KTE-X19 infusion was 16.0 months (range: 13.9 to 18.0 months). The median age was 61.5 years (range: 52 to 73 years), and 21% were ≥ 65 years of age. Seventy-nine percent of subjects were male, and the majority were white (93%). At enrollment, 93% had Stage IV disease, and 57% had bone marrow involvement. Based on the s-MIPI, 43% were classified as low risk, 29% were classified as intermediate risk, and 21% were classified as high risk (s-MIPI data were not available for 1 subject). Fifty-three percent of subjects received ≥ 3 prior regimens, and 43% of subjects relapsed after prior autologous SCT.

## **Efficacy Results:**

### **Primary Endpoint**

The ORR per central assessment of subjects in the Cohort 1 inferential analysis set was 93% (56 of 60 subjects, 95% CI per the Clopper-Pearson method: 83.8%, 98.2%), with a CR rate of 67% (40 of 60 subjects, 95% CI per the Clopper-Pearson method: 53.3%, 78.3%). Because the ORR was significantly higher than the prespecified control rate of 25% at 1-sided significance level of 0.025 ( $p < 0.0001$ ), the primary endpoint was met. Among 42 subjects who initially had a PR or SD, 24 subjects (57%) went on to achieve a CR after a median of 2.2 months (range: 1.8 to 8.3 months). Of the 24 subjects whose responses improved over time, 21 subjects (88%) converted from PR to CR, and 3 subjects (13%) converted from SD to CR. When examined across subgroups defined by demographics, baseline disease characteristics, use of bridging therapy, and use of concomitant tocilizumab or steroids, the ORR was generally consistent with the ORR of 93% observed for all subjects.

In the full analysis set (all subjects who were enrolled/leukapheresed), the ORR per central assessment was 85% (63 of 74 subjects, 95% CI per the Clopper-Pearson method: 75.0%, 92.3%), with a CR rate of 59% (44 of 74 subjects, 95% CI per the Clopper-Pearson method: 47.4%, 70.7%). As in the full analysis set, the ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ( $p < 0.0001$ ).

### **Secondary Endpoints in Cohort 1**

In the inferential analysis set, the ORR using the investigators' assessment of response was 88% (53 of 60 subjects, 95% CI per the Clopper-Pearson method: 77.4%, 95.2%), and the CR rate was 70% (42 of 60 subjects, 95% CI per the Clopper-Pearson method: 56.8%, 81.2%). Objective response and CR using the investigators' assessment had a concordance rate of 95% ( $\kappa = 0.70$ ; 95% CI: 0.39, 1.00) and 90% ( $\kappa = 0.77$ , 95% CI: 0.60, 0.94), respectively, with the ORR and CR rate using central assessment.

Subjects responded a median of 1.0 month (range: 0.8 to 3.1 months) after the KTE-X19 infusion as determined by central assessment. After a median DOR follow-up of 8.6 months, the median KM DOR was not reached, with 34 of 60 subjects in the inferential analysis set (57%) in an ongoing response as of the data cutoff date. The longest response duration was 29.2 months as of the data cutoff date.

PFS rate estimates at 6 months and 12 months using central assessment in the inferential analysis set were 77.0% and 60.9%, respectively, and the KM median PFS was not reached with a median potential follow-up of 12.3 months (range: 7.0 to 32.3 months). As of the data cutoff date, the longest PFS was 30.2 months. Among subjects who achieved a CR, PFS rate estimates at 6 months and 12 months were 100% and 76.6%, and the KM median PFS was not reached.

OS rate estimates for subjects in the inferential analysis set at 6 months and 12 months were 86.7% and 83.2%, respectively, and the KM median OS was not reached after a median potential follow-up of 12.3 months (range: 7.0 to 32.3 months). Among subjects in the inferential analysis set who achieved a CR, OS rate estimates at 6 months and 12 months were 100.0% and 97.2%, respectively, and the median OS was not reached.

Overall, the efficacy trends observed in the full analysis set were consistent with trends observed in the inferential analysis set.

### **Efficacy Results in Cohort 2**

The ORR based on central assessment was 93% (13 of 14 subjects, 95% CI per the Clopper-Pearson method: 66.1%, 99.8%), and the CR rate was 64% (9 of 14 subjects, 95% CI per the Clopper-Pearson method: 35.1%, 87.2%) in the modified intent-to-treat analysis set (comprising all subjects who received KTE-X19 in Cohort 2).

After a median follow-up of 11.3 months for DOR, the median KM DOR using the central assessment of response was not reached, with 8 of 14 subjects in the modified intent-to-treat analysis set (57%) in an ongoing response as of the data cutoff date.

PFS rate estimates using central assessment at 6 months and 12 months were each 77.9%, and the KM median PFS was not reached with a median potential follow-up of 16.0 months (range: 13.9 to 18.0 months).

OS rate estimates at 6 months and 12 months for subjects in Cohort 2 who received KTE-X19 were 92.9% and 78.6%, respectively, and the KM median OS was not reached with a median potential follow-up of 16.0 months (range: 13.9 to 18.0 months).

**Pharmacokinetics/Pharmacodynamic Results:** Results are described in m5.3.4.2.

## Safety Results:

### Extent of Exposure

**Cohort 1:** For conditioning chemotherapy, all subjects received the planned total body surface area-adjusted dose of cyclophosphamide (1500 mg/m<sup>2</sup>). Subjects received a median total body surface area-adjusted dose of fludarabine of 90 mg/m<sup>2</sup>, and all but 1 subject received within 10% of the planned total dose. Conditioning chemotherapy was followed by a median weight-adjusted KTE-X19 dose of  $2.0 \times 10^6$  anti-CD19 CAR T cells/kg (range:  $0.6 \times 10^6$  to  $2 \times 10^6$  cells/kg). The median total number of anti-CD19 CAR T cells in the KTE-X19 infusion was  $160.5 \times 10^6$  anti-CD19 CAR T cells (range:  $51.8 \times 10^6$  to  $202 \times 10^6$  cells), and the median total number of T cells infused was  $260.6 \times 10^6$  T cells (range:  $143.2 \times 10^6$  to  $579.4 \times 10^6$  cells). Sixty-six of 68 subjects (97%) received within 10% of the planned KTE-X19 dose.

**Cohort 2:** All subjects received the planned total body surface area-adjusted dose of cyclophosphamide (1500 mg/m<sup>2</sup>) and fludarabine (90 mg/m<sup>2</sup>) for conditioning chemotherapy, and all subjects received the planned weight-adjusted dose of  $0.5 \times 10^6$  anti-CD19 CAR T cells/kg. The median total number of anti-CD19 CAR T cells in the KTE-X19 infusion was  $39.1 \times 10^6$  anti-CD19 CAR T cells (range:  $29.2 \times 10^6$  to  $50.1 \times 10^6$  cells). The median total number of T cells infused was  $60.3 \times 10^6$  T cells (range:  $40.9 \times 10^6$  to  $100.2 \times 10^6$  cells).

### Deaths

**Cohort 1:** As of the data cutoff date, 16 of 68 subjects (24%) who received KTE-X19 had died. Fourteen subjects died due to PD (of these, 1 death was listed as “other” as of the data cutoff date). Two subjects died due to AEs: 1 subject died due to organizing pneumonia on Day 37 (deemed related to conditioning chemotherapy but unrelated to KTE-X19), and 1 subject died due to staphylococcal bacteremia on Day 134 (deemed related to conditioning chemotherapy and KTE-X19).

**Cohort 2:** As of the data cutoff date, 4 of 14 subjects (29%) who received KTE-X19 had died. Two subjects died due to PD, 1 subject died due to a toxicity associated with an allogeneic SCT regimen on Day 286, and 1 subject died due to Grade 5 cardiac arrest on Day 18 (which was deemed unrelated to leukapheresis, conditional chemotherapy, or KTE-X19).

### Common AEs

**Cohort 1:** All 68 subjects had at least 1 AE, 99% of subjects had at least 1 AE that was Grade 3 or higher, and 68% of subjects had at least 1 SAE. The most common AEs by preferred term in Cohort 1 were pyrexia (94%), anemia (68%), and platelet count decreased (53%). The most common Grade 3 or higher AEs were anemia and neutrophil count decreased (50% each) and WBC decreased (40%).

**Cohort 2:** All 14 subjects had at least 1 AE, 93% of subjects had at least 1 Grade 3 or higher AE, and 57% of subjects had at least 1 SAE. The most common AEs by preferred term in Cohort 2 were pyrexia (93%) and hypotension (79%). The most common Grade 3 or higher AEs in Cohort 2 were hypotension and WBC decreased (50% each), and anemia and neutrophil count decreased (43% each).

### AEs of Special Interest

#### Identified Risks

#### CRS

**Cohort 1:** In total, 91% of subjects had CRS of any grade, and 15% of subjects had CRS that was Grade 3 or higher. No subject had Grade 5 CRS. The median time to CRS onset was 2 days (range: 1 to 13 days) after the KTE-X19 infusion. As of the data cutoff date, all cases of CRS had resolved. The median duration of CRS was 11 days (range: 1 to 50 days).

**Cohort 2:** In total, 93% of subjects had CRS of any grade, and 1 subject had Grade 4 CRS. No subject had Grade 3 or Grade 5 CRS. The median time to CRS onset was 6 days (range: 1 to 11 days) after the KTE-X19 infusion. As of the data cutoff date, CRS had resolved in all subjects. The median duration of CRS was 10 days (range: 3 to 31 days).

### Neurologic Events

**Cohort 1:** In total, 63% of subjects had at least 1 neurologic event of any grade, and 31% of subjects had neurologic events that were Grade 3 or higher. No subject had Grade 5 neurologic event. The median time to onset of neurologic events was 7 days (range: 1 to 32 days) after the KTE-X19 infusion. As of the data cutoff date, neurologic events had resolved in all but 6 subjects. Two subjects had unresolved neurologic events at the time of death: 1 subject had Grade 2 nonserious agitation (deemed related to KTE-X19) and Grade 3 serious confusional state (deemed related to conditioning chemotherapy and KTE-X19), and the other subject had Grade 2 nonserious hyperaesthesia. Ongoing neurologic events for the remaining 4 subjects were Grade 1 or Grade 2. Among those whose neurologic events had resolved, the median neurologic event duration was 12 days (range: 1 to 567 days). Three subjects had neurologic events beyond Day 200 that were attributed to conditioning chemotherapy and KTE X19. Two subjects had events of Grade 1 tremor (from Day 12 to Day 236 and Day 60 to Day 280, respectively) and 1 subject had Grade 2 memory impairment that started on Day 533 and resolved on Day 571 (this subject had other neurologic events that occurred between Day 5 and Day 72).

**Cohort 2:** In total, 93% of subjects had at least 1 neurologic event of any grade, and 43% of subjects had a Grade 3 neurologic event. No subject had a Grade 4 or Grade 5 neurologic event. The median time to event onset was 12 days (range: 3 to 262 days) after the KTE-X19 infusion (1 subject had Grade 1 nonserious memory impairment that started on Day 261, was ongoing as of the data cutoff date, and was deemed unrelated to KTE-X19). Neurologic events had resolved in all but 4 subjects as of the data cutoff date: 1 subject had serious Grade 3 encephalopathy, nonserious Grade 2 confusional state, and nonserious Grade 2 dysarthria at the time of death. One subject had nonserious Grade 1 memory impairment and 2 subjects had nonserious Grade 1 tremor that were ongoing as of the data cutoff date. Among subjects whose neurologic events had resolved, the median event duration was 17 days (range: 4 to 178 days). One subject had a Grade 1 nonserious tremor that started on Day 7, resolved on Day 182 and was deemed related to KTE-X19 (this subject had other neurologic events that occurred between Day 5 and Day 12).

### Cytopenias

**Cohort 1:** The subject incidence of Grade 3 or higher thrombocytopenia, neutropenia, and anemia AEs was 51%, 85%, and 50%, respectively. The subject incidence of Grade 3 or higher thrombocytopenia, neutropenia, and anemia AEs that were present on or after Day 30 was 40%, 41%, and 19%, respectively.

**Cohort 2:** The subject incidence of Grade 3 or higher thrombocytopenia, neutropenia, and anemia AEs were 43%, 79%, and 43%, respectively. The subject incidence of Grade 3 or higher thrombocytopenia, neutropenia, and anemia AEs that were present on or after Day 30 was 29%, 14%, and 7%, respectively.

### Infections

**Cohort 1:** Twenty-two subjects (32%) had infections that were Grade 3 or higher. One subject had a Grade 5 bacterial infection of staphylococcal bacteremia; no subject had a Grade 5 viral, opportunistic, or other infection.

**Cohort 2:** Three subjects (21%) had infections that were Grade 3 or higher; no subject had a bacterial, viral, opportunistic, or other Grade 5 infection.

### Hypogammaglobulinemia

**Cohort 1:** Thirteen subjects (19%) had hypogammaglobulinemia.

**Cohort 2:** No subject had hypogammaglobulinemia.

### Potential Risks

No KTE-X19-related secondary malignancies or cases of immunogenicity were reported in Cohort 1 or Cohort 2, and no subject tested positive for RCR. One subject in Cohort 1 had Grade 3 tumor lysis syndrome (deemed related to KTE-X19). No subject in Cohort 2 had tumor lysis syndrome.

*Other AEs of Interest*

**Cardiac Events**

**Cohort 1:** Cardiac arrhythmia AEs were reported for 57% of subjects; the majority of these events were worst Grade 1 (37%) or worst Grade 2 (18%). One subject had worst Grade 3 atrial flutter and 1 subject had worst Grade 4 atrial fibrillation. The most common cardiac arrhythmia AEs were tachycardia (31%), sinus tachycardia (13%), and atrial fibrillation (5 subjects, 7%).

Three subjects had events of cardiac failure, which were either worst Grade 2 or worst Grade 3. No subject had a cardiac failure event of Grade 4 or Grade 5.

**Cohort 2:** Cardiac arrhythmia AEs were reported for 79% of subjects; the majority of these events were worst Grade 1 (43%) or worst Grade 2 (21%). One subject had Grade 4 atrial fibrillation and 1 subject had Grade 5 cardiac arrest. The most common cardiac arrhythmia events were tachycardia (36%), and atrial fibrillation, sinus tachycardia, and ventricular arrhythmia (14% each). One subject had cardiac failure (worst Grade 3 pulmonary edema); no other events of cardiac failure were reported.

**Autoimmune Reactions/Disorders**

**Cohort 1:** Grade 3 autoimmune colitis was reported for 1 subject (which started on Day 348 and was deemed serious and unrelated to KTE-X19).

**Cohort 2:** No subject had an autoimmune disorder or reaction.

In general, results observed in Cohorts 1 and 2 combined were consistent with results observed in Cohort 1.

**Other:**

Results of the EQ-5D and VAS suggest no long-term impact on health-related quality of life associated with KTE-X19 therapy.

**CONCLUSIONS:**

The primary endpoint of ZUMA-2 was met: KTE-X19 significantly improved ORR in subjects with r/r MCL compared with the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ( $p < 0.0001$ ). This ORR represents a substantial improvement over currently available therapies for patients with r/r MCL whose disease progressed during or after treatment with a BTK inhibitor. Responses were generally durable, with 57% of subjects in the inferential analysis set in an ongoing response as of the data cutoff date. The median DOR was not reached after a median follow-up for DOR of 8.6 months (95% CI: 7.8, 19.6 months), and the median PFS and OS were not reached after a median potential follow-up time of 12.3 months (range: 7.0 to 32.3 months). The safety profile was manageable, as CRS and neurologic events were largely reversible and manageable with supportive care, tocilizumab, and steroids.

KTE-X19 at a dose of  $2 \times 10^6$  anti-CD19 CAR T cells/kg was deemed the optimal dose for treatment of r/r MCL based on the positive risk: benefit profile observed. Overall, the results of ZUMA-2 demonstrate that KTE-X19 is a valuable treatment option for patients with r/r MCL, a population with a critical unmet need.

### 3.1. Publication

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2020;382:1331-42. DOI: 10.1056/NEJMoa1914347

### 3.2. Protocol Amendments and Description

The original protocol, dated 12 March 2015, was amended 6 times during the course of the trial. The first patient has been enrolled on 16 May 2016 in accordance to Trial Protocol Version 2, dated, 21 April 2016. The change of the manufacturing process from axicabtagene ciloleucel (Yescarta) to KTE-X19 has been implemented with Amendment 3, dated 23 August 2016. Amendment 4, dated 13 November 2017, has been introduced in preparation of the intended marketing Authorisation: A) Identification of two separate treatment cohorts (Cohort 1 and Cohort 2), and B) Addition of BTK inhibitors to permissible prior regimens. The Amendment 5, dated 22 June 2018, designed Cohort 1 as the pivotal cohort. The last subject has been enrolled on 16 April 2019 in accordance to trial protocol version 6, dated 29 October 2018.

### 3.3. KTE-C19-102: List of Principal Investigator and Sites

Principal Investigator	Site (Full address)	Country
Wang, Michael, M.D.	MD Anderson Cancer Center 1515 Holcombe Blvd Houston, TX 77030 United States	United States
	City of Hope 1500 East Duarte Road Duarte, CA 91090 United States	United States
	Moffitt Cancer Center 12902 Magnolia Drive Tampa, FL 33612 United States	United States
	2160 South First Avenue Building 112, RM 101 Maywood, IL 60153 United States	United States
	Vanderbilt University 1301 Medical Center Drive Nashville, TN 37232 United States	United States

Principal Investigator	Site (Full address)	Country
	Sarah Cannon - Tennessee 250 25th Avenue North Suite 307 Nashville, TN 37203 United States	United States
	Sarah Cannon - Denver 1721 E 19th Ave Suite 300 Denver, CO 80218 United States	United States
	Hackensack University Medical Center 92 Second Street Hackensack, NJ 07601 United States	United States
	University of Rochester 601 Elmwood Avenue Rochester, NY 14642 United States	United States
	Karmanos Cancer Institute 4100 John R. Street Detroit, MI 48201 United States	United States
	3855 Health Sciences Drive La Jolla, CA 92093 United States	United States
	Cleveland Clinic – Taussig Cancer Center 9500 Euclid Avenue R35 Cleveland, OH 44195 United States	United States
	Dana Farber Cancer Institute 450 Brookline Avenue Boston, MA 02215 United States	United States
	Banner MD Anderson Cancer Center 2946 E Banner Gateway Drive Gilbert, AZ 85234 United States	United States
	University of Miami 1475 NW 12th Avenue Miami, FL 33136 United States	United States

Principal Investigator	Site (Full address)	Country
	University of California Los Angeles 10945 Le Conte Avenue Suite 3360 Los Angeles, CA 90095 United States	United States
	Stanford University 300 Pasteur Drive Room H0101 Stanford, CA 94305 United States	United States
	Duke University 2400 Pratt Street Suite 9000 Durham, NC 27710 United States	United States
	Emory University 1365-C Clifton Road NE Atlanta, GA 30322 United States	United States
	University of Chicago 5841 S Maryland Avenue Chicago, IL 60637 United States	United States
	Robert W. Francz Cancer Research Center 4805 NE Gilsan Street Suite 11N Portland, OR 97213 United States	United States
	Baylor Cancer Hospital 3410 Worth Street Dallas, TX 75246 United States	United States
	Sarah Cannon-Methodist Healthcare System - San Antonio 4410 Medical Drive Suite 410 San Antonio, TX 78229 United States	United States
	Swedish Cancer Institute 1221 Madison Street Seattle, WA 98104 United States	United States



Principal Investigator	Site (Full address)	Country
	Fox Chase Cancer Center 7604 Central Avenue Philadelphia, PA 19111 United States	United States
	Ohio State University 320 W 10th Avenue Columbus, OH 43210 United States	United States
	Erasmus MC S Gravendijkwal 230 Rotterdam, Zuid-Holland, 3015 CE The Netherlands	Netherlands
	University Medical Center Groningen Dept. of Hematology, Hanzeplein 1 Groningen, The Netherlands, 9700 RB	Netherlands
	Academisch Medisch Centrum Dept. Of Hematology Meibergdreef 9 Amsterdam, Noord-Holland 1105 AZ The Netherlands	Netherlands
	Hopital Saint Louis Hopital Saint Louis 1, Avenue Claude Vellefaux Paris, France 75475	France
	Academisch Medisch Centrum Hopital Haut Leveque-Centre Francois Magendie Avenue Magellan Pessac Cedex, France 33604	France
	CHU de Rennes Hopital Pont Chaillou-CHU Rennes 2, rue Henri Le Guilloux Rennes, France 35033 Cedex 09	France
	Universitätsklinik Dresden Fetscherstrasse 74 Dresden, Germany 01307	Germany
	Universitaetsklinikum Wuerzburg Medizinische Klinik und Poliklinik der Universitaet Wuerzburg Oberdürrbacherstr. 6 Wuerzburg, Germany 97080	Germany