19 July 2022
EMA/683619/2022
Committee for Advanced Therapies (CAT)
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecartus

International non-proprietary name: brexucabtagene autoleucel

Procedure No. EMEA/H/C/005102/II/0008/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALL	acute lymphoblastic leukemia
allo-SCT	allogeneic stem cell transplant
ANC	absolute neutrophil count
AUC0-28	area-under-the-curve from Day 0 to Day
auto-SCT	autologous stem cell transplant
B-ALL	B-cell precursor acute lymphoblastic leukemia
CAR	chimeric antigen receptor
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete remission
CRh	complete remission with partial hematologic recovery
Cri	complete remission with incomplete hematologic recovery
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CXCL10	C-X-C motif chemokine 10
DOR	duration of remission
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EQ-5D	European Quality of Life 5 Dimensions
EU	European Union
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft-versus-host disease
HCT	historical clinical trial
ICH	International Council for Harmonisation
IFN	interferon

IL	interleukin
IL-1RA	interleukin-1 receptor antagonist
IND	Investigational New Drug
IV	intravenous
KM	Kaplan-Meier
LLOQ	lower level of quantification
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MEDS	Medidata Enterprise Data Store
mITT	modified intent-to-treat
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not estimable
NHL	non-Hodgkin lymphoma
OCR	overall complete remission
OS	overall survival
PBMC	peripheral blood mononuclear cell
PDCO	Paediatric Committee
Ph	Philadelphia chromosome
PIP	paediatric investigation plan
PT	preferred term
r/r	relapsed/refractory
RCR	replication-competent retrovirus
RFS	relapse-free survival
SAE	serious adverse event
SCA	synthetic control arm
SAWP	Scientific Advice Working Party
SCT	stem cell transplant
SMD	standardized mean difference
SOC	system organ class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor

TNF	tumor necrosis factor
US	United States

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Kite Pharma EU B.V. submitted to the European Medicines Agency on 1 June 2021 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB
B.II.d.1.z	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	Type IB	I, II, IIIA and IIIB

Group of variations including an extension of indication to include treatment of adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL) for Tecartus and a type IB variation to change the Drug Product Dose specification for the new indication. As a consequence, sections 2.2, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 1.1 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template.

The group of variations requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Tecartus was designated as an orphan medicinal product EU/3/19/2220 on 13 Nov 2019 in the following condition: Treatment of adult patients with relapsed or refractory mantle cell lymphoma

Orphan designation was granted by the European Commission for Tecartus for the treatment of ALL (EU orphan designation number EU/3/20/2344, date of decision 19 Oct 2020).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Tecartus as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Tecartus

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0142/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001862-PIP01-15-M02 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 31 May 2018 (EMEA/H/SA/3117/6/2018/PA/ADT/III). The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CAT were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	1 June 2021
Start of procedure:	19 June 2021
CAT Rapporteur Assessment Report	20 August 2021
PRAC Rapporteur Assessment Report	23 August 2021
PRAC members comments	25 August 2021
CAT and CHMP members comments	31 August 2021
PRAC Outcome	2 September 2021
Updated CAT Rapporteur(s) (Joint) Assessment Report	7 September 2021
CAT Request for Supplementary Information (RSI)	10 September 2021
CAT Rapporteur Assessment Report	23 February 2022
PRAC Rapporteur Assessment Report	24 February 2022
PRAC members comments	1 March 2022
CAT and CHMP members comments	8 March 2022
PRAC Outcome	10 March 2022
Updated CAT Rapporteur Assessment Report	16 March 2022
CAT Request for Supplementary Information (RSI)	18 March 2022

Timetable	Actual dates
CAT Rapporteur Assessment Report	15 June 2022
PRAC members comments	28 June 2022
SAG experts meeting to address questions raised by the CAT (Annex 3)	24 June 2022
Updated PRAC Rapporteur Assessment Report	1 July 2022
CAT and CHMP members comments	5 July 2022
PRAC Outcome	7 July 2022
Updated CAT Rapporteur Assessment Report	11 July 2022
Updated CAT Rapporteur Assessment Report	18 July 2022
CAT opinion (adopted via written procedure):	19 July 2022
CHMP opinion:	21 July 2022
The CHMP adopted a report on similarity of Tecartus with authorised orphan medicinal product(s) on date (Appendix 1)	21 July 2022
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Tecartus in comparison with existing therapies (Appendix 2)	21 July 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Acute lymphoblastic leukemia (ALL) is a serious heterogeneous group of lymphoid disorders resulting from the clonal proliferation of immature precursor B- or T-cell lymphocytes (blasts) in blood, bone marrow, and other lymphatic (e.g. lymph nodes and spleen) and non-lymphatic organs (e.g. CNS, liver and bones). The disease occurs with a bimodal age distribution: 55% of cases diagnosed in patients < 20 years of age, and 28% of cases diagnosed in adult patients ≥ 45 years of age {National Comprehensive Cancer Network 2020}. The estimated overall incidence of ALL in the EU is 1.28 per 100,000 individuals per year, with a higher incidence rate (1.45 per 100,000 individuals per year) among adults aged 75 to 99 years {Hoelzer 2016}. Five-year overall survival rates for children are 89%, survival rates for adults remain low at approximately 20% to 40% (approximately 20% for adults ≥ 60 years of age), and the majority of ALL deaths are in adults {Siegel 2020}.

ALL can be classified in 3 subtypes: B-cell precursor ALL, mature B-cell ALL, and T-cell ALL. B-ALL represents the most common form of ALL in adult patients. Further, 25% of adult patients with ALL have Ph-positive (Ph^+) disease {National Comprehensive Cancer Network 2020}. Ph^+ status confers a very poor prognosis with 5-year OS and relapse-free survival (RFS) rates of 8% and 0%, respectively {Pullarkat 2008}.

The pathogenic causes of ALL are unknown. However, a couple of endogenous factors as defect congenital DNA repair mechanisms and exogenous factors (secondary neoplasia after radiotherapy or chemotherapy) are considered to contribute to the development of ALL.

Biologic features

CD19, the target antigen of KTE-X19, is a transmembrane protein, which is expressed in the B-cell lineage. CD19 expression is maintained in most B-cell malignancies (CLL, a subset of multiple myeloma, subtypes of non-Hodgkin B-cell lymphoma) and ALL.

Clinical presentation, diagnosis and stage/prognosis

The prognosis for r/r B-ALL after failure of first line treatment has improved by the bispecific CD19-directed CD3 T-cell engaging agent blinatumomab, which is approved in the EU as monotherapy for treatment of adults with CD19 positive r/r B-precursor ALL. Ph-positive patients should have received prior treatment with at least 2 TKIs. Blinatumomab is also indicated as monotherapy in paediatrics one year old or older with Ph-negative CD19-positiv B-precursor ALL, refractory or after at least two prior therapy regimens or after prior allogenic hSCT. The EU-approval of inotuzumab ozogamicin in 2017, a CD22-directd antibody-drug conjugate for the treatment of adults with r/r CD22-positive B-precursor ALL also contributed to an improvement of the rates for overall survival for patients in the refractory/relapsed situation.

Unmet medical need

With each subsequent relapse, the prognosis gets worse. A retrospective analysis of 1,706 adult subjects with Ph^- r/r B-ALL found that the CR rate after first, second, and third or greater salvage therapy was 40%, 21%, and 11%, respectively. Median OS decreased with each subsequent line of therapy; median OS after first, second, and third or greater salvage therapy was 5.8, 3.4, and 2.9 months, respectively {Gokbuget 2016b, Kantarjian 2003, O'Brien 2013}. Patients in second or later relapse may receive therapies utilized in the second line, such as allo- or auto-SCT. However, only few patients are eligible for SCT. Blinatumomab or inotuzumab may be evaluated also as third line treament if not previously used; however, outcomes with these treatments are typically not as favourable in patients being treated in the third line and beyond. Subjects receiving blinatumomab as a third or later line of therapy for B-ALL had a median OS of 5.1 months compared with 11.1 months for those receiving blinatumomab as their second line {Dombret 2019}. The combined CR/CRi/CRh rate was also lower for subjects receiving blinatumomab as a third or later line therapy compared with those receiving blinatumomab as the second-line therapy (39.5% vs 51.0%, respectively). In the INO-VATE study, the CR/CRi rate was 77.8% for subjects receiving inotuzumab as the second line and 66.1% for those receiving inotuzumab as the third-line therapy {Kantarjian 2019}.

Results of the TOWER study with a median DOR of 7.3 months among subjects achieving CR/Cri/CRh indicate that durability of response to blinatumomab was limited. Twenty-four percent of subjects in the blinatumomab arm underwent a subsequent allo-SCT. Moreover, mortality rates following subsequent allo-SCT were high; among 38 subjects who achieved a CR/CRi/CRh to blinatumomab and underwent allo-SCT, 10 subjects (26%) died during a median follow-up period of 206 days. The importance of CR rates in oncological trials, especially in clinical trials of leukemia is acknowledged, as CR is associated with more durable response {Saygin 2016}, fewer infections and a reduced need for blood product support {U. S. Department of Health and Human Services (DHHS) 2018}. In accordance to ESMO Guidelines patients in the refractory disease stage or in second or later relapse are recommended to participate in clinical

trials for novel treatment, what per se supports the need for new therapy concepts. In addition to these efficacy limitations, there are concerns regarding safety. Binatumomab requires continuous intravenous (IV) infusion, and hospitalisation is recommended for a minimum of 9 days of the first cycle and the first 2 days of the second cycle {BLINCYTO 2020}, while inotuzumab is associated with an increased risk of veno-occlusive hepatic disease, which could interfere with the potentially curative effects of allo-SCT.

2.1.2. About the product

Tecartus is a gene therapy medicinal product containing autologous T cells genetically modified whereby a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction using an MSCV based gamma-retroviral vector to express a CAR comprising an anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domains and CD3-zeta signalling domain . The transduced anti-CD19 CAR T cells are expanded ex vivo and infused back into the patient, where they can recognise and eliminate CD19 expressing target cells. Tecartus binds to CD19 expressing cancer cells. Following anti-CD19 CAR T cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain 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 apoptosis and necrosis of CD19 expressing target cells.

2.1.3. Scientific advice

Scientific advice was obtained by the SAWP in May 2018 (procedure number: EMEA/H/SA/3117/6/2018/PA/ADT/III). The advice addressed the design of the phase 2 portion of the ZUMA-3 study, specifically the inclusion criteria relating to prior exposure of blinatumomab and inotuzumab.

2.2. Quality aspects

The Quality change being proposed concerns the drug product dose when Tecartus is manufactured for the new B-ALL indication.

When manufactured for the currently authorised MCL indication, Tecartus drug product is filled at a target dose of 2.0 × 10e6 cells per kg patient weight (maximum of 2.0 × 10e8 cells for patients >100 kg). When manufactured for the proposed B-ALL indication, Tecartus drug product will be filled at a target dose of 1.0 × 10e6 cells per kg patient weight (maximum of 1.0 × 1e08 cells for patients >100 kg) to align with clinical safety and efficacy data.

The dose of KTE-X19 is a calculated value derived from patient body weight, measurements of viable cell concentration, and % Transduction. KTE-X19 is manufactured to a target dose of either 1.0 × 106 anti-CD19 CAR-positive viable T cells per kg patient weight (maximum allowable dose: 1.0 × 108 anti-CD19 CAR-positive viable T cells for a ≥ 100 kg patient) for Acute Lymphoblastic Leukaemia (ALL) patients, or 2.0 × 106 anti-CD19 CAR-positive viable T cells per kg patient weight (maximum allowable dose: 2.0 × 108 anti-CD19 CAR-positive viable T cells for a ≥ 100 kg patient) for Mantle Cell Lymphoma (MCL) patients.

2.2.6 Discussion on quality aspects

Besides mantle cell lymphoma (MCL; authorised indication), patients with B-ALL are included to be treated with Tecartus. The manufacturing process is the same and also all DS/DP specifications are the same as for the initial indication of MCL. The only difference is the target dose of CAR-19 positive cells Here the specification on the DP levels is 1-2x10e6 cell/kg in MCL and 1x10e6 cells/kg in B-ALL. The respective inclusion of the additional specification of the dose (which is based on weight, viable cells and CAR-19 positive cells) is considered acceptable.

The MAH did not provide any batch data of DS/DP batches manufactured from B-ALL patient material. The MAH was asked to provide a tabulated overview of all available clinical batch data on B-ALL. This data should include the results of the IPC.

Overall, the batch data for Tecartus indicate a certain variation which is donor dependent. A comparable variation is expected for B-ALL material. Therefore, it may not be possible to see whether there is a certain trending for one of the indications. A comparable range in terms of CD3+ purity is expected to be acceptable for B-ALL compared to MCL, but needs to be confirmed by data.

The MAH was asked to provide a tabulated overview of all available clinical batch data that have been manufactured based on the starting material derived from B-ALL patients. This table should include the results for the in-process controls.

The MAH provided the requested clinical batch data, including a tabulated overview on the results of the in-process controls. The MAA has been updated by including the batch data in section 3.2.P.5.4.1, respectively. The issue was considered resolved.

2.2.7 Conclusion on quality aspects

The quality IB variation is considered approvable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Uncontrolled Efficacy and Safety Studies							
KTE-C19-103 (ZUMA-3)	Evaluate the safety and efficacy of KTE-X19 in adult subjects with r/r B-precursor ALL	Phase 1/2, open-label; safety and efficacy; multicenter	Conditioning chemotherapy[a] KTE-X19 anti-CD19 CAR T cell infusion: • 2 x 10^6 cells/kg • 1 x 10^6 cells/kg • 0.5 x 10^6 cells/kg in 68 mL • 0.5 x 10^6 cells/kg in 40 mL	Phase 1 54 leukapheresed; 45 treated Phase 2 71 leukapheresed; 55 treated Enrollment completed	Adults with r/r B-ALL (r/r defined as: primary refractory, first relapse following a remission of ≤ 12 months, r/r after second line or higher therapy or r/r after allogenic SCT)	Single infusion of KTE-X19	Study ongoing; Primary Analysis Clinical Study Report (m5.3.5.2)

2.3.2. Pharmacokinetics

Methods

The pharmacokinetic profile of KTE-X19 was assessed by means of measuring the peak, area-under-the-curve from Day 0 to Day 28 (AUC0-28; defined from baseline [Day 0] to Day 28), time-to-peak, and levels in blood over time for anti-CD19 CAR T cells at multiple time points after KTE-X19 infusion. The pharmacokinetic methods used in ZUMA-3 were developed and qualified internally by Kite Pharma, Inc. (REP-01261 and REP-16761) to detect and quantify anti-CD19 CAR T cells in blood by droplet digital polymerase chain reaction (ddPCR). The ddPCR method is specific for the anti- CD19 CAR transgene present in genomic DNA derived from cryopreserved peripheral blood mononuclear cells (PBMCs) of subjects who have received KTE-X19. As multiple gene copies can be integrated into a single human T cell, the ddPCR method is used to estimate anti-CD19 CAR transgene vector copy number (VCN). The ddPCR method quantifies the number of copies of the anti-CD19 CAR transgene and the housekeeping gene adaptor-related protein complex 3 subunit beta 1 (AP3B1) in DNA using specific primers and probes.

Table 1. Summary of Pharmacokinetic Methods

Category/Method	Description
Pharmacokinetics	
PBMC sampling times	• At enrollment/leukapheresis • Day 0[a]

	• After infusion on Days 7, 14, 28, Month 3, then every 3 months through Month 24 and annually thereafter
	• At unscheduled hospital readmission with any KTE-X19-related AEs, then weekly, and on day of discharge
	• At the time of disease progression
Assays	
Assay for anti-CD19 CAR T cells in PBMC by ddPCR	Qualified ddPCR method (BED-02852, REP-16761) for levels of anti-CD19 CAR T cells in PBMC; see m5.3.1.4
Harmonization of ddPCR method for PK Monitoring in ZUMA-1 and ZUMA-2	PK data derivation method alignment between qPCR and ddPCR (REP-25066) reporting data as anti-CD19 CAR T cells/µl of blood

Abbreviations: AE, adverse event; BED, business enabling document; CAR, chimeric antigen receptor; ddPCR, droplet digital polymerase chain reaction; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic; REP, report. a The Day 0 time point was taken before KTE-X19 infusion.

Results

All phase I cohorts:

Median peak anti-CD19 CAR T-cell levels were highest in subjects treated at the 1e6 dose level with modified toxicity management (37.7 cells/µL), followed by subjects treated at the following dose levels (from the highest to the lowest): 1e6 cells/kg with original toxicity management (26.5 cells/µL); 0.5e6 cells/kg (68 mL; 23.1 cells/µL); 2e6 cells/kg (8.6 cells/µL); and 0.5e6 cells/kg (40 mL; 4.7 cells/µL). Concerning the median AUC0-28, median time-to-peak was 8 days for subjects treated either at 1e6 cells/kg with modified toxicity management or 0.5e6 cells/kg (40 mL); 9 days in subjects treated at either 1e6 dose cells/kg with original toxicity management or 0.5e6 cells/kg (68 mL); and 15 days in subjects treated at 2e6 cells/kg. Two subjects in the Phase 1 1e6 dose cohort (modified toxicity management) had undetectable anti-CD19 CAR T cells in blood at both Day 7 and Week 2: 1 subject achieved a CR and 1 subject relapsed per the investigators' assessment.

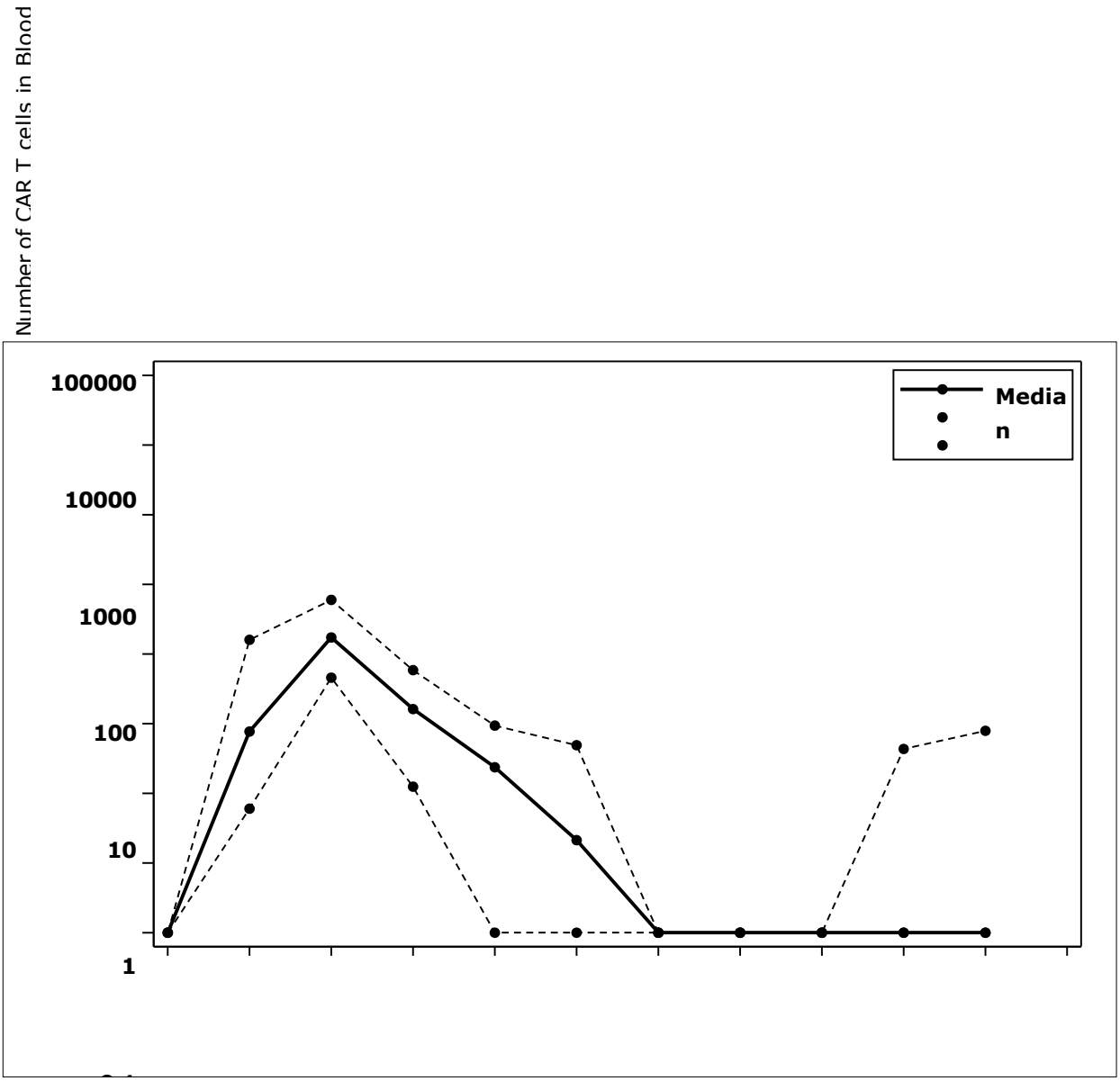
Combined phase 1 and phase 2 cohorts:

Median peak anti-CD19 CAR T-cell levels and AUC0-28 for subjects in Phase 2 (median peak: 20.6 cells/µL; median AUC0-28: 220.60 cells/µL•days) were similar to those for subjects in the combined Phase 1 and Phase 2 1e6 dose cohorts (median peak: 24.3 cells/µL; median AUC0-28: 242.90 cells/µL•days). The pattern of CAR T-cell expansion was similar in Phase 2 and in the combined Phase 1 and Phase 2 1e6 dose cohorts. Median anti-CD19 CAR T-cell time-to-peak was 15 days for subjects in Phase 2 and for those in the combined Phase 1 and Phase 2 1e6 dose cohorts. By Month 6, levels of anti-CD19 CAR T cells in blood declined to undetectable levels in 22 of 28 subjects (79%) with evaluable samples and by Month 12, levels of anti-CD19 CAR T cells in blood declined to undetectable levels in 18 of 20 subjects (90%) with evaluable samples (Listing 14.5.7.2). Anti-CD19 CAR T-cell levels in most Phase 2 subjects declined to undetectable levels at Month 6. Three subjects at Month 15 and one subject at Month 18 had low levels of anti-CD19 CAR T-cell that were marginally above the ddPCR assay detection limit. Peak levels of anti-CD19 CAR T cells for these subjects were substantially higher relative to levels at Months 15 and/or 18. Detection of anti-CD19 CAR T cells in blood samples at Months 15 and/or 18 is likely attributable to assay sensitivity, with minor fluctuations in anti-CD19 CAR T-cell levels over time above or below the assay LOD.

The median peak anti-CD19 CAR T-cell level for subjects in Phase 2 was 20.6 cells/µL, and the median time-to-peak was 15 days after the KTE-X19 infusion. The median area under-the-curve from Day 0 to Day 28 (AUC0-28) was 220.6 cells/µL•days. For subjects with evaluable samples, levels of anti-CD19 CAR T cells in blood declined to undetectable levels in 22 of 28 subjects (79%) by Month 6 and in 18 of 20 subjects (90%) by Month 12.

Five subjects in Phase 2 had no detectable anti-CD19 CAR T cells in blood at any time point evaluated. None of the 5 subjects had a CR or CRi based on best response by central assessment.

Figure 1. Median (Q1, Q3) Line Plot of Number of Anti-CD19 CAR T Cells in Blood (Cells/µL) Over Time (Phase 2, Safety Analysis Set, N = 55)



Data cutoff date = 09SEP2020. Abbreviation: CAR, chimeric antigen receptor; Q, quartile; Zuma-3 P2, number of subjects in Phase 2
Value of 0.001 on y-axis is used to indicate the limit of detection.

Table 2. Summary of Anti-CD19 CAR T Cells in Blood (Cells/µL) Over Time (Phase 2 and Combined Phase 1 and Phase 2 1e6 Dose Level, Safety Analysis Set)

	Phase 2 (N = 55)	Combined Phase 1 and Phase 2 1e6 Dose Cohorts (N = 78)
Peak (cells/µL)		
n	50	66
Mean (STDEV)	74.98 (220.53)	109.33 (385.27)
Median (Q1, Q3)	20.62 (4.58, 62.97)	24.31 (5.97, 62.97)
Min, max	0.00, 1,533.40	0.00, 2,776.95
AUC_{0-28} (cells/µL•days)		
n	50	66
Mean (STDEV)	847.74 (2,751.89)	1,054.67 (3,412.39)
Median (Q1, Q3)	220.60 (56.25, 676.94)	242.90 (82.12, 676.94)
Min, max	0.00, 19,390.42	0.00, 20,450.90
Time-to-Peak (Days)		
n	50	66
Mean (STDEV)	15.54 (6.78)	14.50 (6.42)
Median (Q1, Q3)	15 (11, 16)	15 (8, 15)
Min, max	7, 32	7, 32
Baseline		
n	52	70
Mean (STDEV)	0.00 (0.00)	0.00 (0.00)
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Min, max	0.00, 0.00	0.00, 0.00
Day 7		
n	43	58
Mean (STDEV)	23.26 (59.66)	74.06 (365.58)
Median (Q1, Q3)	0.77 (0.06, 15.99)	1.74 (0.11, 34.79)
Min, max	0.00, 322.24	0.00, 2,776.95
Week 2		
n	42	57
Mean (STDEV)	67.07 (234.89)	56.09 (202.26)
Median (Q1, Q3)	17.28 (4.58, 59.75)	16.13 (5.97, 53.05)
Min, max	0.00, 1,533.40	0.00, 1,533.40

Week 4

n	41	53
Mean (STDEV)	22.52 (81.04)	18.84 (71.47)
Median (Q1, Q3)	1.62 (0.12, 5.87)	2.18 (0.48, 5.93)
Min, max	0.00, 469.22	0.00, 469.22

Week 8

n	37	47
Mean (STDEV)	0.82 (1.33)	0.79 (1.22)
Median (Q1, Q3)	0.24 (0.00, 0.94)	0.24 (0.00, 1.03)
Min, max	0.00, 5.57	0.00, 5.57

Month 3

n	31	44
Mean (STDEV)	0.31 (0.46)	0.36 (0.61)
Median (Q1, Q3)	0.02 (0.00, 0.49)	0.04 (0.00, 0.50)
Min, max	0.00, 1.73	0.00, 3.05

Month 6

n	28	36
Mean (STDEV)	0.12 (0.29)	0.10 (0.26)
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Min, max	0.00, 1.10	0.00, 1.10

Month 9

n	22	29
Mean (STDEV)	0.09 (0.30)	0.07 (0.26)
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Min, max	0.00, 1.33	0.00, 1.33

Month 12

n	20	26
Mean (STDEV)	0.03 (0.10)	0.02 (0.09)
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Min, max	0.00, 0.44	0.00, 0.44

Month 15

n	9	14
Mean (STDEV)	0.19 (0.30)	0.12 (0.26)
Median (Q1, Q3)	0.00 (0.00, 0.43)	0.00 (0.00, 0.00)

Min, max	0.00, 0.76	0.00, 0.76
Month 18		
n	3	7
Mean (STDEV)	0.26 (0.46)	0.11 (0.30)
Median (Q1, Q3)	0.00 (0.00, 0.79)	0.00 (0.00, 0.00)
Min, max	0.00, 0.79	0.00, 0.79
Month 24		
n	–	4
Mean (STDEV)	–	0.00 (0.00)
Median (Q1, Q3)	–	0.00 (0.00, 0.00)
Min, max	–	0.00, 0.00

Data cutoff date = 09SEP2020. Abbreviations: AUC, area-under-the-curve; CAR, chimeric antigen receptor; max, maximum; min, minimum; Q, quartile; STDEV, standard deviation. AUC0-28 is defined as the AUC in a plot of number of CAR T cells in blood against scheduled visit from Day 0 to Day 28. Peak is defined as the maximum number of CAR T cells in blood measured after infusion. Time-to-peak is defined as the number of days from KTE-C19 infusion to the date when the number of CAR T cells in blood first reached the maximum postbaseline level.

Results by subgroups

Anti-CD19 CAR T-cell levels in blood (median peak and AUC0-28) were numerically lower in subjects < 65 years of age compared with subjects ≥ 65 years of age. Anti-CD19 CAR T-cell levels were the highest in Asian subjects followed by (from the highest to the lowest) subjects who had missing race information, subjects who reported their race as other, and White subjects. It is noticeable that the number of subjects ≥ 65 years of age and who were not White, was small. Anti-CD19 CAR T-cell levels (median peak and AUC0-28) were numerically lower in females than in males.

Table 3. Summary of Anti-CD19 CAR T-cell Peak and AUC_{0-28} in Blood by Age (Ph 2, Safety Analysis Set)

	< 65 Years of Age N = 47	≥ 65 Years of Age N = 8
Peak (cells/µL)		
n	43	7
Mean (STDEV)	81.20 (237.54)	36.75 (15.26)
Median (Q1, Q3)	17.44 (2.18, 65.85)	34.79 (25.36, 46.66)
Min, max	0.00, 1,533.40	15.99, 62.97
AUC_{0-28} (cells/µL•days)		
n	43	7
Mean (STDEV)	917.73 (2,965.75)	417.82 (157.49)
Median (Q1, Q3)	137.67 (15.29, 693.03)	424.96 (293.88,

		508.06)
Min, max	0.00, 19,390.42	222.67, 698.13

Data cutoff date = 09SEP2020. AUC0-28, area-under-the-curve from D0 to D28; CAR, chimeric antigen receptor; Q, quartile; STDEV, standard deviation. Notes: Peak is defined as the maximum number of CAR T cells in blood measured after infusion.

Table 4. Summary of Anti-CD19 CAR T-cell Peak and AUC_{0-28} in Blood by Sex (Phase 2, Safety Analysis Set)

	Female (N = 22)	Male (N = 33)
Peak (cells/µL)		
n	21	29
Mean (STDEV)	101.57 (331.04)	55.72 (76.94)
Median (Q1, Q3)	13.11 (4.02, 59.75)	31.00 (4.61, 62.97)
Min, max	0.00, 1,533.40	0.00, 322.24
AUC_{0-28} (cells/µL•days)		
n	21	29
Mean (STDEV)	1,248.54 (4,186.40)	557.51 (725.45)
Median (Q1, Q3)	126.22 (56.25, 460.94)	329.81 (79.27, 676.94)
Min, max	0.00, 19,390.42	0.00, 2,624.52

Data cutoff date = 09SEP2020. Abbreviations: AUC_{0-28}, area-under-the-curve from Day 0 to Day 28; CAR, chimeric antigen receptor; max, maximum; min, minimum; Q, quartile; STDEV, standard deviation. Notes: AUC_{0-28} is defined from Day 0 to Day 28. Peak is defined as the maximum number of CAR T cells in blood measured after infusion.

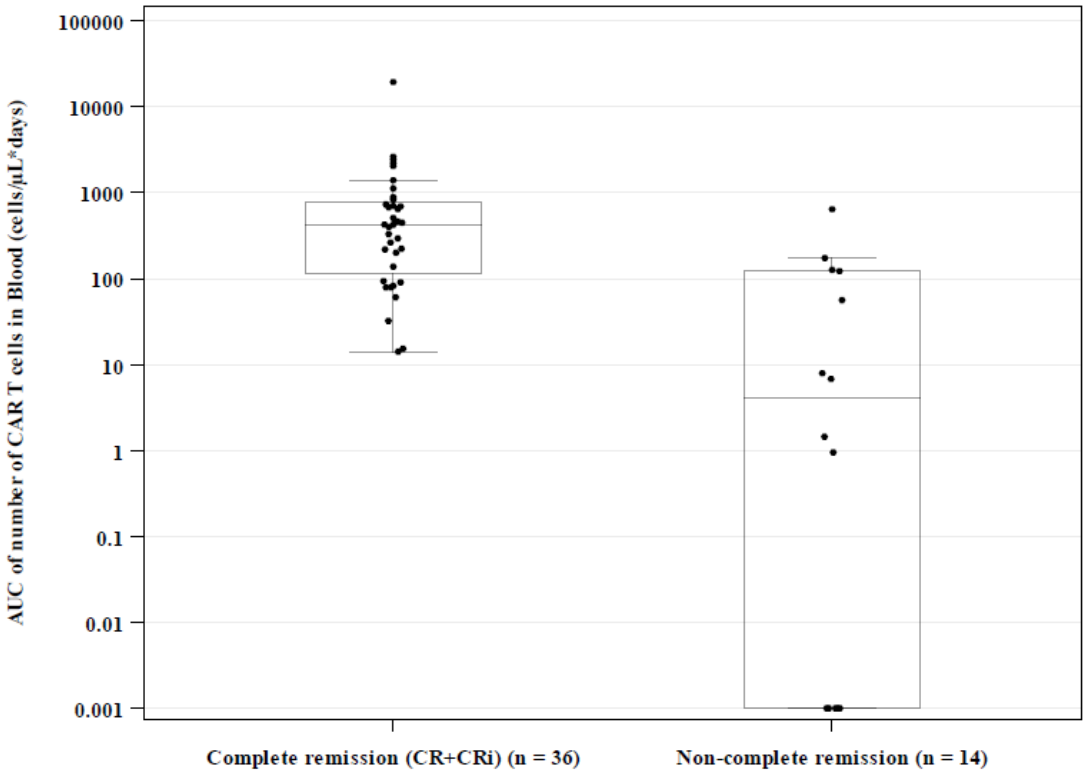
Results by use of tocilizumab/corticosteroids

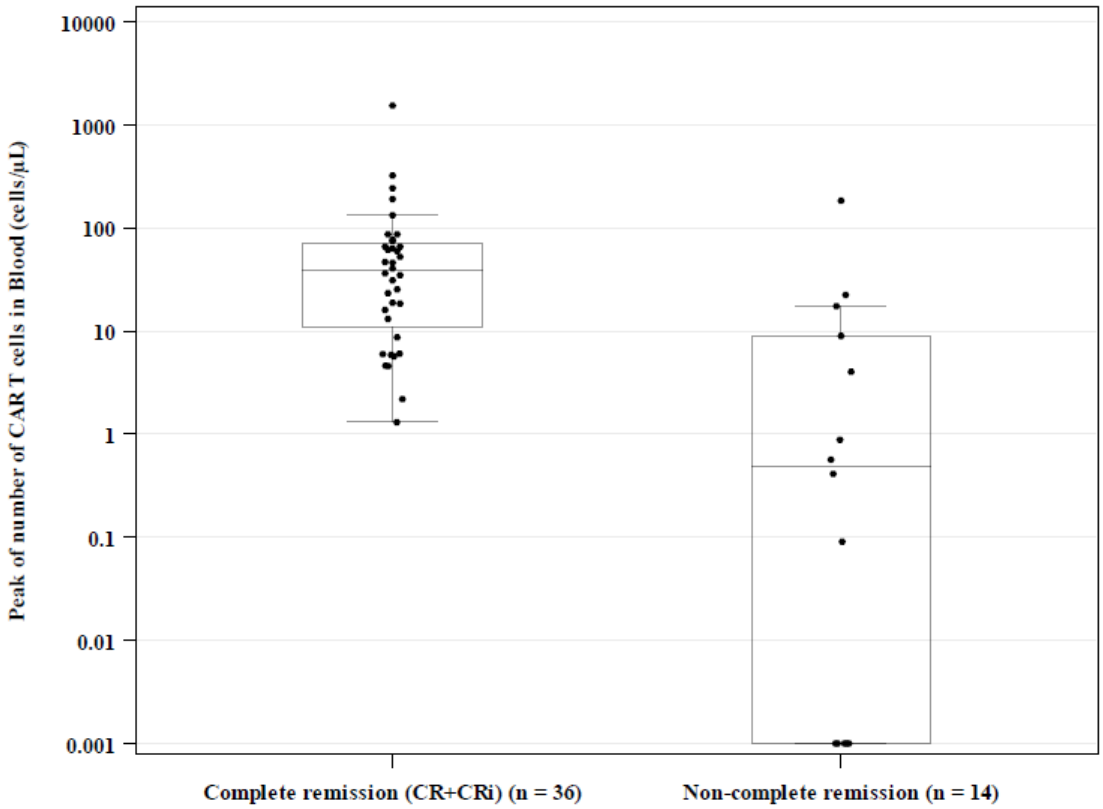
Median peak anti-CD19 CAR T-cell levels and AUC0-28 were higher in subjects who received tocilizumab alone or tocilizumab and corticosteroids than in subjects who received corticosteroids alone or who did not receive either of these medications. These results may be regarded to be attributed to the fact that higher anti-CD19 CAR T-cell levels in blood could lead to more severe AEs, subsequently managed with tocilizumab alone or tocilizumab and corticosteroids.

Results on association of PK of KTE-X19 PK and Response

Median peak anti-CD19 CAR T-cell levels and AUC0-28 were the highest in subjects who had achieved a CR, followed by (from the highest to the lowest) subjects who achieved a CRi, subjects who had blast-free hypoplastic or aplastic bone marrow, and subjects who had no response to KTE-X19. Subjects with CR/CRi had higher median peak anti-CD19 CAR T-cell levels and AUC0-28 in blood relative to subjects who had non-CR (non-CR/CRi) ($p < 0.001$ for median peak and AUC0-28 values) (Figure 2). Three of 39 subjects who achieved CR or CRi and 2 of 16 subjects who were non-CR/CRi had no anti-CD19 CAR T-cell data at all postinfusion visits.

Figure 2. Phase 2, mITT Analysis Set, N=55: Anti-CD19 CAR T-cell Peak Levels (Cells/µL) and AUC0-28 (Cells/µL•Days) in Blood by CR/ CRi Based on Central Assessment



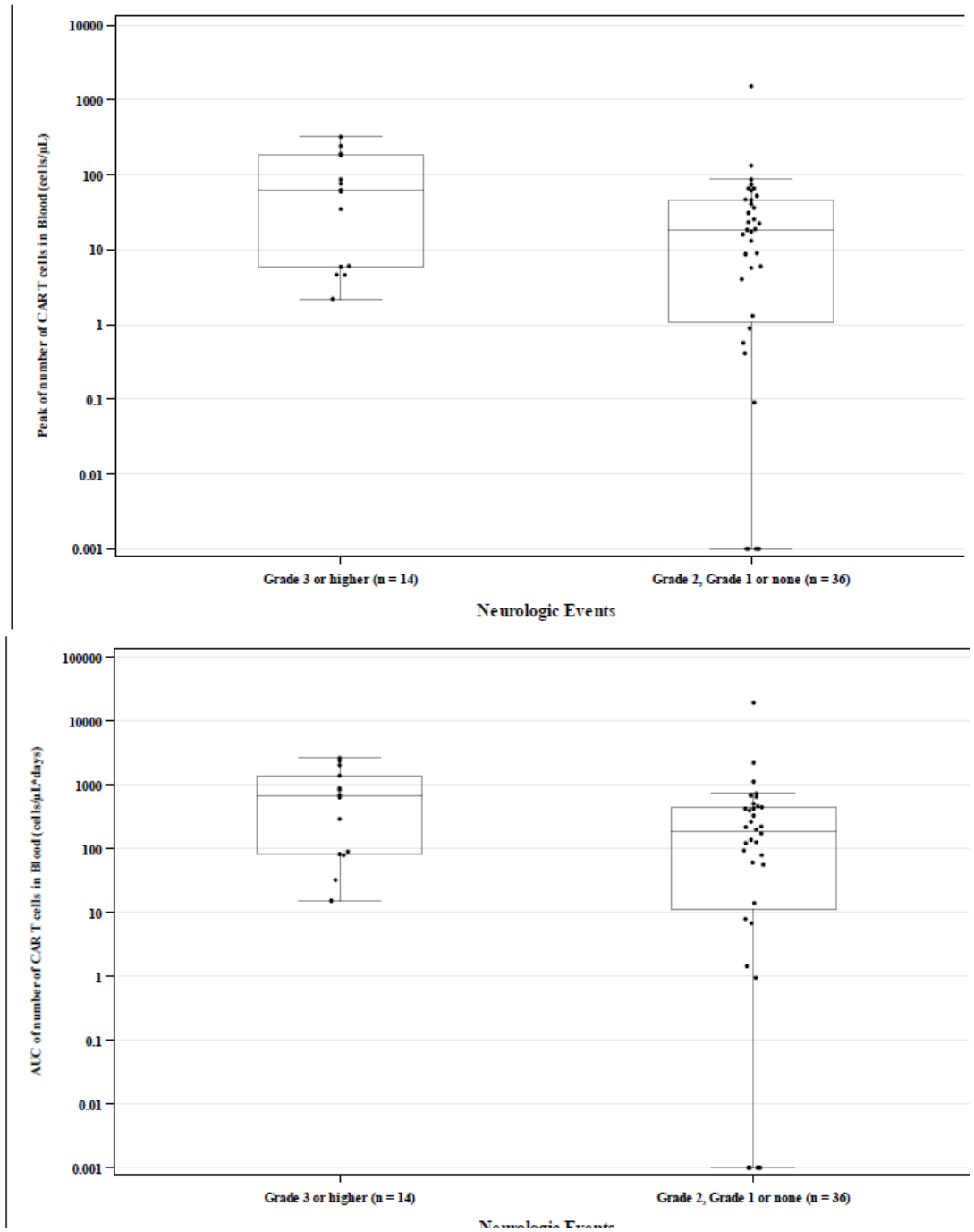


Results on association of PK of KTE-X19 and Safety Outcomes

Peak and AUC0-28 of anti-CD19 CAR T-cell levels in blood were examined for associations with CRS and neurologic events in Phase 2. Among the 55 subjects in the Phase 2 safety analysis set, 13 subjects had worst Grade 3 or higher CRS and 42 subjects had worst Grade 2 or lower CRS. No associations were observed between anti-CD19 CAR T-cell peak and AUC0-28 with frequency of worst Grade 3 or higher CRS relative to worst Grade 2 or lower CRS. Median peak anti-CD19 CAR T-cell levels were numerically lower, but not statistically different, in subjects with worst Grade 3 or higher CRS versus subjects with worst Grade 2 or lower CRS (16.7 vs 22.8 cells/µL). Similarly, the median AUC0-28 was numerically lower, but not statistically different, in subjects with worst Grade 3 or higher CRS versus subjects with worst Grade 2 or lower CRS (174.4 vs 240.8 cells/µL•days)

Among subjects in the Phase 2 safety analysis set, 14 subjects had worst Grade 3 or higher neurologic AEs, and 41 subjects had worst Grade 2 or lower neurologic AEs. A potential association was observed between median anti-CD19 CAR T-cell peak and AUC0-28 with frequency of worst Grade 3 or higher neurologic AEs versus worst Grade 2 or lower neurologic AEs. Median peak anti-CD19 CAR T-cell levels were 3.4-fold higher in subjects with worst Grade 3 or higher neurologic AEs versus subjects with worst Grade 2 or lower neurologic AEs (61.4 vs 17.9 cells/µL). Similarly, the median AUC0-28 was 3.6-fold higher in subjects with worst Grade 3 or higher neurologic AEs versus subjects with worst Grade 2 or lower neurologic AEs (670.2 vs 186.6 cells/µL•days).

Figure 3. Anti-CD19 CAR T-cell Peak (Cells/µL) and AUC0-28 (Cells/µL•Days) in Blood by Worst Grade 3 or Higher Neurologic AEs Versus Grade 2 or Lower Neurologic AEs (Phase 2, Safety Analysis Set, N = 55)



Results on association of B-cell levels with PK of KTEX-19 and Efficacy Outcomes

Associations between B-cell levels, anti-CD19 CAR T-cell levels, and ongoing response based on central assessment (ongoing CR/CRi, relapse, and lack of response [no-CR/CRi]) were evaluated in Phase 2 subjects. At Day 28, 7 of 9 subjects (77.8%) who achieved ongoing CR/CRi and had evaluable samples and 9 of 11 subjects (81.8%) who relapsed and had evaluable samples had B-cell levels below the lower level of quantification (LLOQ). One of 4 non-responders (25.0%) who had evaluable samples had B-cell levels below LLOQ. For subjects who achieved ongoing CR/CRi and had evaluable samples at the time

points described, B-cell recovery was observed in 6 of 10 subjects (60.0%) at Month 3, in 8 of 10 subjects (80.0%) at Month 6, and in 10 of 10 subjects (100%) at Month 12. Fourteen subjects in ongoing response, who either underwent allo-SCT (9 subjects) or started a new anticancer therapy (5 subjects), were not included in this analysis.

Results on association of B-ALL CD19 Expression and PK of KTE-X19

CD19 expression ranged from 47% to 100% across all subjects in Phase 2. High CD19 expression was defined as ≥ 95%, and low CD19 expression was defined as <95%. The range of CD19 expression was 95% to 100% in the high group and 47% to 92% in the low group. In Phase 2, 53 of 55 subjects had evaluable samples for CD19 expression at baseline, and 41 subjects had high CD19 expression and 12 subjects had low CD19 expression. Samples from 2 subjects were unavailable for testing.

According to table 4 there is an indication of lower anti-CD19 CAR-T cell expansion by peak and AUC0-28 in subjects with high tumor CD19 expression (median peak = 13.1 cells/µL and median AUC0-28 = 137.7 cells/µL•days) than in subjects with low tumor CD19 expression (median peak = 31.0 cells/µL and median AUC0-28 = 423.1 cells/µL•days). However, the number of subjects with low CD19 expression is quite small (N = 12).

Table 5. Summary of Anti-CD19 CAR T-cell Peak and AUC_{0-28} in Blood by Baseline CD19 Expression in Bone Marrow Based on Central Assessment (Phase 2, Safety Analysis Set)

	Percentage of Bone Marrow Lymphoblasts Expressing CD19 by Central Flow Cytometry Assessment	
	High (≥ 95%) (N = 41)	Low (< 95%) (N = 12)
Peak (cells/µL)		
n	37	11
Mean (STDEV)	48.43 (75.05)	170.01 (452.67)
Median (Q1, Q3)	13.11 (4.02, 61.33)	31.00 (22.43, 62.97)
Min, max	0.00, 322.24	0.88, 1,533.40
AUC_{0-28} (cells/µL•days)		
n	37	11
Mean (STDEV)	481.74 (715.40)	2,106.19 (5,738.05)
Median (Q1, Q3)	137.67 (32.28, 645.66)	423.10 (173.31, 698.13)
Min, max	0.00, 2,624.52	6.79, 19,390.42

Data cutoff date = 09Sep2020. Abbreviations: AUC, area-under-the-curve; CAR, chimeric antigen receptor; max, maximum; min, minimum; Q, quartile; STDEV, standard deviation. AUC0-28 is defined as the AUC in a plot of number of CAR T cells in blood against scheduled visit from Day 0 to Day 28. Peak is defined as the maximum number of CAR T cells in blood measured after infusion.

Results on Association of Bridging Therapy and PK of KTE-X19

Fifty-one of 55 subjects in Phase 2 received bridging therapy prior to lymphodepletion chemotherapy and infusion of KTE-X19. Results as presented in Table 5 indicate a numerically lower median anti-CD19 CAR T-cell peak levels in subjects who received bridging therapy (median peak = 18.6 cells/µL and median AUC0-28 = 209.2 cells/µL•days) than in subjects who did not receive bridging therapy (median peak = 56.1 cells/µL and median AUC_{0-28} = 546.0 cells/µL•days).

Table 6. Summary of Anti-CD19 CAR T-cell Peak and AUC_{0-28} in Blood According to Bridging Therapy (Phase 2, Safety Analysis Set)

	Bridging Therapy Received	
	Yes (N = 51)	No (N = 4)
Peak (cells/µL)		
n	46	4
Mean (STDEV)	76.97 (229.86)	51.98 (32.28)
Median (Q1, Q3)	18.62 (4.02, 62.97)	56.07 (30.68, 73.29)
Min, max	0.00, 1,533.40	8.96, 86.83
AUC_{0-28} (cells/µL•days)		
n	46	4
Mean (STDEV)	876.89 (2,868.55)	512.47 (314.43)
Median (Q1, Q3)	209.18 (32.28, 645.66)	545.97 (262.57, 762.36)
Min, max	0.00, 19,390.42	126.22, 831.70

Data cutoff date = 09Sep2020
Abbreviations: AUC, area-under-the-curve; CAR, chimeric antigen receptor; max, maximum; min, minimum; Q, quartile; STDEV, standard deviation.
AUC_{0-28} is defined as the AUC in a plot of number of CAR T cells in blood against scheduled visit from Day 0 to Day 28.
Peak is defined as the maximum number of CAR T cells in blood measured after infusion.

Results on association of PK of KTX-19 and Blast Percentage

The association of median peak anti-CD19 CAR T-cell levels and AUC0-28 in blood relative to blast percentage quartile intervals in the bone marrow at screening in Phase 2 can be described as an inverse association. Results indicate that subjects with the highest blast percentages (> 50%) had lower anti-CD19 CAR T-cell peak and AUC than subjects with lower blast percentages (< 50%).

Table 7. Summary of Median Peak Anti-CD19 CAR T-cell Levels and AUC_{0-28} in Blood by Quartiles of Blast Percentage in Bone Marrow at Screening (Phase 2, Safety Analysis Set)

% Blast in Bone Marrow Sample	Median Peak (Cells/µL)	Median AUC_{0-28} (Cells/µL•Days)
> 5% to 25% (n = 16)	40.47	424.96
> 25% to 50% (n = 9)	22.08	332.88
> 50% to 75% (n = 8)	18.35	204.54
> 75% to 100% (n = 22)	8.96	122.27

Data cutoff date = 09SEP2020
Abbreviations: AUC_{0-28}, area-under-the-curve from Day 0 to Day 28; CAR, chimeric antigen receptor.
AUC_{0-28} is defined from Day 0 to Day 28
Peak is defined as the maximum number of CAR T cells in blood measured after infusion.

2.3.3. Pharmacodynamics

Methods

A subset of 18 homeostatic, inflammatory, and immunde-modulating cytokines, chemokines, and immune effector molecules known to be involved in mediating the antitumor activity and to play a role in CAR T-cell treatment-related toxicity were preselected and serum analytes were evaluated at

several timepoints. Assays for 16 of 18 preselected serum analytes have been qualified. Granzyme B and perforin have been measured according manufactures' recommendations.

Table 8. *Summary of Pharmacodynamic Methods*

Category/Method	Description
Serum Analytes	
	At enrollment/leukapheresis At Day 0[a] After infusion on Days 3, 7, 14 and 28 At unscheduled hospital readmission with any KTE-X19-related AEs, then weekly, and on day of discharge At the time of disease progression
Assays	
Meso Scale Diagnostics, LLC (MSD®) V-PLEX® Plus Cytokine Panel 1	GM-CSF[b], IL-1α, IL-5, IL-7[b], IL-12/IL-23p40, IL-15[b], IL-16, IL-17A, and TNF-β (BED-02454, REP-21328 and REP-00255)
MSD® V-PLEX Plus Vascular Injury Panel 2	SAA, CRP[b], VCAM-1[b], and ICAM-1[b] (BED-01484 and REP-00256)
MSD® Proinflammatory Panel 1	IFN-γ[b], IL-1β, IL-2[b], IL-4, IL-6[b], IL-8[b], IL-10[b], IL-12p70, IL-13, and TNF-α[b] (BED-02361 and REP-00257)
MSD® Chemokine Panel 1	Eotaxin, MIP-1β, eotaxin-3, TARC, CXCL10 (IP-10)[b], MIP-1α, MCP-1 (CCL2), MDC, and MCP-4 (BED- 01482 and REP-00258)
ProteinSimple® Simple Plex™ IL-1RA, Granzyme A, Granzyme B, and B7-H1 (PD-L1) Assay	IL-1RA[b], granzyme A[b, c], granzyme B[b, c], and B7-Homolog 1[b] (BED-03436, REP-00380, REP-23291 and REP-23174)
ProteinSimple® Simple Plex™ IL-2Rα Assay	IL-2Rα (BED-02157 and REP-17900)
MILLIPLEX® MAP Human CD8+ T-Cell Panel	granzyme A, granzyme B, sFASL, and perforin (SOP-00332)
ProteinSimple® Simple Plex™ Ferritin, gp130, IL-6Ra and RANTES Assay	Ferritin[b], gp130[b, c], IL-6Ra[b, c], and RANTES[b, c] (BED-03317 and REP-22686)

Abbreviations: AE, adverse event; BED, business enabling document; CCL2, C-C motif chemokine ligand 2; CRP, C-reactive protein; CXCL, C-X-C motif chemokine; ELISA, GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IL-2Rα, interleukin-2 receptor alpha; IP, interferon-inducible protein; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; MSD, Meso Scale Diagnostics; PD-L1, programmed death-ligand 1; REP, report; SAA, serum amyloid A; sFASL, soluble FAS ligand; SOP, standard operating procedure; TARC, thymus- and activation-regulated chemokine; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule. a The Day 0 time point was taken before KTE-X19 infusion b Assay qualified for analyte in serum c Analytes not used in the ZUMA-3 analysis

B-Cell Evaluation

On-target/off-tumor effect of KTE-X19 on normal CD19-expressing B cells, the presence and percentage of CD19+, CD20+, or CD19+CD20+ B cells in cryopreserved peripheral blood mononuclear cells (PBMCs) were evaluated by a flow cytometry assay leveraging pre- and post-treatment PBMC. B-cell levels were calculated as a percentage of CD19+, CD20+, or CD19+CD20+ B cells relative to viable CD45+

leukocytes in a flow cytometry assay. It should be noted that this assay does not reliably distinguish between normal and leukemic CD19+CD20+cells present in PBMC, which is known.

Other Analytes

The MRD− rate (minimal residual disease) was defined as the incidence of an MRD− response, where MRD− was defined as MRD < 10-4 per the standard assessment by flow cytometry performed by the central laboratory. Subjects were considered MRD− overall, if they achieved an MRD− response at any prespecified postinfusion visit (ie, Day 28, Week 8, or Month 3); otherwise, subjects were considered MRD+ overall. Best overall MRD response was examined herein for exploratory associations with KTE-X19 expansion kinetics.

Bone marrow aspirates collected at in predefined intervals described in the ZUMA-3 protocol schedule of assessment at screening, Day −4 (only for subjects who received bridging), Day 28, Week 8, and Month 3 after KTE-X19 infusion, were examined in Rolle, Switzerland for EU sites. In addition, peripheral blood was collected at screening or Day −4 for use as an assay calibration sample, if needed. The B-ALL MRD flow cytometry assay measures the following markers and is designed to identify and enumerate B-ALL blasts: CD3, CD9, CD10, CD13, CD19, CD20, CD33, CD34, CD38, CD45, CD58, and CD71.

Results

Selected Serum Analytes

Among all evaluable subjects in Phase 2, the main observations were the following:

Day 0 (after lymphodepleting chemotherapy): Median serum levels of homeostatic cytokines IL-7 and IL-15 increased by ≥ 2-fold and median serum levels of perforin decreased by ≥ 2-fold relative to baseline.

Day 3: Median IL-2, IL-6, IL-7, IL-10, IL-15, and interferon [IFN]-γ serum levels were elevated by ≥ 2-fold relative to baseline in most subjects. The majority of the other 18 preselected serum analytes were comparable relative to baseline (< 2-fold change).

Day 7: Median CRP, C-X-C motif chemokine (CXCL)10, granzyme B, IFN-γ, interleukin-1 receptor antagonist (IL-1RA), IL-2, interleukin-2 receptor (IL-2R)α, IL-6, IL-8, IL-10, and IL-15 were elevated by ≥ 2-fold relative to baseline in most subjects. Median serum levels of the majority of the 18 other preselected serum analytes were comparable relative to baseline.

TNF-alpha: 34 of 55 subjects (61.8%) demonstrated a 2-fold higher change in serum levels over baseline and they generally returned to baseline by week 4.

Median time-to-peak for the 18 preselected serum analytes, except for ferritin and perforin, was between 7 and 8 days after infusion of KTE-X19. Median time-to-peak was 9 days for ferritin and 15 days for perforin. Most of the 18 preselected serum analytes were elevated by ≥ 2-fold at peak compared with baseline in ≥ 50% of subjects (exceptions: intracellular adhesion molecule, perforin, and vascular cell adhesion molecule).

Week 4: Eleven of 18 preselected serum analytes returned to near or below baseline levels; 7 analytes remained elevated by ≥ 2-fold in ≥ 20% of subjects (CXCL10, IFN-γ, IL-1RA, IL-6, IL-7, IL-10, and IL-15).

Table 9. Summary of Subjects with ≥ 2-fold Change from Baseline in 18 Preselected Serum Analytes (Phase 2, Safety Analysis Set, N=55)

Analyte	Peak (N = 55) n (%)	Day 0 (N = 55) n (%)	Day 3 (N = 51) n (%)	Day 7 (N = 52) n (%)	Week 2 (N = 50) n (%)	Week 4 (N = 46) n (%)
CRP (mg/L)	38 (69.1)	16 (29.1)	15 (29.4)	26 (50.0)	7 (14.0)	3 (6.5)
CXCL10 (pg/mL)	48 (87.3)	16 (29.1)	14 (27.5)	39 (75.0)	19 (38.0)	15 (32.6)
Ferritin (ng/mL)	39 (70.9)	3 (5.5)	3 (5.9)	25 (48.1)	23 (46.0)	7 (15.2)
Granzyme B (pg/mL)[a]	39 (70.9)	4 (7.3)	7 (13.7)	25 (48.1)	10 (20.0)	5 (10.9)
ICAM-1 (ng/mL)	18 (32.7)	2 (3.6)	1 (2.0)	12 (23.1)	5 (10.0)	1 (2.2)
IFN-γ (pg/mL)[a]	53 (96.4)	9 (16.4)	24 (47.1)	48 (92.3)	15 (30.0)	15 (32.6)
IL-1RA (pg/mL)	44 (80.0)	10 (18.2)	9 (17.6)	31 (59.6)	15 (30.0)	13 (28.3)
IL-2 (pg/mL)[a]	47 (85.5)	4 (7.3)	33 (64.7)	34 (65.4)	8 (16.0)	3 (6.5)
IL-2Rα (ng/mL)	37 (67.3)	3 (5.5)	5 (9.8)	29 (55.8)	27 (54.0)	5 (10.9)
IL-6 (pg/mL)[a]	54 (98.2)	10 (18.2)	12 (23.5)	46 (88.5)	38 (76.0)	38 (82.6)
IL-7 (pg/mL)	43 (78.2)	35 (63.6)	33 (64.7)	27 (51.9)	26 (52.0)	28 (60.9)
IL-8 (pg/mL)	39 (70.9)	10 (18.2)	11 (21.6)	32 (61.5)	12 (24.0)	9 (19.6)
IL-10 (pg/mL)[a]	52 (94.5)	12 (21.8)	17 (33.3)	42 (80.8)	29 (58.0)	14 (30.4)
IL-15 (pg/mL)	51 (92.7)	44 (80.0)	46 (90.2)	43 (82.7)	29 (58.0)	16 (34.8)
Perforin (ng/mL)	19 (34.5)	1 (1.8)	1 (2.0)	11 (21.2)	7 (14.0)	9 (19.6)
TNF-α (pg/mL)	34 (61.8)	3 (5.5)	6 (11.8)	28 (53.8)	9 (18.0)	5 (10.9)
VCAM-1 (ng/mL)	11 (20.0)	2 (3.6)	2 (3.9)	8 (15.4)	2 (4.0)	3 (6.5)
GM-CSF (pg/mL)[a]	30 (54.5)	1 (1.8)	4 (7.8)	26 (50.0)	4 (8.0)	1 (2.2)

Data cutoff date = 09SEP2020
Abbreviations: CRP, C-reactive protein; CXCL, C-X-C motif chemokine; GM-CSF, granulocyte macrophage-colony stimulating factor; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IL-2R, interleukin-2 receptor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.
Notes: The fold increase is defined as the value at each visit/baseline. Peak is defined as the maximum level of cytokine from baseline to Week 4. Number and percentage of subjects with a ≥ 2-fold change from baseline were presented.
a. Because the median baseline levels of these analytes were below the lower limit of quantification, the true fold change over baseline at peak and later time points is not determinable.

B-Cell Levels in Blood over the Time

In Phase 2, at baseline, 47 of 49 tested subjects (95.9%) had detectable B cells; the median B-cell percentage in PBMC was 22.7% (range: 0.05% to 87.6%). At Day 28 (the first time point at which B cells were measured after KTE-X19 infusion), 9 of the 36 tested subjects (25.0%) had detectable B cells and the median B-cell percentage was 0.05% (range: 0.02% to 56.7%). At Month 12, all 22 subjects (100%) with evaluable samples had detectable B cells (median: 20.1% [range: 0.02% to 93.7%]).

In the combined Phase 1 cohorts (Phase 1 subjects treated at all dose levels, N = 45), all subjects with evaluable baseline PBMC samples (n = 35) had detectable B cells. At Day 28, 13 of 25 subjects (52.0%) with evaluable samples had detectable B cells, and the median B-cell percentage was 0.40% (range: 0.02% to 96.7%). At Month 12, all 12 subjects (100%) with evaluable PBMC samples had detectable B cells (median: 13.9% [range: 4.4% to 40.8%]).

Table 10. Summary of B-cell Levels (%) Over Time (Phase 2 and Combined Phase 1 Cohorts, Safety Analysis Set)

Visits/Parameter	Phase 2 (N = 55)	Combined Phase 1 Cohorts (N = 45)
Baseline		
All tested subjects, N (%)	49 (89.1)	35 (77.8)
No B-cells, N (%)	2 (4.1)	0
With B-cells	–	–
n (%)	47 (95.9)	35 (100.0)
Mean (STDEV), of % B cell	33.99 (28.09)	47.94 (35.41)
Median (Q1, Q3), of % B cell	22.67 (9.38, 56.12)	43.22 (7.30, 81.50)
Min, Max of % B cell	0.05, 87.55	0.03, 94.63
Day 28		
All tested subjects, N (%)	36 (65.5)	25 (55.6)
No B-cells, N (%)	27 (75.0)	11 (44.0)
With B-cells	–	–
n (%)	9 (25.0)	13 (52.0)
Mean (STDEV), of % B cell	8.22 (19.02)	33.26 (44.56)
Median (Q1, Q3), of % B cell	0.05 (0.03, 0.07)	0.40 (0.03, 92.88)
Min, Max of % B cell	0.02, 56.70	0.02, 96.74
Month 3		
All tested subjects, N (%)	32 (58.2)	24 (53.3)
No B-cells, N (%)	12 (37.5)	3 (12.5)
With B-cells	–	–
n (%)	20 (62.5)	20 (83.3)
Mean (STDEV), of % B cell	10.11 (14.10)	7.20 (8.73)
Median (Q1, Q3), of % B cell	2.49 (0.13, 20.33)	2.47 (0.16, 12.78)
Min, Max of % B cell	0.02, 47.55	0.02, 26.14
Month 6		
All tested subjects, N (%)	28 (50.9)	24 (53.3)
No B-cells, N (%)	2 (7.1)	2 (8.3)
With B-cells	–	–
n (%)	26 (92.9)	22 (91.7)
Mean (STDEV), of % B cell	19.16 (22.46)	11.16 (19.33)
Median (Q1, Q3), of % B cell	12.11 (1.42, 26.27)	3.27 (0.37, 14.46)
Min, Max of % B cell	0.02, 86.27	0.10, 84.97
Month 12		

All tested subjects, N (%)	22 (40.0)	12 (26.7)
No B-cells, N (%)	0	0
With B-cells	–	–
n (%)	22 (100.0)	12 (100.0)
Mean (STDEV), of % B cell	26.36 (24.25)	18.28 (13.03)
Median (Q1, Q3), of % B cell	20.13 (6.27, 38.08)	13.89 (6.53, 29.91)
Min, Max of % B cell	0.02, 93.71	4.41, 40.84
Month 15		
All tested subjects, N (%)	10 (18.2)	10 (22.2)
No B-cells, N (%)	2 (20.0)	0
With B-cells	–	–
n (%)	8 (80.0)	10 (100.0)
Mean (STDEV), of % B cell	22.00 (19.02)	16.57 (13.52)
Median (Q1, Q3), of % B cell	19.76 (7.00, 32.62)	12.01 (8.95, 19.28)
Min, Max of % B cell	0.06, 57.15	3.70, 44.13
Month 18		
All tested subjects, N (%)	1 (1.8)	2 (4.4)
No B-cells, N (%)	0	0
With B-cells	–	–
n (%)	1 (100.0)	2 (100.0)
Mean (STDEV), of % B cell	40.61 (-)	13.57 (4.99)
Median (Q1, Q3), of % B cell	40.61 (40.61, 40.61)	13.57 (10.04, 17.10)
Min, Max of % B cell	40.61, 40.61	10.04, 17.10
Month 24		
All tested subjects, N (%)	–	7 (15.6)
No B-cells, N (%)	–	0
With B-cells	–	–
n (%)	–	7 (100.0)
Mean (STDEV), of % B cell	–	21.11 (13.54)
Median (Q1, Q3), of % B cell	–	23.88 (6.73, 35.28)
Min, Max of % B cell	–	3.84, 39.47

Data cutoff date = 09SEP2020. Abbreviations: Max, maximum; min, minimum; Q, quartile; STDEV, standard deviation. Subjects with undetermined B-cell category are not displayed in tables but considered as tested for B cell. The percentages of subjects with no B cells or with B cells are calculated using the number of tested subjects as the denominator.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetic, pharmacodynamic and other translational medicine analyses presented are derived from data from n=55 subjects treated with KTE-X19 in the ZUMA-3 clinical trial with a data cutoff date of 09 September 2020 and a potential median study follow-up of 16.4 months. The assessments were based on current knowledge of mechanism of action of KTE-X19. Pharmacodynamic (PD) endpoints were levels of cytokines in serum and levels of B-cells over the time; levels of anti-CD19 CAR T cells in blood was the pharmacokinetic (PK) endpoint in the study. Exploratory endpoints were investigation of associations among PD, PK, efficacy and safety outcomes. The median total number of anti-CD19 CAR T cells in KTE-X19 infusion products was 75.7 x 106 cells (range: 39.3 x 106 to 101.0 x 106 cells), and the median total number of T cells infused was 128.4 x 106 cells (range: 65.5 x 106 to 277.8 x 106 cells). All but one of the 55 subjects (98%) received within 10% of the planned target dose. The median time-to-peak of anti-CD19 CAR T cell levels in blood occurred at Day 15 after infusion of KTE-X19. Both median anti-CD19 CAR T cell levels and AUC0-28 were higher in patients who were in CR/CRi compared to patients, who did not achieve CR/CRi and/or relapsed, in patients who were MRD negative versus patients who were MRD positive, in males versus females and in subjects with grade 2 or higher CRS.

The 18 preselected serum analytes had their peak generally around Day 7-8 after administration of KTE-X19 and decreased to baseline-levels by Week 4. The following key associations with grade 3 or higher CRS and/or neurotoxicity have been observed:

- Positive association for Grade 3 or higher CRS and peak serum levels of ferritin, granzyme B, IL-2Rα, IL-6, IL-8, IL-10, IL-15, IFN-γ, TNF-α, and GMCSF.
- Positive association for Grade 3 or higher neurologic AEs and peak serum levels of IL-1RA and IL-6.
- Positive association for Grade 2 or higher neurologic AEs and peak serum levels of IL-1RA, IL-2Rα, IL-10, and IFN-γ.

These results can be considered consistent with the known mechanism of action of anti-CD19 CAR T cells in general, which is induction of cytokines and inflammatory cytokines after lymphodepletion and chemokines after CAR T-cell infusion.

Results on association of KTE-X19 characteristics with PK, efficacy and safety outcomes revealed no potential trend by median peak of CAR T cells or AUC0-28.There was also no significant relationship observed between product characteristics by quartile and key efficacy (CR/CRi) and safety outcomes (CRS and neurologic AEs). However, those observations are of limited value due to the small number of subjects in the respective subgroups.

Notwithstanding, some important results regarding possible associations of product characteristics by quartile and adverse events could be identified:

- Higher incidence of Grade 3 or higher CRS in subjects who received products that produced lower IFN-γ in co-culture and in subjects who received a lower total number of anti-CD19 CAR T cells.
- Higher incidence of Grade 3 or higher neurologic AEs or serious Grade 3 or higher neurologic AEs in subjects who received products with higher levels of IFN-γ produced in co-culture, a higher total number of anti-CD19 CAR T cells, lower percentages of CD4+ T cells, higher percentages of CD8+ T cells, and a lower CD4:CD8 ratio.
- Higher incidence of serious infections or Grade 3 or higher serious infections in subjects who received products that had lower levels of IFN-γ produced in co-culture and in subjects who received products with a lower percentage of CD4+ T cells, a higher percentage of CD8+ T cells, and a lower CD4:CD8 ratio.

2.3.5. Conclusions on clinical pharmacology

The results presented on clinical pharmacology for KTE-X19 in n=55 adult patients with r/r ALL (ZUMA-3) largely are comparable with those provided for the marketing authorisation of Tecartus in the indication mantle cell lymphoma after 2 or more lines of systemic therapy, granted on 14 December 2020 as a conditional approval. However, due to the limited number of patients, results on the pharmacology of KTE-X19, particularly in specific clinically meaningful subgroup analyses such as Ph-positive and/or negative patients, tumor burden at baseline etc., should be considered with caution.

IFN-γ, CD8+ cells and CD4+ cells seem to be clinically important in view of both analysis on their suitability as potential surrogate markers for CAR T cell persistence and in view of relation to the occurrence of adverse events ≥ grade 3. According to the literature database, investigations on correlations between CAR T cells in blood IFN-γ- and further important IFN-levels in plasma as well as the role of CD8+ and CD4+ on efficacy and safety of CAR T cell therapy are ongoing; currently, however there seems to be no final conclusion on their suitability as markers. Further investigations on pharmacology parameters, subgroups considered, and possible relationships between KTE-X19 product specifics and occurrence of adverse events would be needed.

The presented data is acceptable to support the clinical pharmacology of the new indication in ALL in the context of the CMA.

2.4. Clinical efficacy

2.4.1. Main study

ZUMA-3: Phase I/II multi-center study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r B-cell precursor ALL

Methods

Study participants

Main inclusion criteria

1. Age 18 or older

2. Relapsed or refractory B-precursor ALL defined as one of the following:

- Primary refractory disease
- First relapse if first remission ≤ 12 months
- Relapsed or refractory disease after two or more lines of systemic therapy
- Relapsed or refractory disease after allogeneic transplant provided subject is at least 100 days from stem cell transplant at the time of enrollment and off of immunosuppressive medications for at least 4 weeks prior to enrollment
- Subjects with Ph+ disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least 2 different TKIs

3. Eastern cooperative oncology group (ECOG) performance status of 0 or 1

4. ANC ≥ 500/µL unless in the opinion of the PI cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy

5. Platelet count ≥ 50,000/µL unless in the opinion of the PI cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy

6. Absolute lymphocyte count ≥ 100/µL

7. Adequate renal, hepatic, pulmonary and cardiac function

8. In subjects previously treated with blinatumomab, CD19 tumor expression on blasts obtained from bone marrow or peripheral blood must be documented after completion of the most recent prior line of therapy. If CD19 expression is quantified, then blasts must be ≥ 90% CD19 positive.

Main exclusion criteria

1. Diagnosis of Burkitt's leukemia/Lymphoma according to WHO classification or chronic myelogenous leukemia lymphoid blast crisis

2. History of malignancy other than non-melanoma skin cancer or carcinoma in situ

3. CNS abnormalities:

- Presence of CNS-3 disease defined as detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 WBCs per mm3 with or without neurological changes, and
- Presence of CNS-2 disease defined as detectable cerebrospinal blast cells in a sample of CSF with <5 WBCs per mm3 with neurological changes
- History or presence of any CNS disorder

4. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment

5. Primary immunodeficiency

6. Prior medication:

- Salvage systemic therapy within 1 week or 5 half-lives (whichever is shorter) prior to enrollment
- Prior CD19 directed therapy other than blinatumomab
- History of CTCAE grade 4 neurologic event or grade 4 CRS (Lee et al, 2014) with prior CD19-directed therapy
- Treatment with alemtuzumab within 6 months prior to enrollment, clofarabine or cladribine within 3 months prior to enrollment, or PEG-asparaginase within 3 weeks
- Donor lymphocyte infusion (DLI) within 28 days prior to enrollment
- Any drug used for GVHD within 4 weeks prior to enrollment or immunosuppressive antibody used within 4 weeks prior to enrollment
- At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy prior to enrollment
- Corticosteroid therapy at a pharmacologic dose and other immunosuppressive drugs must be avoided for 7 days prior to enrollment

7. Presence of any indwelling line or drain

8. Live vaccine ≤ 4 weeks prior to enrollment

9. History of autoimmune disease resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

Treatments

In ZUMA-3 Phase 1, 45 subjects were enrolled and treated at 0.5 x 10^6, 1 x 10^6, or 2 x 10^6 anti-CD19 CAR T cells/kg. The dose of 1 x 10^6 anti-CD19 CAR T cells/kg showed the highest efficacy, a manageable safety profile, and the most favorable benefit-risk profile across the doses evaluated. Therefore, the dose of 1 x 10^6 anti-CD19 CAR T cells/kg (maximum dose of 1 x 10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg) was considered the recommended Phase 2 dose.

In the Phase 2 portion of ZUMA-3, 55 subjects were treated with KTE-X19 at a dose of 1.0 x 10^6 anti-CD19 CAR T cells/kg. The primary analysis was planned to occur when the overall study enrollment was complete and the last treated subject in Phase 2 modified intent-to-treat (mITT) analysis set had had the opportunity to complete the Month 6 disease assessment. At the time of the data cutoff date for the primary analysis, all subjects in the mITT analysis set had had the opportunity to be followed for at least 10 months after the KTE X19 infusion. This overview summarizes the results of the primary efficacy and safety analyses for subjects in ZUMA-3 Phase 2 with a data cutoff date of 09 September 2020. Subjects in Phase 1 were not part of the pivotal analysis.

KTE-X19 was administered after a lymphodepleting chemotherapy regimen (conditioning therapy) consisting of fludarabine 25 mg/m2/day on Day −4, Day −3, and Day −2; and cyclophosphamide 900 mg/m2/day administered IV on Day −2.

Objectives

Outcomes/endpoints

Primary endpoint
OCR rate (CR and CRi) per central assessment

Major secondary endpoints

- MRD^- rate defined by central assessment
- DOR
- OCR per investigator assessment
- Incidence of AEs
- OS

Sample size

The planned enrollment to this study (phase 1 and 2) was 100 subjects.

During Phase 2, approximately 50 subjects in the modified-intention to treat (mITT) set were planned to be assessed to evaluate the efficacy and safety of KTE-X19. With this sample size the study was expected to have approximately 93% power to distinguish between an active therapy with a 65% true

overall complete remission rate from a therapy with an overall complete remission rate of 40% or less with a 1-sided alpha level of 0.025.

Of note in the original study protocol, a different calculation was presented, assuming with the same planned sample size of approximately n=50 a power of 86% to distinguish between an active therapy with a 40% true overall complete remission rate from a therapy with an overall complete remission rate of 20% or less with a 1-sided alpha level of 0.025. This planning included a futility assessment after n=20 patients.

Randomisation

This is a single arm study.

Blinding (masking)

This is a single arm study, and therefore open-label.

Statistical methods

Analysis and covariates

An exact binomial test was planned to be used to compare the observed response rate to the threshold of 40%. This is acceptable for a phase 2 exploratory study. However, there is concern that heterogeneity in patients' prognosis might have an impact on results in this single arm study, thus limiting a confirmatory interpretation.

Upon request, the applicant confirmed that CR rates are heterogeneous in the literature (an I^2 estimate of 52% was observed for the results of the meta-analysis of CR rates).

The applicant referred to literature stating that heterogeneous definitions of CR may be the reason for this observed heterogeneity. It is agreed that this may be an explanation, however, this does not resolve uncertainty on possible CR rates. Thus, uncertainty remains.

Significance level and multiplicity

The planned significance level of 0.025 (one-sided) is in principle acceptable. However, the phase 2 part of the study is intended to be interpreted as a single pivotal study, implying that results should be compelling, also by means of statistical significance

A hierarchical approach was chosen to test the secondary endpoint of minimum residual disease negative rate against the threshold of 30% upon rejection of the primary null hypothesis of complete remission ≤40%. A hierarchical approach is acceptable. The hierarchical testing was introduced in amendment 4 (10 March 2017).

Interim analyses

According to the latest version of the protocol, one interim analysis was planned for safety only.

However there were several changes to interim analyses:

Initially, two interim analyses were planned after 20 and 35 patients in phase 2 in the mITT set had the opportunity to be followed for 8 weeks or 28 days after infusion respectively, with assessments planned for futility and safety. This was subsequently changed several times during the course of the study:

In amendment 3 (28 July 2016), the second interim analysis with 35 patients was planned to assess early demonstration of efficacy, and a Lan-DeMets alpha-spending function with O'Brian-Fleming type boundaries was planned for multiplicity control.

Assessment of efficacy at interim analysis 2 was removed in amendment 4 (10 March 2017), but the interim analysis was kept for other purposes.

Finally, in protocol amendment 6 (31 October 2018) the second interim analysis was removed.

The timing of the interim analyses was amended several times throughout the study as well.

Changes to the protocol

As discussed above, there were several relevant changes to interim analyses, hypotheses and multiplicity.

Although most of them were introduced before the first patient was enrolled to phase 2 (on 01 October 2018), this may reflect that the study was initially planned as an exploratory trial with some uncertainty. Given the above discussion, the assessors conclude that not all uncertainty can be resolved, and a confirmatory interpretation remains difficult. However, given the circumstances, an ad-hoc interpretation of results seems warranted.

Historical control and meta-analyses of outcomes in r/r ALL

The rationale for a prespecified 40% OCR historical control rate was informed by rates observed in published studies of second-line or later chemotherapy and SCT regimens and in pivotal studies of blinatumomab. The blinatumomab studies, which included patient populations similar to those enrolled in ZUMA-3, resulted in CR/CRh rates of approximately 42%; the CR rates were 32.4% in the Phase 2 study (Study MT103-211) and 33.6% in the Phase 3 TOWER study. By comparison, standard-of-care chemotherapy for subjects in the TOWER study yielded a CR rate of 15.7% and CR/CRh rate of 20.1% {BLINCYTO 2019, Kantarjian 2017}.

In order to allow matched subject comparison, a prespecified, retrospective, matched-cohort study derived from individual subject-level data sampled from historical clinical trials (HCTs) contained within the Medidata Enterprise Data Store (MEDS) database. MEDS is a collection of thousands of previous clinical trials with subject-level data recorded through the Medidata electronic data capture system, Rave. This companion study, referred to as SCHOLAR-3, was matched to the ZUMA-3 Phase 2 mITT analysis set and was intended to provide context for interpreting the ZUMA-3 results and confirm the prespecified control response rate.

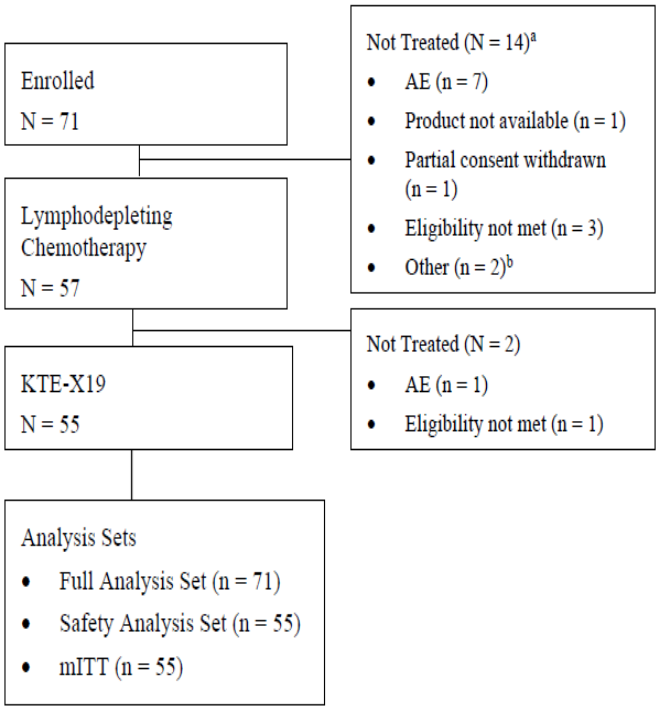
A total of 40 subjects previously naïve to blinatumomab and inotuzumab treatment were included in the study; 20 from ZUMA-3 matched to 20 from historical trials; this was referred to as synthetic control arm 1 (SCA-1). A further 49 blinatumomab or inotuzumab pretreated subjects were also included in the study; 29 from ZUMA-3 matched to 20 from historical trials; this was referred to as synthetic control arm 2 (SCA-2). Data for OCR and OS were available for SCA-1; only OS data were available for SCA-2. No appropriate matches from HCTs were found for 6 subjects from the ZUMA-3 mITT population; these subjects were thus excluded.

Note that 29 subjects in SCA-2 were originally matched with 29 subjects from ZUMA-3; however, 9 subjects in SCA-2 were later excluded from the analysis since they did not have a documented relapse prior to starting a subsequent therapy. In a post hoc analysis, OCR rate and OS were compared between all subjects from ZUMA-3, irrespective if they had previously been pre-treated with blinatumomab or

inotuzumab, versus matched subjects from HCTs who had not previously been treated with blinatumomab or inotuzumab; this was referred to as synthetic control arm 3 (SCA-3).

Results

Participant flow



Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; mITT, modified intent-to-treat.

a Products were not successfully manufactured for 6 subjects (see Section 8.4.2). Subjects were reported by the sites as not treated for the following reasons: AE (1 subject), product not available (1 subject), partial consent withdrawn (1 subject), eligibility not met (1 subject), and other (2 subjects).

b One subject experienced clinical deterioration after product was not successfully manufactured from 3 leukapheresis attempts, and 1 subject was considered not clinically stable to proceed with CAR T-cell therapy after product was not successfully manufactured from the initial leukapheresis attempt.

Recruitment

Conduct of the study

Relevant dates to the conduct of the ZUMA-3 trial

Event	Date
First subject screened in Phase 1	01 March 2016
First subject enrolled in Phase 1	07 March 2016
Last subject enrolled in Phase 1	12 July 2018

First subject enrolled in Phase 2	01 October 2018
Last subject enrolled in Phase 2	09 October 2019
Last observation for the primary analysis and for this report	09 September 2020
Data cutoff date	09 September 2020

Baseline data

Phase 2 mITT analysis set/safety set (all enrolled and treated with KTE-X19 subjects): n= 55

The median age was 40.0 years (range: 19 to 84 years); 8 subjects (15%) were ≥ 65 years of age. Thirty-three subjects (60%) were male; the majority were White (37 subjects, 67%). Forty-one subjects (75%) were enrolled in the US, and 14 subjects (25%) were enrolled in the EU.

Eighteen subjects (33%) had primary refractory disease, 43 subjects (78%) had r/r disease after 2 or more lines of therapy, and 16 subjects (29%) had first relapse with first remission ≤ 12 months. Fifteen subjects (27%) were Ph+. Subjects had a median of 2 prior lines of therapy (range: 1 to 8 prior lines), and 26 subjects (47%) had received 3 or more lines of therapy. Twenty-three subjects (42%) had previously received an allo-SCT. Twelve subjects (22%) had previously received inotuzumab, twenty-five subjects (45%) had previously received blinatumomab (12 subjects (22%) as the last prior therapy). The median blast percentage in bone marrow at screening was 65.0% (range: 5.01% to 100%), and the median blast percentage at baseline (ie, the last assessment before lymphodepleting chemotherapy) was 60.0% Forty subjects (73%) had M3 bone marrow involvement (> 25% blasts) at baseline. Six subjects (11%) had extramedullary disease at screening.

Table 11. Demographics (Phase 2, mITT Analysis Set)

	Phase 2 (N = 55)
Age (years)	
n	55
Mean (STDEV)	42.2 (16.1)
Median	40.0
Min, Max	19, 84
Age category, n (%)	
< 65 Years	47 (85)
≥ 65 Years	8 (15)
Sex, n (%)	
Male	33 (60)
Female	22 (40)

Ethnicity, n (%)	
Hispanic or Latino	11 (20)
Not Hispanic or Latino	42 (76)
Missing	2 (4)
Race, n (%)	
American Indian or Alaska Native	1 (2)
Asian	3 (5)
Black or African American	1 (2)
White	37 (67)
Other	9 (16)
Missing	4 (7)
Country of enrolled sites, n (%)	
Germany	3 (5)
France	10 (18)
Netherlands	1 (2)
United States	41 (75)

Data cutoff date = 09SEP2020. Abbreviation: Max, maximum; Min, minimum; STDEV, standard deviation. Note: Percentages are based on the number of subjects treated with any dose of KTE-X19.

Phase 2 full analysis set (all enrolled and leukapheresed subjects): n=71

The median age was 44.0 years (range: 19 to 84 years); 11 subjects (15%) were ≥ 65 years of age. Forty-one subjects (58%) were male; the majority were White (51 subjects, 72%). Fifty-two subjects (73%) were enrolled in the US, 18 subjects (25%) were enrolled in the EU, and 1 subject (1%) was enrolled in Canada.

Twenty-one subjects (30%) had primary refractory disease, 54 subjects (76%) had r/r disease after 2 or more lines of prior therapy, and 20 subjects (28%) had first relapse with first remission ≤ 12 months. Subjects had a median of 2 prior lines of therapy (range: 1 to 8 prior lines), and 35 subjects (49%) had received 3 or more lines of therapy. Twenty-eight subjects (39%) had previously received an allo-SCT. Sixteen subjects (23%) had previously received inotuzumab, thirty-three subjects (46%) had previously received blinatumomab (13 subjects (18%) as the last prior therapy). Nineteen subjects (27%) were Ph+. The median blast percentage in bone marrow at screening was 70.0% (range: 5% to 100%), and the median blast percentage at baseline (ie, the last assessment before lymphodepleting chemotherapy) was 66.5% (range: 0% to 98%). Fifty-four subjects (76%) had M3 bone marrow involvement (> 25% blasts) at baseline. Eight subjects (11%) had extramedullary disease at screening.

Table 12. Baseline and Disease Characteristics (Phase 2, Full Analysis Set)

Phase 2

(N = 71)

Height (cm)	
n	70
Mean (STDEV)	171.2 (10.8)
Median	171.3
Min, Max	142, 192
Weight (kg)	
n	71
Mean (STDEV)	80.5 (27.8)
Median	75.3
Min, Max	41, 203.9
Age (years)	
Median	44
Sex, n (%)	
Male	41 (58)
Female	30 (42)
ECOG performance status, n (%)	
0	18 (25)
1	53 (75)
Philadelphia chromosome t(9;22) mutation, n (%)	
Yes	19 (27)
No	52 (73)
Prior blinatumomab, n (%)	
Yes	33 (46)
No	38 (54)
Blinatumomab as the last prior therapy, n (%)	
Yes	13 (18)
No	58 (82)
Prior inotuzumab, n (%)	
Yes	16 (23)

No	55 (77)
Prior allogeneic SCT, n (%)	
Yes	28 (39)
No	43 (61)
Prior autologous SCT, n (%)	
Yes	3 (4)
No	68 (96)
Number of lines of prior therapy, n (%)	
1	11 (15)
2	25 (35)
3	19 (27)
4	11 (15)
5	3 (4)
6	1 (1)
8	1 (1)
Median	2.0
Min, Max	1, 8
Primary refractory, n(%)	
Yes	
No	21 (30)
	50 (70)
Relapsed or refractory to 2nd or greater line therapy, n (%)	
Yes	
No	54 (76)
Relapsed or refractory disease after allogeneic SCT, n (%)	17 (24)
Yes	
No	
First relapse with first remission ≤ 12 months, n (%)	
Yes	
No	29 (41)
Response to the last prior therapy, n (%)	42 (59)

	20 (28)
	51 (72)
CR	21 (30)
CRi	1 (1)
PR	2 (3)
NR	23 (32)
PD	14 (20)
Not evaluated	10 (14)
Prior radiotherapy, n (%)	
Yes	16 (23)
No	5 (77)
% blasts in bone marrow at screening	
n	70
Mean (STDEV)	58.6 (32.0)
Median	70.0
Min, Max	5, 100
≤ 5%	1 (1)
> 5% to 25%	17 (24)
> 25%	52 (73)
Missing	1 (1)
% blasts in bone marrow at baseline	
n	70
Mean (STDEV)	58.9 (32.5)
Median	66.5
Min, Max	0, 98
≤ 5%	6 (8)
> 5% to 25%	10 (14)
> 25%	54 (76)

Missing	1 (1)
% blasts in bone marrow after bridging chemotherapy	
n	48
Mean (STDEV)	54.7 (32.8)
Median	62.5
Min, Max	0, 98
≤ 5%	5 (7)
> 5% to 25%	7 (10)
> 25%	36 (51)
Missing	23 (32)
Extramedullary disease at screening, n (%)	
Yes	8 (11)
No	63 (89)
CNS disease at baseline, n (%)	
CNS-1 CNS-2	69 (97) 2 (3)
CD19 % lymphoblast at baseline by central lab	
n	67
Mean (STDEV)	92.5 (19.6)
Median	100.0
Min, Max	0, 100
CD19 % lymphoblast baseline category based on central lab, n (%)	
≥ 95	52 (73)
< 95	15 (21)
Missing	4 (6)
Baseline extramedullary disease target lesion (SPD) (mm2) a	
n	4
Mean (STDEV)	23942.5 (46974.4)
Median	685.0

Min, Max	0, 94400
Baseline spleen measurement (LVD) (mm)	
n	1
Mean (STDEV)	140.0 (NA)
Median	140.0
Min, Max	140, 140
MLL translocation t(4;11) t(8;14), n (%)	
Yes	4 (6)
No	66 (93)
Missing	1 (1)
Complex karyotype (≥ 5 chromosomal abnormalities), n (%)	
Yes	17 (24)
No	53 (75)
Missing	1 (1)
Low hypodiploidy (30-39 chromosomes), n (%)	
Yes	1 (1)
No	69 (97)
Missing	1 (1)

Numbers analysed

Table 13. Disposition of Subjects in the study (Phase 2, Full Analysis Set)

	Phase 2 (N = 71)
Subjects who underwent leukapheresis, n (%)	71 (100)
Subjects who received CSF prophylaxis, n (%)	64 (90)
Subjects who received bridging therapy, n (%)	64 (90)
Subjects who received conditioning chemotherapy, n (%)	57 (80)
Subjects who did not receive conditioning chemotherapy and did not receive KTE-X19 infusion by reasons, n (%)	14 (20)
Adverse event	7 (10)

Product not available	1 (1)
Partial consent withdrawn	1 (1)
Other	5 (7)a
Eligibility not met	3 (4)
Subjects who received conditioning chemotherapy but not KTE-X19 infusion by reasons, n (%)	2 (3)
Adverse event	1 (1)
Other	1 (1)
Eligibility not met	1 (1)
Subjects who received KTE-X19, n (%)	55 (77)
Subjects who received bridging therapy, n (%)	51 (72)
Subjects completed infusion, n (%)	55 (77)
Primary reasons for ending the study, n (%)	37 (52)
Subjects who didn't receive KTE-X19, n (%)	14 (20)
Death	10 (14)
Investigator decision	3 (4)
Other	1 (1)
Subjects who received KTE-X19, n (%)	23 (32)
Death	20 (28)
Full consent withdrawn	3 (4)
Follow-up time for subjects who received KTE-X19	
Actual follow-up time from KTE-X19 dose (months) b	
N	55
Mean (STDEV)	11.5 (6.3)
Median (Q1, Q3)	12.4 (7.6, 17.2)
Min, Max	0.3, 22.1
Potential follow-up time from KTE-X19 dose (months) c	
N	55
Mean (STDEV)	16.7 (3.4)
Median (Q1, Q3)	16.4 (13.8, 19.6)
Min, Max	10.3, 22.1
Subjects with ≥ 1 month potential follow-up c, n (%)	55 (100)

Subjects with ≥ 3 months potential follow-up c, n (%)	55 (100)
Subjects with ≥ 6 months potential follow-up c, n (%)	55 (100)
Subjects with ≥ 9 months potential follow-up c, n (%)	55 (100)
Subjects with ≥ 12 months potential follow-up c, n (%)	51 (93)
Subjects with ≥ 15 months potential follow-up c, n (%)	36 (65)
Subjects with ≥ 18 months potential follow-up c, n (%)	22 (40)

Data cutoff date = 09Sep2020.

Outcomes and estimation

From Phase 2, mITT analysis set.

Primary efficacy endpoint: OCR

The OCR rate in the mITT analysis set was 70.9% (39 of 55 subjects, 95% CI: 57%, 82%), with a CR rate of 56.4% (31 of 55 subjects, 95% CI: 42%, 70%). Among the 39 subjects who achieved a CR or CRi, the median time to response was 1.1 months (range: 0.85 to 2.99 months).

Table 14. Summary BOR per central assessment (Phase 2 mITT)

Response Category, n (%)	Phase 2 (N = 55)
Number of OCR (CR + CRi)	39 (70.9)
95% CI (Clopper-Pearson method)	57, 82
P-value of exact test for OCR rate ≤ 40%	<.0001
CR	31 (56.4)
95% CI (Clopper-Pearson method)	42, 70
CRi	8 (14.5)
95% CI (Clopper-Pearson method)	6, 27
CRh	0 (0)
BFBM	4 (7.3)
PR	0 (0)
NR	9 (16.4)
Unknown or not evaluable	3 (5.5)

Data cutoff date = 09Sep2020. Abbreviations: BFBM, blast-free hypoplastic or aplastic bone marrow; CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; mITT, modified intent-to-treat; NR, no response; OCR, overall complete remission; PR, partial response.

There is also a combined analysis of OCR rate for all subjects treated at the 1e6 dose level in Phases 1 and 2 provided. Results are as follows: Among the 78 subjects, treated, the OCR rate per investigator assessment was 74.4% (58 of 78 subjects, 95% CI: 63%, 84%), with a CR rate of 62.8% (49 of 78 subjects, 95% CI: 51%, 74%).

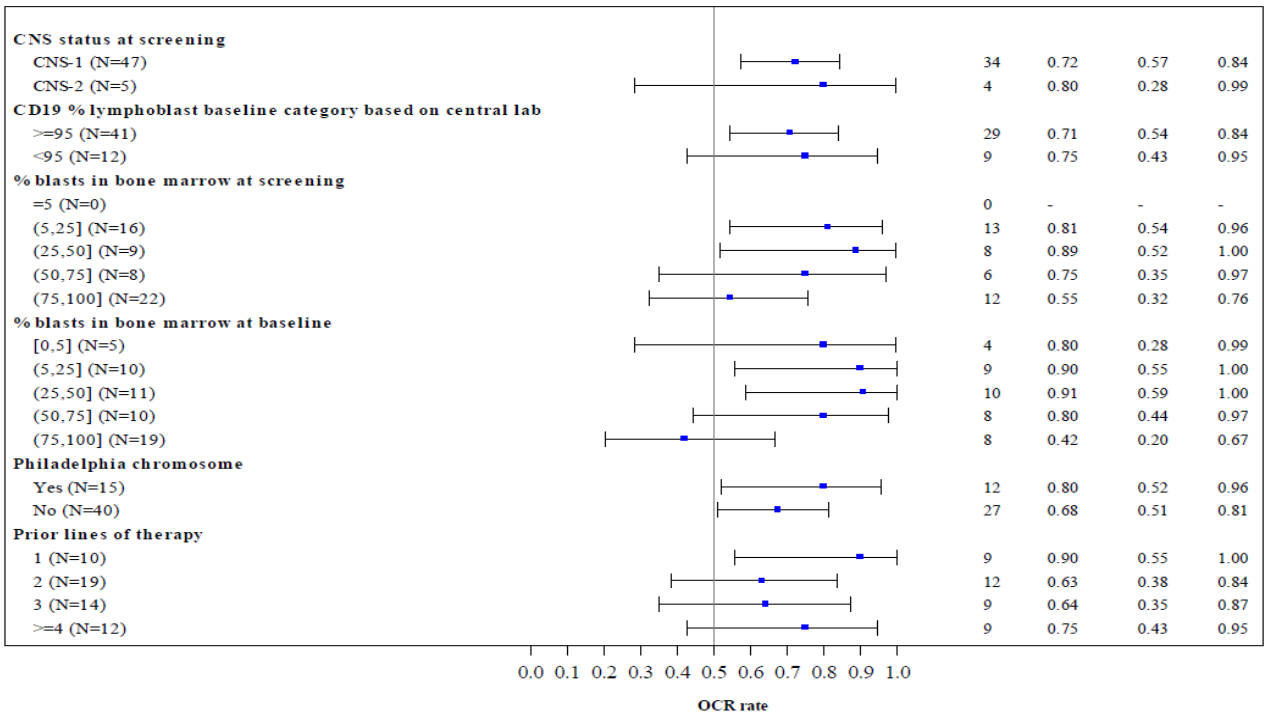
Subgroup analyses

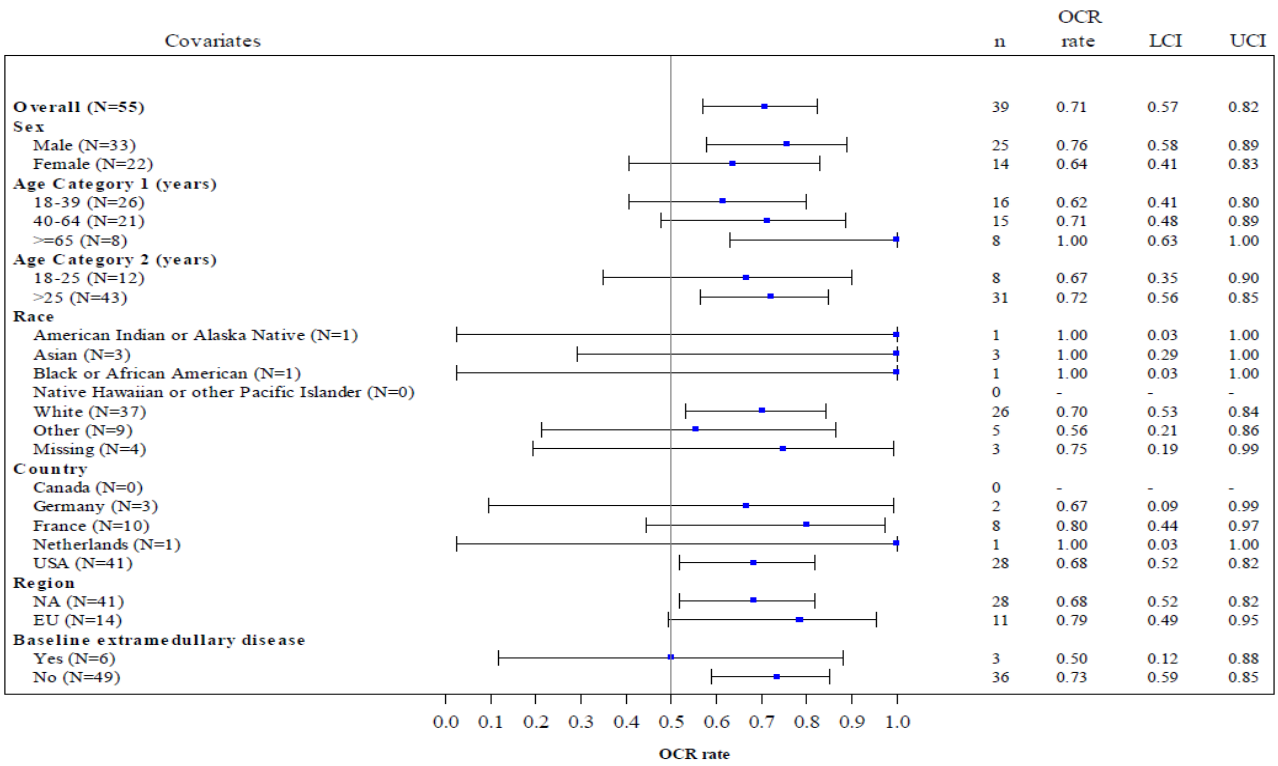
OCR and CR in the mITT population per central assessment were investigated by demographics, baseline characteristics, and prior therapies.

The lowest OCR rate in terms of the tumor stage was of 42% observed among subjects with the highest disease burden (> 75% to 100% blasts in bone marrow) at baseline (N = 19). OCR rates were 90% for subjects with only 1 prior line of therapy (n = 10). Results per prior treatment [note: OCR rate for subjects with only 1 prior line of therapy (n = 10) was 80%]:

- 60% for subjects who had received prior blinatumomab (n = 25)
- 67% for subjects with prior inotuzumab (n = 12)
- 70% for subjects with prior SCT (N = 23)
- 67% for subjects with prior blinatumomab and inotuzumab (n = 6)
- 73% for subjects with prior SCT and blinatumomab (n = 11)
- 80% for subjects with prior SCT and inotuzumab (n = 5) and
- 100% for subjects with prior SCT, blinatumomab, and inotuzumab (N = 2).

Figure 3. Forest Plot for Subgroup Analysis of OCR rate per central Assessment (Phase 2, mITT)




Covariates
n
OCR rate
LCI
UCI
Overall (N=55) 39 0.71 0.57 0.82
Sex
Male (N=33) 25 0.76 0.58 0.89
Female (N=22) 14 0.64 0.41 0.83
Age Category 1 (years)
18-39 (N=26) 16 0.62 0.41 0.80
40-64 (N=21) 15 0.71 0.48 0.89
>=65 (N=8) 8 1.00 0.63 1.00
Age Category 2 (years)
18-25 (N=12) 8 0.67 0.35 0.90
>25 (N=43) 31 0.72 0.56 0.85
Race
American Indian or Alaska Native (N=1) 1 1.00 0.03 1.00
Asian (N=3) 3 1.00 0.29 1.00
Black or African American (N=1) 1 1.00 0.03 1.00
Native Hawaiian or other Pacific Islander (N=0) 0 - - -
White (N=37) 26 0.70 0.53 0.84
Other (N=9) 5 0.56 0.21 0.86
Missing (N=4) 3 0.75 0.19 0.99
Country
Canada (N=0) 0 - - -
Germany (N=3) 2 0.67 0.09 0.99
France (N=10) 8 0.80 0.44 0.97
Netherlands (N=1) 1 1.00 0.03 1.00
USA (N=41) 28 0.68 0.52 0.82
Region
NA (N=41) 28 0.68 0.52 0.82
EU (N=14) 11 0.79 0.49 0.95
Baseline extramedullary disease
Yes (N=6) 3 0.50 0.12 0.88
No (N=49) 36 0.73 0.59 0.85
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
OCR rate

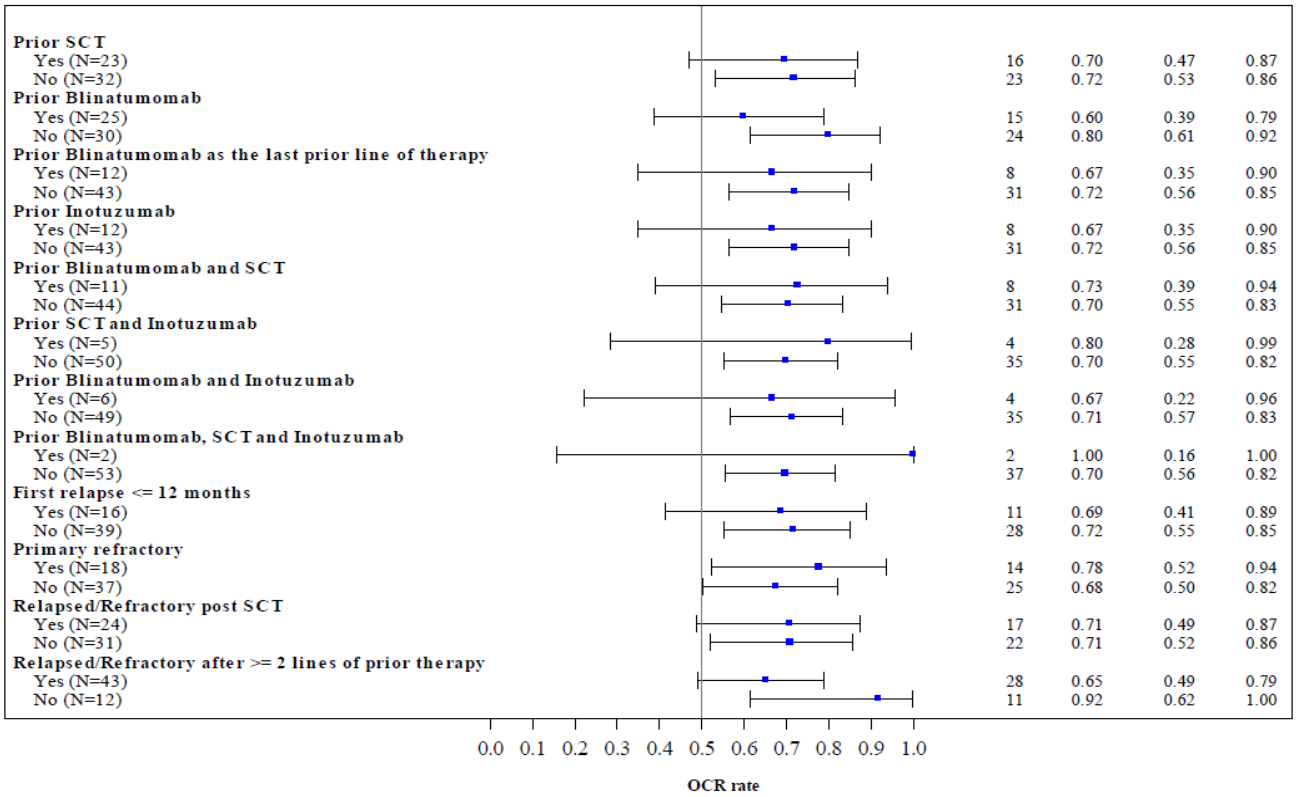
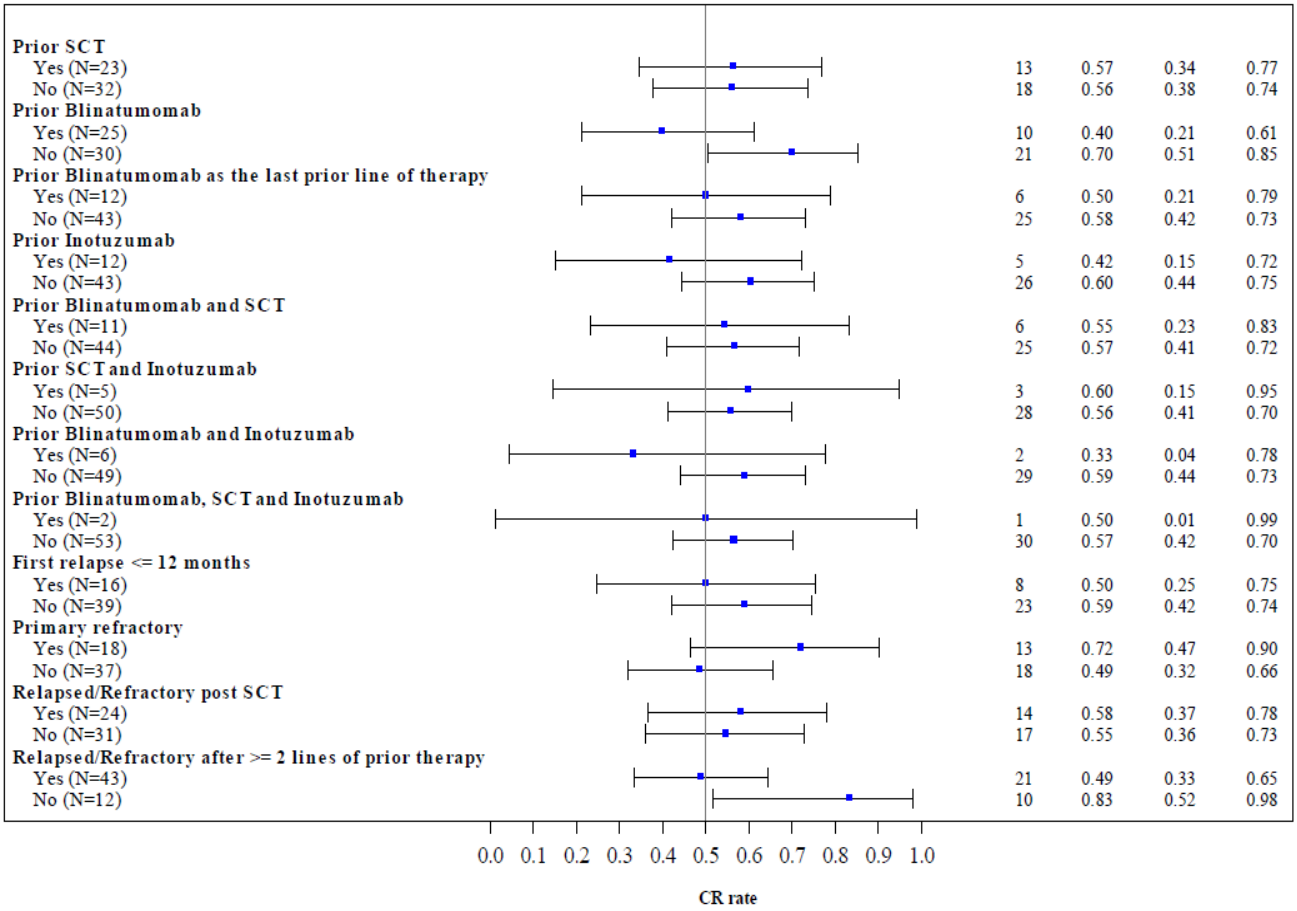
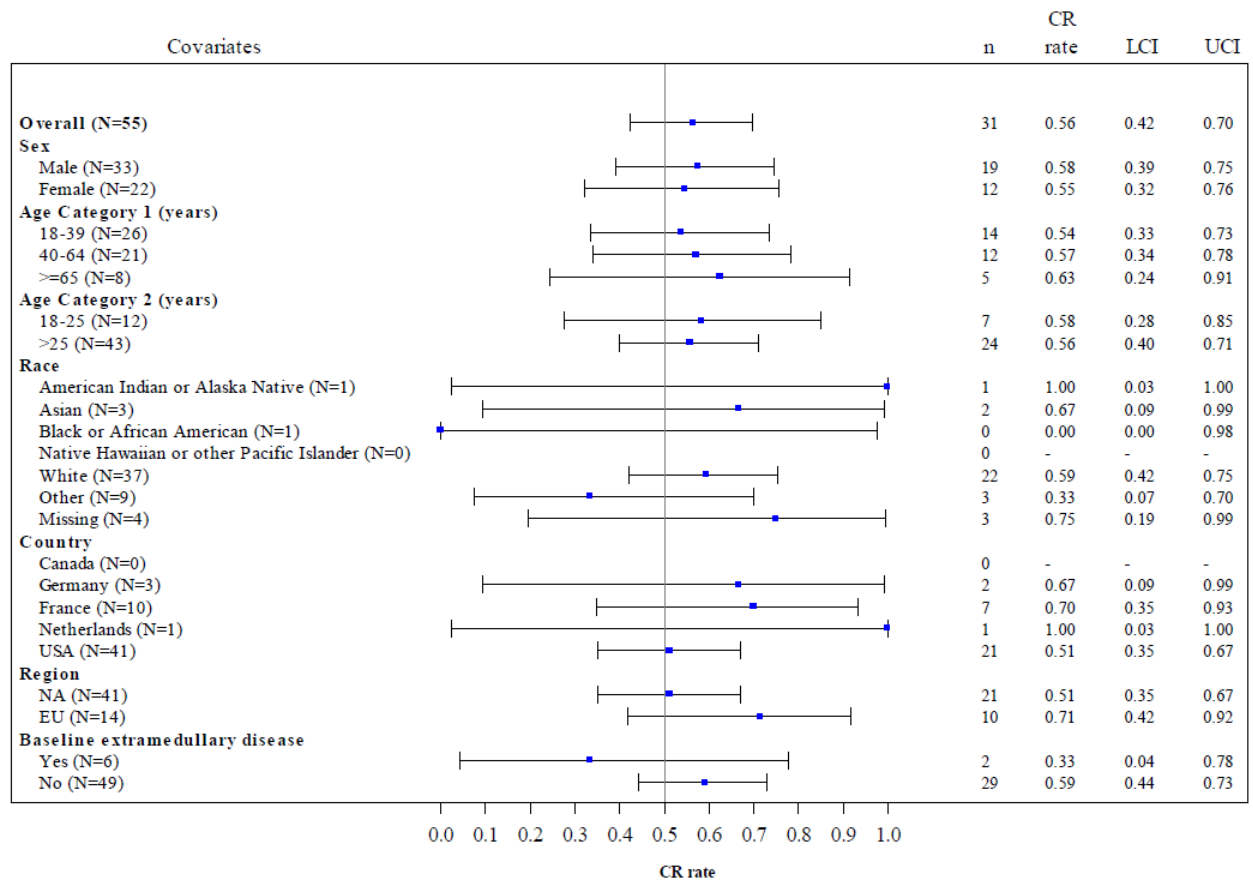
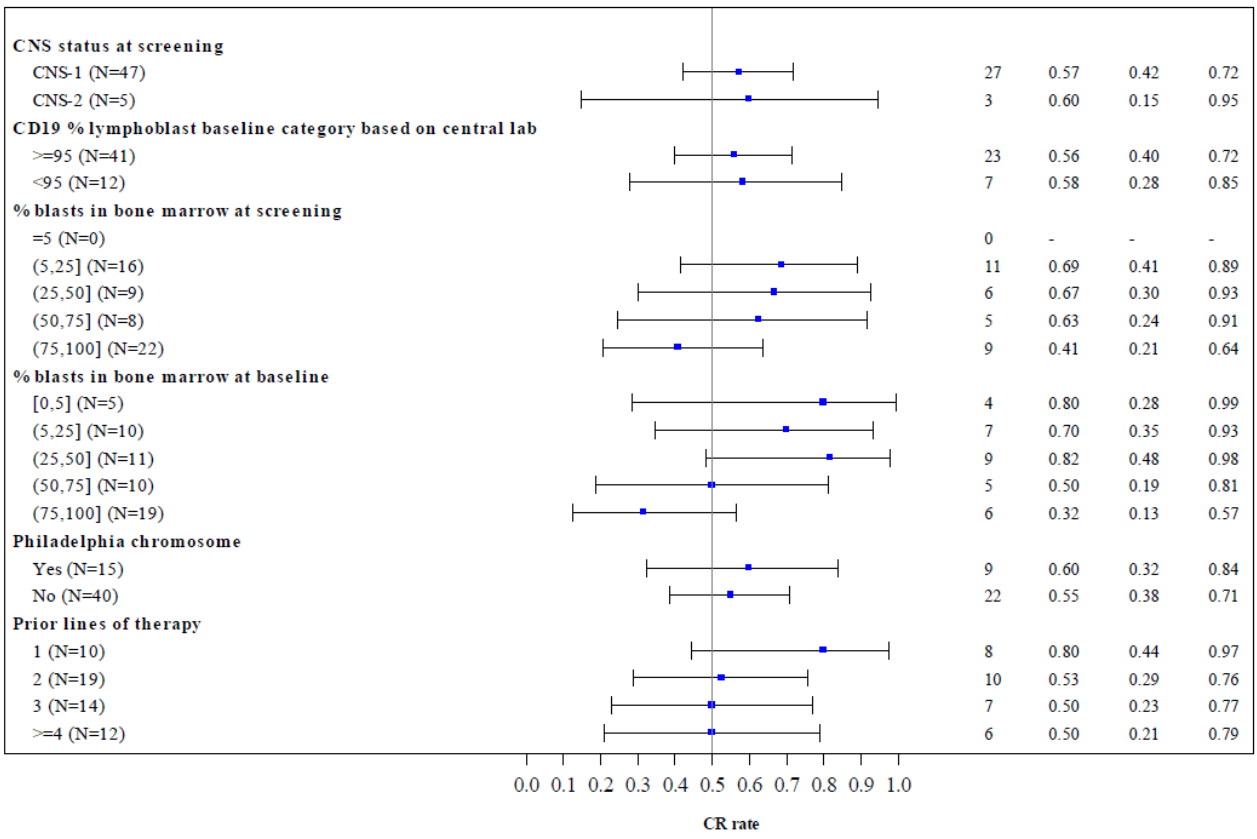

Prior SCT
Yes (N=23) 16 0.70 0.47 0.87
No (N=32) 23 0.72 0.53 0.86
Prior Blinatumomab
Yes (N=25) 15 0.60 0.39 0.79
No (N=30) 24 0.80 0.61 0.92
Prior Blinatumomab as the last prior line of therapy
Yes (N=12) 8 0.67 0.35 0.90
No (N=43) 31 0.72 0.56 0.85
Prior Inotuzumab
Yes (N=12) 8 0.67 0.35 0.90
No (N=43) 31 0.72 0.56 0.85
Prior Blinatumomab and SCT
Yes (N=11) 8 0.73 0.39 0.94
No (N=44) 31 0.70 0.55 0.83
Prior SCT and Inotuzumab
Yes (N=5) 4 0.80 0.28 0.99
No (N=50) 35 0.70 0.55 0.82
Prior Blinatumomab and Inotuzumab
Yes (N=6) 4 0.67 0.22 0.96
No (N=49) 35 0.71 0.57 0.83
Prior Blinatumomab, SCT and Inotuzumab
Yes (N=2) 2 1.00 0.16 1.00
No (N=53) 37 0.70 0.56 0.82
First relapse <= 12 months
Yes (N=16) 11 0.69 0.41 0.89
No (N=39) 28 0.72 0.55 0.85
Primary refractory
Yes (N=18) 14 0.78 0.52 0.94
No (N=37) 25 0.68 0.50 0.82
Relapsed/Refractory post SCT
Yes (N=24) 17 0.71 0.49 0.87
No (N=31) 22 0.71 0.52 0.86
Relapsed/Refractory after >= 2 lines of prior therapy
Yes (N=43) 28 0.65 0.49 0.79
No (N=12) 11 0.92 0.62 1.00
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
OCR rate

Figure 4. Forest Plot for Subgroup Analysis of CR per Central Assessment (Phase 2, mITT)




Covariates
n
CR rate
LCI
UCI
Overall (N=55) 31 0.56 0.42 0.70
Sex
Male (N=33) 19 0.58 0.39 0.75
Female (N=22) 12 0.55 0.32 0.76
Age Category 1 (years)
18-39 (N=26) 14 0.54 0.33 0.73
40-64 (N=21) 12 0.57 0.34 0.78
>=65 (N=8) 5 0.63 0.24 0.91
Age Category 2 (years)
18-25 (N=12) 7 0.58 0.28 0.85
>25 (N=43) 24 0.56 0.40 0.71
Race
American Indian or Alaska Native (N=1) 1 1.00 0.03 1.00
Asian (N=3) 2 0.67 0.09 0.99
Black or African American (N=1) 0 0.00 0.00 0.98
Native Hawaiian or other Pacific Islander (N=0) 0 - - -
White (N=37) 22 0.59 0.42 0.75
Other (N=9) 3 0.33 0.07 0.70
Missing (N=4) 3 0.75 0.19 0.99
Country
Canada (N=0) 0 - - -
Germany (N=3) 2 0.67 0.09 0.99
France (N=10) 7 0.70 0.35 0.93
Netherlands (N=1) 1 1.00 0.03 1.00
USA (N=41) 21 0.51 0.35 0.67
Region
NA (N=41) 21 0.51 0.35 0.67
EU (N=14) 10 0.71 0.42 0.92
Baseline extramedullary disease
Yes (N=6) 2 0.33 0.04 0.78
No (N=49) 29 0.59 0.44 0.73
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
CR rate


CNS status at screening
CNS-1 (N=47) 27 0.57 0.42 0.72
CNS-2 (N=5) 3 0.60 0.15 0.95
CD19 % lymphoblast baseline category based on central lab
>=95 (N=41) 23 0.56 0.40 0.72
<95 (N=12) 7 0.58 0.28 0.85
% blasts in bone marrow at screening
=5 (N=0) 0 - - -
(5,25] (N=16) 11 0.69 0.41 0.89
(25,50] (N=9) 6 0.67 0.30 0.93
(50,75] (N=8) 5 0.63 0.24 0.91
(75,100] (N=22) 9 0.41 0.21 0.64
% blasts in bone marrow at baseline
[0,5] (N=5) 4 0.80 0.28 0.99
(5,25] (N=10) 7 0.70 0.35 0.93
(25,50] (N=11) 9 0.82 0.48 0.98
(50,75] (N=10) 5 0.50 0.19 0.81
(75,100] (N=19) 6 0.32 0.13 0.57
Philadelphia chromosome
Yes (N=15) 9 0.60 0.32 0.84
No (N=40) 22 0.55 0.38 0.71
Prior lines of therapy
1 (N=10) 8 0.80 0.44 0.97
2 (N=19) 10 0.53 0.29 0.76
3 (N=14) 7 0.50 0.23 0.77
>=4 (N=12) 6 0.50 0.21 0.79
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
CR rate

Data cutoff date = 09Sep2020. Abbreviations: CNS, central nervous system; EU, European Union; LCI, lower confidence interval; mITT, modified intent-to-treat; NA, North America; OCR, overall complete remission; SCT, stem cell transplant; UCI, upper confidence interval; USA, United States of America. Note: LCI and UCI are the lower and upper limits of the 95% confidence interval of OCR using Clopper-Pearson method.

Secondary efficacy endpoints

1. MRD- rate in the mITT anlysis set

The overall MRD− rate was 76% (42 of 55 subjects; 95% CI: 63%, 87%). 13 subjects were not considered MRD− overall, 9 subjects were non-responders, and 3 subjects were not evaluable for MRD-disease response, and 1 subject with a CR did not have MRD assessments performed. Among subjects with CR or CRi, the MRD− rate was 97% (38 of 39 subjects; 95% CI: 87%, 100%). One subject who achieved a CR did not have samples sent to the central laboratory for MRD assessment.

Table 15. Summary of MRD (Phase 2, mITT analysis set)

MRD status	Phase 2 (N = 55)
MRD negativity status [a], n (%)	
MRD negative at day 28, n (%)	38 (69)
MRD negative at week 8, n (%)	33 (60)
MRD negative at month 3, n (%)	23 (42)
MRD negative rate overall [a], n (%)	42 (76)[b]
95% confidence interval	63, 87
p-value of exact test for MRD negativity rate ≤ 30%	<.0001
MRD negative rate among OCR (CR or CRi) subjects [c], n (%)	38 (97)
95% confidence interval	87, 100
p-value of exact test for MRD negativity rate ≤ 30%	<.0001
MRD negative rate among CR subjects [d], n (%)	30 (97)
95% confidence interval	83, 100
MRD negative rate among CRi subjects [d], n (%)	8 (100)
95% confidence interval	63, 100
MRD negative rate among CRh subjects [d], n (%)	0 (0)
MRD negative rate among BFBM subjects [d], n (%)	4 (100)
95% confidence interval	40, 100

2. OCR per investigator assessment

OCR rate per investigator assessment was 72.7% (40 of 55 subjects, 95% CI: 59%, 84%), with a CR rate of 60.0% (33 of 55 subjects, 95% CI: 46%, 73%). OCR using the investigators' assessment had a concordance rate of 95% (κ = 0.87; 95% CI: 0.72, 1.00) with OCR using central assessment.

Table 16. Summary of BOR per investigator assessment (phase 2, mITT)

Response Category, n (%)	Phase 2 (N = 55)

Number of OCR (CR + CRi)	40 (72.7)
95% CI (Clopper-Pearson method)	59, 84
P-value of exact test for OCR rate ≤ 40%	<.0001
CR	33 (60.0)
95% CI (Clopper-Pearson method)	46, 73
CRi	7 (12.7)
95% CI (Clopper-Pearson method)	5, 24
CRh	0 (0)
BFBM	3 (5.5)
PR	0 (0)
NR	9 (16.4)
Unknown or not evaluable	3 (5.5)

Data cutoff date = 09Sep2020. Abbreviations: BFBM, blast-free hypoplastic or aplastic bone marrow; CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; mITT, modified intent-to-treat; NR, no response; OCR, overall complete remission; PR, partial response. Source: Table 14.2.1.2 and Table 14.2.2.2

3. DOR by central assessment

Among the 39 subjects in the mITT analysis set who achieved a CR or CRi, the KM median DOR was 12.8 months (95% CI: 8.7 months, not estimable [NE]), while 26 subjects were censored:

- 12 subjects in ongoing remission as of DCO,
- 9 subjects had an allo-SCT, and
- 5 subjects started new anticancer therapy.

The KM median DOR was 14.6 months (95% CI: 9.6 months, NE) for subjects with CR and 8.7 months (95% CI: 1.0, 12.8 months) for subjects with CRi.

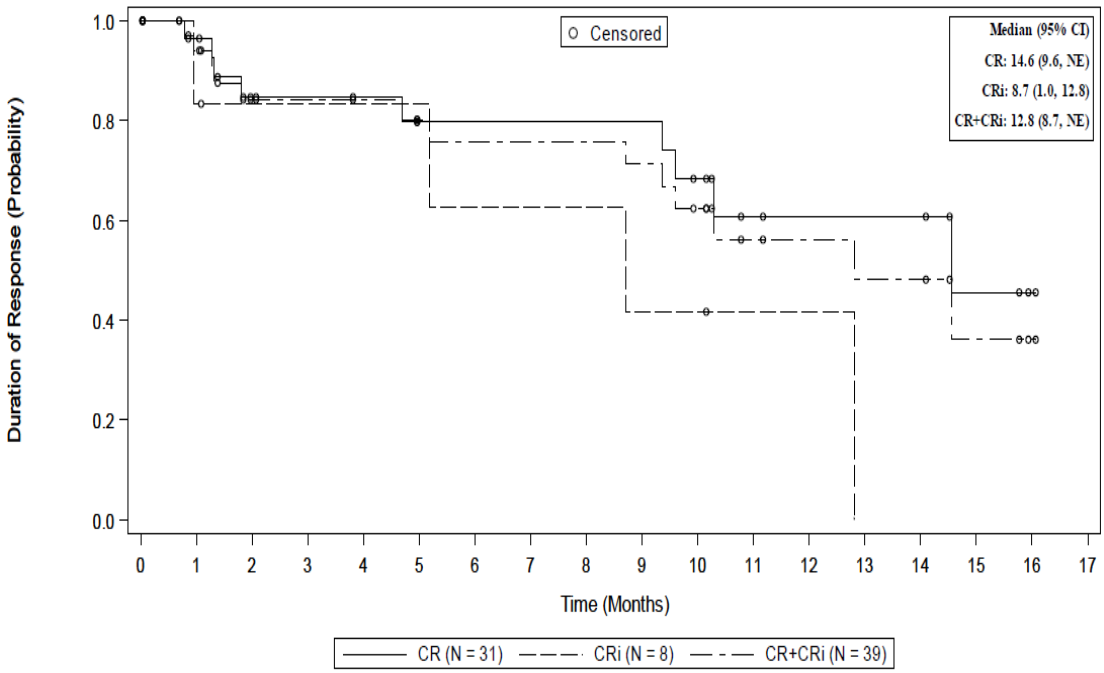
Table 17. DOR per central Assessment (Phase 2, mITT analysis set)

DOR	Phase 2 (N = 55)
Number of subjects with OCR, n	39
Events, n (%)	13 (33)
Censored, n (%)	26 (67)
KM median (95% CI) DOR (months)	12.8 (8.7, NE)
Min, Max DOR (months)	(0.03+, 16.07+)
Events	
Relapse, n (%)	12 (31)
Death, n (%)	1 (3)
Censoring reason	
Ongoing remission, n (%)	12 (31)
Allogeneic SCT, n (%)	9 (23)

Started new anti-cancer therapy, n (%)	5 (13)
Lost to follow up, n (%)	0 (0)
Withdrawal of consent, n (%)	0 (0)
Event-free rates % (95% CI) by KM estimation[a] at	
3 months	84.2 (66.0, 93.1)
6 months	75.7 (55.2, 87.8)
9 months	71.3 (50.0, 84.7)
12 months	56.1 (33.5, 73.7)
Median (95% CI) follow-up time (months) (reverse KM approach)	10.2 (2.1, 11.2)

Figure 5. KM Plot of DOR

Figure 8. KM Plot of DOR by Best Overall Response Groups per Central Assessment (Phase 2, mITT Analysis Set: Subjects With a CR or CRi)



CR at risk	31	26	19	18	17	14	14	14	14	14	11	7	6	6	6	3	1	0
(CR censored)	(0)	(4)	(8)	(9)	(10)	(12)	(12)	(12)	(12)	(12)	(13)	(16)	(17)	(17)	(17)	(19)	(21)	(22)
CRi at risk	8	5	4	4	4	4	3	3	3	2	2	1	1	0	0	0	0	0
(CRi censored)	(0)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
CR+CRi at risk	39	31	23	22	21	18	17	17	17	16	13	8	7	6	6	3	1	0
(CR+CRi censored)	(0)	(6)	(11)	(12)	(13)	(15)	(15)	(15)	(15)	(15)	(16)	(20)	(21)	(21)	(21)	(23)	(25)	(26)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; NR, not reached.

4. Rate of Allo-SCT after treatment with KTE-X19 (mITT analysis set)

Ten of 55 subjects (18%) were treated with allo-SCT while in remission after the initial KTE-X19 infusion; of these, 7 subjects had achieved a CR and 2 subjects had achieved a CRi to KTE-X19 treatment (based on the central assessment). One subject received an allo-SCT after achieving a CRi per investigator

assessment, however, was considered to have a best response of BFBM per central assessment. The median time from KTE-X19 infusion to allo-SCT was 98 days (range: 60 to 207 days). Of the 10 subjects who received allo-SCT after KTE-X19 infusion, 1 subject (10%) died within 100 days after allo-SCT. The remaining 9 subjects (90%) were in ongoing remission 100 days after the transplant.

5. Overall Survival (OS)

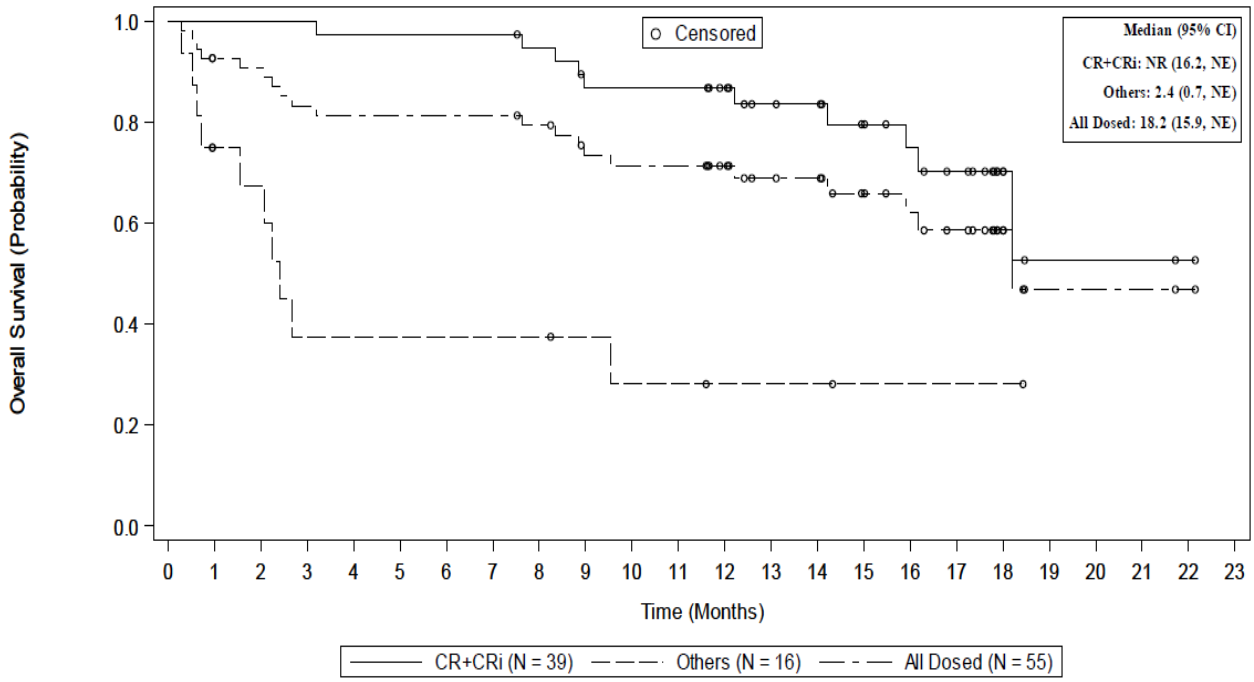
KM estimates of OS at Month 12 and Month 18 were 71.4% (95% CI: 57.0%, 81.7%) and 58.6% (95% CI: 41.8%, 72.1%), respectively. The KM median OS was 18.2 months (95% CI: 15.9 months, NE), with a reverse KM median follow-up time for OS of 15.5 months (95% CI: 13.1, 17.6 months). The KM median OS was not reached (95% CI: 16.2 months, NE) for subjects with CR or CRi and was 2.4 months (95% CI: 0.7 months, NE) for all other subjects in the mITT analysis set. The KM median OS was not reached (95% CI: 18.2 months, NE) for subjects with CR and was 9.0 months (95% CI: 3.2, 14.2 months) for subjects with CRi. With regard to patients who were MRD-, the KM median OS was not reached (95% CI: 16.2 months, NE) and was 9.5 months (95% CI: 2.2 months, NE) for subjects who were MRD+ and 1.5 months (95% CI: 0.3, 2.7 months) for subjects with missing MRD assessments.

Table 23. OS (Phase 2, mITT Analysis Set)

OS	Phase 2 (N = 55)
Number of subjects, n	55
Death, n (%)	20 (36.4)
Censored, n (%)	35 (63.6)
Alive on or after DCO, n (%)	32 (58.2)
Full withdrawal of consent, n (%)	3 (5.5)
KM median (95% CI) OS (months)	18.2 (15.9, NE)
Min, Max OS (months)	(0.30, 22.14+)
Survival free rates (%) (95% CI) by KM estimation at	
3 months	83.3 (70.3, 90.9)
6 months	81.4 (68.1, 89.5)
9 months	73.4 (59.2, 83.3)
12 months	71.4 (57.0, 81.7)
15 months	65.9 (50.6, 77.5)
18 months	58.6 (41.8, 72.1)
Median (95% CI) follow-up time (months) (reverse KM approach)	15.5 (13.1, 17.6)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; DCO, data cutoff date; KM, Kaplan-Meier; Max, maximum; Min, minimum; mITT, modified intent-to-treat; NE, not estimable; OS, overall survival.
Notes: Overall survival for subjects treated with KTE-X19 is defined as the time from KTE-X19 infusion date to the date of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date, with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date. '+' indicates censoring.

Figure 9. **KM Plot of OS: Complete Responders Versus Others (Phase 2, mITT Analysis Set)**



CR+CRi at risk	39	39	39	39	38	38	38	38	36	32	32	32	29	24	23	19	16	13	6	2	2	2	1	0
(CR+CRi censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(2)	(2)	(5)	(9)	(10)	(13)	(15)	(17)	(24)	(27)	(27)	(27)	(28)	(29)
Others at risk	16	10	9	5	5	5	5	5	5	4	3	3	2	2	2	1	1	1	1	0	0	0	0	0
(Others censored)	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(3)	(3)	(4)	(4)	(4)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(6)
All Dosed at risk	55	49	48	44	43	43	43	43	41	36	35	35	31	26	25	20	17	14	7	2	2	2	1	0
(All Dosed censored)	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(5)	(5)	(5)	(9)	(13)	(14)	(18)	(20)	(22)	(29)	(33)	(33)	(33)	(34)	(35)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; NR, not reached; OS, overall survival.

- Subgroup analyses of OS at Month 12 (mITT analysis set)

The KM estimate of OS at Month 12 in the mITT analysis set was examined in diverse clinical relevant subgroups of age, race, gender, baseline disease characteristics, prior lines of therapy etc. (*source: Figure 11, clinical efficacy report body*). OS rates were comparable for subjects who had been previously treated with blinatumomab (53%, n = 25); inotuzumab (54%, n = 12); SCT (78%, n= 23); SCT and blinatumomab (64%, n= 11); SCT and inotuzumab (60%, n = 5); and SCT, blinatumomab, and inotuzumab (50%, n = 2). Moreover, OS rates were 100% among elderly subjects ≥ 65 years of age (n = 8), 50% among subjects with extramedullary disease at baseline (n = 6), and 93% among subjects who were Ph+ (n = 15). These rates were generally consistent with the KM estimate of OS at Month 12 of 71.4% observed for the overall population.

6. RFS by central assessment (mITT analysis set)

KM estimates of RFS rates at Month 6 and Mont 12 were 57.6% (95% CI: 42.6%, 69.9%) and 44.3% (95% CI: 28.6%, 59.0%), respectively. The KM median RFS was 11.6 months (95% CI: 2.7, 15.5 months), with a reverse KM median follow-up time for RFS of 11.7 months (95% CI: 3.2, 15.0 months). Twenty-six subjects were censored:

- 12 subjects in ongoing remission as of the data cutoff date

- 9 subjects had an allo-SCT, and
- 5 subjects started new anticancer therapy.

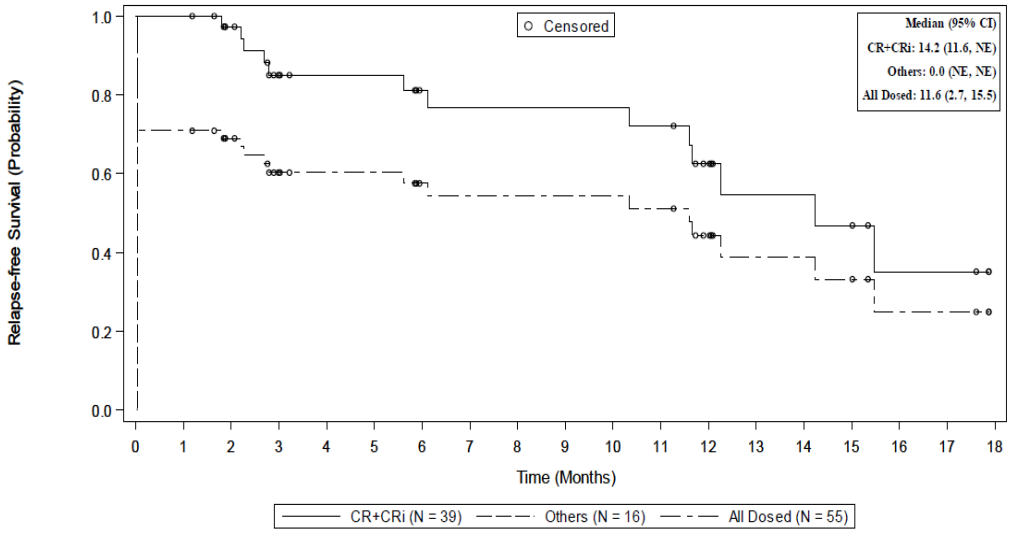
Twelve subjects relapsed, 1 subject died, and 16 subjects did not have a best response of CR or CRi. Among subjects with CR or CRi, the KM median RFS was 14.2 months (95% CI: 11.6 months, NE). The KM median RFS was 15.5 months (95% CI: 11.6 months, NE) for subjects with CR and 11.7 months (95% CI: 1.8, 14.2 months) for subjects with CRi. The KM median RFS was 12.3 months (95% CI: 10.3 months, NE) for subjects who were MRD− and 0.0 months (95% CI: NE) for subjects who were MRD+ or had missing MRD assessments. Subgroup analysis of RFS had been conducted for Month 6 only and not for Month 12. Given the generally small number of patients in the respective subgroups, overall, the rates were generally consistent, observed for the overall population.

Table 18. RFS per central assessment (mITT analysis set)

RFS	Phase 2 (N = 55)
Number of subjects, n	55
Events, n (%)	29 (52.7)
Censored, n (%)	26 (47.3)
KM median (95% CI) RFS (months)	11.6 (2.7, 15.5)
Min, Max RFS (months)	(0.03, 17.87+)
Events	
Relapse, n (%)	12 (21.8)
Death, n (%)	1 (1.8)
Subject's best overall response not CR or CRi, n (%)	16 (29.1)
Censoring reason	
Ongoing remission, n (%)	12 (21.8)
Allogeneic SCT, n (%)	9 (16.4)
Started new anti-cancer therapy, n (%)	5 (9.1)
Lost to follow up, n (%)	0 (0)
Withdrawal of consent, n (%)	0 (0)
Event-free rates % (95% CI) by KM estimation at	
3 months	60.3 (45.7, 72.1)
6 months	57.6 (42.6, 69.9)
9 months	54.4 (39.0, 67.4)
12 months	44.3 (28.6, 59.0)
Median (95% CI) follow-up time (months) (reverse KM approach)	11.7 (3.2, 15.0)

Data cutoff date = 09Sep2020. Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan-Meier; Max, maximum; Min, minimum; mITT, modified intent-to-treat; NE, not estimable; RFS, relapse-free survival; SCT, stem cell transplant. Notes: Percentages are based on the number of subjects in the mITT analysis set. RFS for subjects who received KTE-X19 is defined as the time from the KTE-X19 infusion date to the date of relapse or death from any cause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response are counted as events on the KTE-X19 infusion date. '+' indicates censoring.

Figure 12. **KM Plot of RFS per Central Assessment: Complete Responders Versus Others (Phase 2, mITT Analysis Set)**



CR+CRi at risk	39	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0
(CR+CRi censored)	(0)	(0)	(5)	(10)	(12)	(12)	(15)	(15)	(15)	(15)	(15)	(15)	(18)	(21)	(21)	(21)	(23)	(23)	(26)
Others at risk	16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(Others censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
All Dosed at risk	55	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0
(All Dosed censored)	(0)	(0)	(5)	(10)	(12)	(12)	(15)	(15)	(15)	(15)	(15)	(15)	(18)	(21)	(21)	(21)	(23)	(23)	(26)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; NR, not reached; RFS, relapse-free survival.

Table 9. Summary of Select ZUMA-3 Efficacy Endpoints

	mITT Analysis Set (N = 55)	Full Analysis Set (N = 71)
OCR (CR + CRi) rate (95% CI)	70.9% (57%, 82%)	54.9% (43%, 67%)
CR rate (95% CI)	56.4% (42%, 70%)	43.7% (32%, 56%)
MRD negative rate overall[a,b] (95% CI)	76% (63%, 87%)	59% (47%, 71%)
MRD negative rate among OCR (CR or CRi) subjects[a,c] (95% CI)	97% (87%, 100%)	97% (87%, 100%)
KM median (95% CI) OS[d] (months)	18.2 (15.9, NE)	19.2 (10.4, NE)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan-Meier; mITT, modified intent-to-treat; MRD, minimal residual disease; NE, not estimable; OCR, overall complete remission; OS, overall survival.
Note: 95% CIs are based on the Clopper-Pearson method.
a MRD status is determined by the central laboratory. Numerators for MRD negative rate are based on an MRD-negative finding at any postinfusion visit.
b Percentage is based on the number of subjects in the mITT analysis set.
c Percentage is based on the number of subjects with OCR (CR or CRi). Disease response is based on central assessment.
d OS for the mITT analysis set is defined as the time from the KTE-X19 infusion date to the date of death from any cause. OS for the full analysis set is defined as the time from the enrollment date to the date of death from any cause.

Efficacy in the Phase 2 full analysis set (FAS)

The OCR rate was 54.9% (39 of 71 subjects, 95% CI: 43%, 67%), with a CR rate of 43.7% (31 of 71 subjects, 95% CI: 32%, 56%). With regard to DOR, the results were identical to the results in the mITT analysis set, as DOR war defined only for subjects who achieved and OCR.

Table 26. Summary of Best Overall Response per Investigator Assessment (Phase 2, Full Analysis Set)

Response Category, n (%)	Phase 2 (N = 71[a])
Number of OCR (CR + CRi)	40 (56.3)
CR	33 (46.5)
CRi	7 (9.9)
CRh	0 (0)
BFBM	3 (4.2)
PR	0 (0)
NR	9 (12.7)
Unknown or not evaluable	19 (26.8)[b]

Table 14.2.5.1.2. Duration of Response Using Independent Review (Phase 2, Full Analysis Set)

Duration of Response (DOR)	Phase 2 (N = 71)
Number of subjects with OCR, n	39
Events, n (%)	13 (33)
Censored, n (%)	26 (67)
KM median (95% CI) DOR (months)	12.8 (8.7, NE)
Min, Max DOR (months)	(0.03+, 16.07+)
Events	
Relapse, n (%)	12 (31)
Death, n (%)	1 (3)
Censoring reason	
Ongoing remission, n (%)	12 (31)
Allogeneic SCT, n (%)	9 (23)
Started new anti-cancer therapy, n (%)	5 (13)
Lost to follow up, n (%)	0 (0)
Withdrawal of consent, n (%)	0 (0)
Event-free rates % (95% CI) by KM estimation at	
3 months	84.2 (66.0, 93.1)
6 months	75.7 (55.2, 87.8)
9 months	71.3 (50.0, 84.7)
12 months	56.1 (33.5, 73.7)
Median (95% CI) follow-up time (months) (reverse KM approach)	10.2 (2.1, 11.2)

Data cutoff date = 09Sep2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of response; KM, Kaplan-Meier; NE, not estimable; OCR, overall complete remission; SCT, stem cell transplant.
Note: Percentages are based on the number subjects in full analysis set with overall complete remission (CR+CRi). DOR is defined as the time from the first complete remission (CR or CRi) to relapse or death from any cause in the absence of documented relapse. '+' indicates censoring.

Data Source: ADSL, ADEFF, ADTTE Program Name: t_dor_phase2 Output Generated: 20201211T10:11

Concerning the OS rates, KM estimates at Month 12 and Month 18 were 62.3% (95% CI: 49.4%, 72.7%) and 51.8% (95% CI: 37.5%, 64.3%), respectively. The KM median OS was 19.2 months (95% CI: 10.4 months, NE), with a reverse KM median follow-up time for OS of 16.0 months (95% CI: 13.6, 18.3 months). This compares largely to a KM median OS of 18.2 months in the mITT analysis set, and the difference is due to the calculation of OS from the time of enrollment (full analysis set) versus from the time of KTE-X19 infusion (mITT).

Table 27. OS (Phase 2, Full Analysis Set)

OS	Phase 2 (N = 71)
Number of subjects, n	71
Death, n (%)	30 (42.3)
Censored, n (%)	41 (57.7)
Alive on or after DCO, n (%)	38 (53.5)
Full withdrawal of consent, n (%)	3 (4.2)
KM median (95% CI) OS (months)	19.2 (10.4, NE)
Min, Max OS (months)	(0.69+, 23.26+)
Survival free rates (%) (95% CI) by KM estimation at	
3 months	85.3 (74.4, 91.8)
6 months	70.2 (57.6, 79.6)
9 months	68.6 (56.0, 78.3)
12 months	62.3 (49.4, 72.7)
15 months	60.1 (47.0, 70.9)
18 months	51.8 (37.5, 64.3)
Median (95% CI) follow-up time (months) (reverse KM approach)	16.0 (13.6, 18.3)

With regard to RFS, figures are provided in the following table 18. There are no meaningful differences between RFS mITT analysis set and RFS full analysis set.

Table 19. RFS per Central Assessment (Phase 2, Full Analysis Set)

RFS	Phase 2 (N = 71)
Number of subjects, n	71
Events, n (%)	40 (56.3)
Censored, n (%)	31 (43.7)
KM median (95% CI) RFS (months)	7.0 (0.0, 13.2)
Min, Max RFS (months)	(0.03, 19.02+)
Events	
Relapse, n (%)	12 (16.9)
Death, n (%)	1 (1.4)
Subject's best overall response not CR or CRi, n (%)	27 (38.0)
Censoring reason	
Ongoing remission, n (%)	12 (16.9)
Allogeneic SCT, n (%)	9 (12.7)
Started new anti-cancer therapy, n (%)	5 (7.0)
Lost to follow up, n (%)	0 (0)
Withdrawal of consent, n (%)	0 (0)
Response not yet assessed, n (%)	5 (7.0)
Event-free rates % (95% CI) by KM estimation at	
3 months	58.5 (46.0, 69.1)
6 months	53.0 (40.2, 64.2)
9 months	47.5 (34.1, 59.8)
12 months	44.7 (31.2, 57.4)
Median (95% CI) follow-up time (months) (reverse KM approach)	12.6 (4.2, 13.2)

Additional analyses provided upon request per DCO 23 July 2021

The additional analyses included the following: 1) an updated central assessment of 23 subjects from ZUMA-3 Phase 1 treated with the same pivotal dose as subjects from Phase 2, leading to an increased sample size of 78 treated subjects; 2) a 21-month follow-up analysis with a substantially longer median follow-up of 20.5 months (range: 0.3, 32.6 months, data cut off [DCO] 23 July 2021) over the primary analysis with a median follow-up of 12.4 months (range: 0.3, 22.1 months, DCO 09 September 2020); and 3) an update of the SCHOLAR-3 results with a full analysis set (FAS) analysis to include subjects who did not receive KTE-X19 infusion in ZUMA-3. In addition, SCHOLAR-3 analyses for the original modified intent-to-treat (mITT) analysis set were repeated with a more recent date cutoff (DCO 23 July 2021).

Among the 78 subjects treated with the pivotal dose in the combined Phase 1 + Phase 2 analysis set, 37% had previously received an allo-SCT, 49% had received prior blinatumomab, and 22% of the subjects had received prior inotuzumab therapy. The median number of prior therapies was 2 (range: 1 to 8); 19% had received 1 line, 33% had received 2 lines, 24% had received 3 lines, and 23% had received ≥ 4 lines of prior therapy. A total of 31% of the subjects had primary refractory disease, 77% had r/r disease to ≥ 2 line of therapy, 38% had r/r disease after allo-SCT, and 28% had first relapse with first remission lasting ≤ 12 months. The median percentage of blasts in bone marrow at baseline was 63.0% (range: 0% to 98%); 12% of the subjects had an extramedullary disease. The updated

central assessment data of the 78 subjects treated with the pivotal dose in the combined Phase 1 + Phase 2 analysis set continue to demonstrate a significant clinically meaningful benefit compared with currently available therapies. Risks associated with KTE-X19 treatment in ZUMA-3, such as CRS and neurologic events, mostly occurred in the first month after cell infusion and were largely reversible and manageable with medical intervention.

The results of the 21-month follow-up analysis demonstrated that the efficacy outcomes obtained with KTE-X19 in the Phase 2 mITT analysis set and FAS continue to be better than reported outcomes obtained with current standard of care (SOC) therapies. Efficacy outcomes were numerically better in subjects who had received only 1 prior line of therapy compared with subjects who had received > 1 prior line of therapy before KTE-X19. Furthermore, subjects who had received an allogeneic stem cell transplant (allo-SCT) as well as SCT-naïve subjects greatly benefited from KTE-X19 irrespective of their previous transplant status, while the flexibility for treating physician remained should they consider a subsequent allo-SCT. Better efficacy outcomes were obtained with KTE-X19 in blinatumomab-naïve and inotuzumab-naïve subjects, whereas a prior exposure to blinatumomab or inotuzumab suggests a potential reduction in the efficacy of KTE-X19. However, even in subjects who had previously been treated with blinatumomab or inotuzumab, KTE-X19 resulted in efficacy outcomes that were better than what have been reported for current SOC therapies.

The updated SCHOLAR-3 analyses performed on the original ZUMA-3 mITT population and the expanded analyses performed on the FAS were consistent with the outcomes of the primary analysis. Clinically meaningful, statistically significant improvements in overall complete remission (OCR) rate, complete remission (CR) rate, relapse-free survival (RFS), and overall survival (OS) were demonstrated for KTE-X19 versus subjects receiving SOC therapies in historical control trials matched for key baseline characteristics and prior therapies, further supporting the clinical relevance and benefits of KTE-X19 over available therapies.

Table 20. Efficacy Outcomes in Subjects With 1 Versus >1 Prior Lines of Therapy (Phase 2 mITT Analysis Set)

	mITT (N=55)		
	Overall	**1 Prior Line, n=10**	**>1 Prior Line, n=45**
OCR rate (95% CI)	**71%** (57%, 82%)	**90%** (55%, 100%)	**67%** (51%, 80%)
CR rate (95% CI)	**56%** (42%, 70%)	**80%** (44%, 97%)	**51%** (36%, 66%)
OS rate at 24 months (95% CI)	**56%** (41%, 68%)	**70%** (33%, 89%)	**52%** (36%, 66%)
RFS rate at 18 months (95% CI)	**35%** (21%, 51%)	**NA**[a] (NE, NE)	**33%** (18%, 49%)

Data cutoff date = 23Jul2021

Table 21. Efficacy Outcomes in Subjects With 1 Versus >1 Prior Lines of Therapy (Phase 2 Full Analysis Set)

	Full Analysis Set (N=71)		
	Overall	**1 Prior Line, n=11**	**>1 Prior Line, n=60**
OCR rate (95% CI)	**55%** (43%, 67%)	**82%** (48%, 98%)	**50%** (37%, 63%)
CR rate (95% CI)	**44%** (32%, 56%)	**73%** (39%, 94%)	**38%** (26%, 52%)
OS rate at 24 months (95% CI)	**49%** (36%, 61%)	**64%** (30%, 85%)	**46%** (32%, 59%)
RFS rate at 18 months (95% CI)	**29%** (17%, 42%)	**36%** (2%, 78%)	**27%** (15%, 40%)

Data cutoff date = 23Jul2021

Table 22. Efficacy Outcomes in Subjects With Prior Lines of Therapy (Phase 1 + Phase 2 Subjects Dosed With 1.0 x 10^6 CAR T Cells/kg Body Weight)

	Phase 2 + Phase l Subjects Dosed With 1.0 x 10^6 CAR T Cells/kg Body Weight (N=78)		
	Overall	**1 Prior Line, n=15**	**>1 Prior Line, n=63**
OCR rate (95% CI)	**73%** (62%, 82%)	**87%** (60%, 98%)	**70%** (57%, 81%)
CR rate (95% CI)	**60%** (49%, 71%)	**80%** (52%, 96%)	**56%** (42%, 68%)
OS rate at 24 months (95% CI)	**52%** (40%, 63%)	**57%** (29%, 78%)	**50%** (37%, 63%)
RFS rate at 18 months (95% CI)	**38%** (25%, 51%)	**32%** (5%, 65%)	**38%** (24%, 52%)

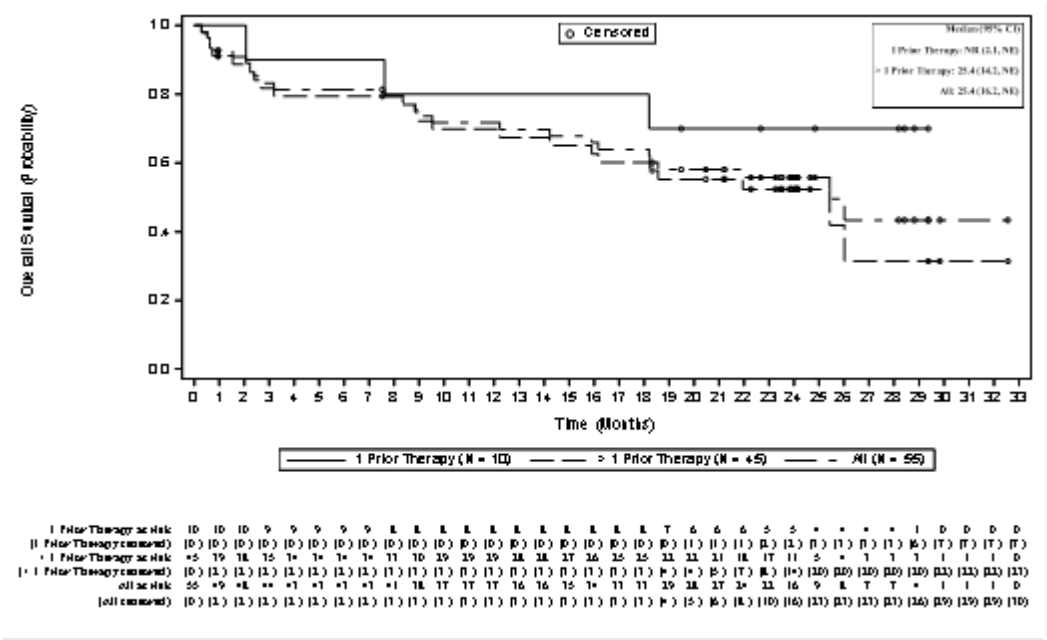
Data cutoff date = 23Jul2021

While CR rates in ZUMA-3 for subjects who had received > 1 prior line of therapy were lower than CR rates for subjects with only 1 prior line of therapy, CR rates of 51% in Phase 2 mITT analysis set, 38% in Phase 2 FAS, and 56% in the combined Phase 1 + Phase 2 analysis set for subjects who had received > 1 prior line of therapy were numerically higher than CR rate of 33.6% reported for blinatumomab in TOWER study and 35.8% reported for inotuzumab in INO-VATE study.

In addition, the data also suggest superior OS for subjects who received KTE-X19 in earlier line of therapy. The KM median OS was not reached among the 10 subjects in the mITT analysis set or among the 11 subjects in the FAS who had received only 1 line of prior therapy. Among the 45 subjects in the Phase 2 mITT analysis set and among the 60 subjects in the FAS who had received > 1 prior line of therapy, the KM median OS was 25.4 months (95% CI: 14.2 months, NE)and 19.3 months (95% CI: 9.7 months, NE) respectively. In the combined Phase 1 + Phase 2 analysis set comprising a total of 78 subjects who received the pivotal dose of 1.0 x 10^6 CAR T cells/kg body weight, the KM median OS was not reached (95% CI: 7.6 months, NE) among the 15 subjects who had received only 1 line of prior therapy; among the 63 subjects who had received > 1 prior line of therapy, the KM median OS was 25.4 months (95% CI: 15.9 months, NE)

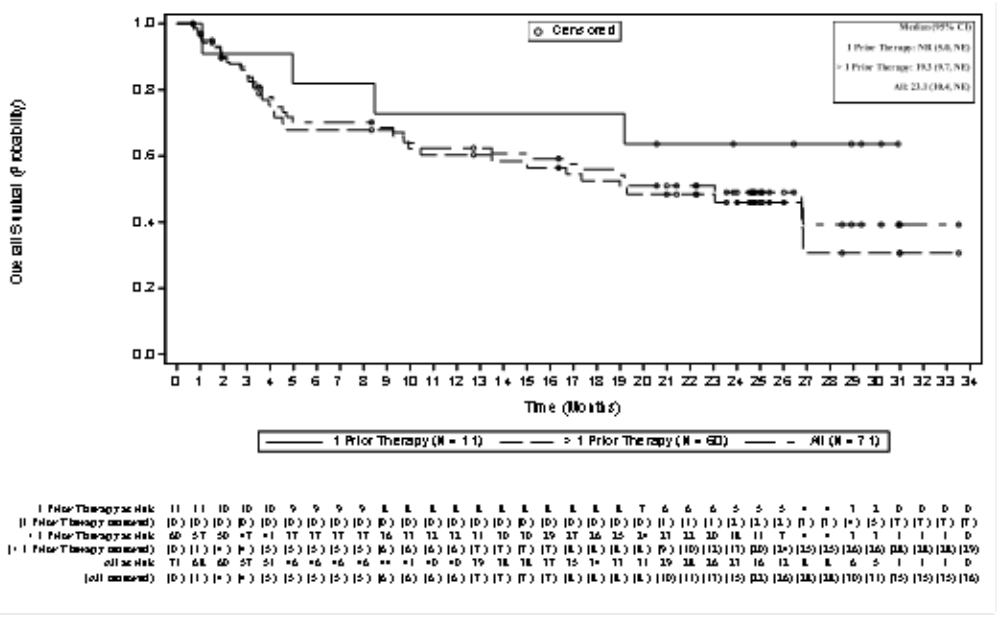
The KM median OS values of 19 to 25 months obtained with KTE-X19 in ZUMA-3 among subjects who had received > 1 prior line of therapy are approximately 3-fold longer than the median OS of 7.7 months obtained with current SOC.

Figure 6. **KM Plot of OS by Number of Prior Therapies per Central Assessment: 1 vs >1 Prior Line (Phase 2 mITT Analysis Set)**



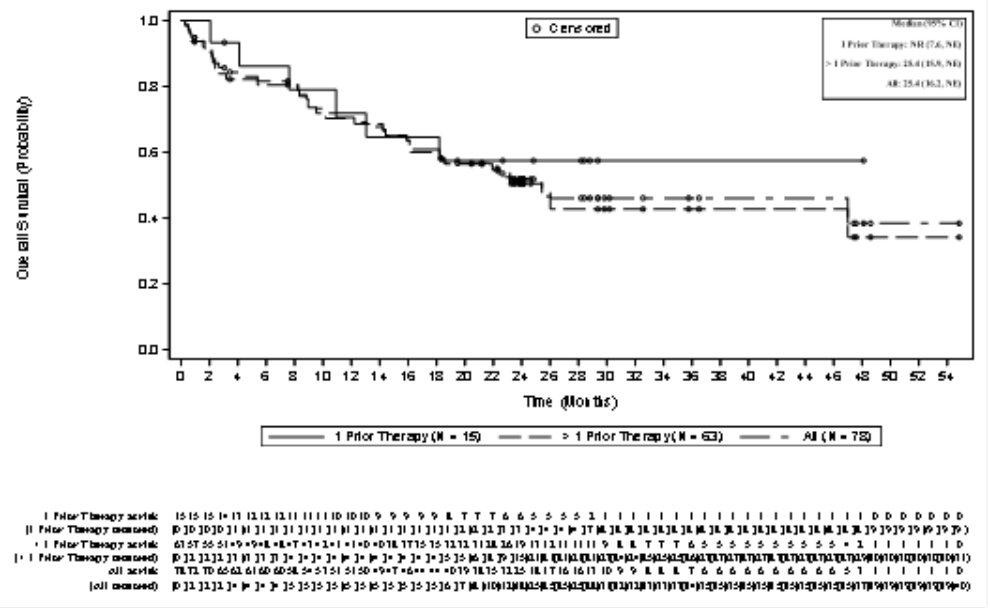
Data cutoff date = 23Jul2021

Figure 7. **KM Plot of OS by Number of Prior Therapies per Central Assessment: 1 vs >1 Prior Line (Phase 2 Full Analysis Set)**



Data cutoff date = 23Jul2021

Figure 8. **KM Plot of OS by Number of Prior Therapies per Central Assessment: 1 vs >1 Prior Line (Phase 2 + Phase I Subjects Dosed With 1.0 x 10^6 CAR T Cells/kg Body Weight)**



Data cutoff date = 23Jul2021

Out of the 10 subjects in Phase 2 mITT analysis set who had received only 1 prior line of therapy, 4 subjects had a primary refractory disease, 5 subjects had a first relapse with first remission lasting less than 12 months, and a total of 2 subjects had r/r disease after allo-SCT. After KTE-X19 infusion, 8 out of the 10 subjects achieved a CR, and 9 out of the 10 subjects achieved a CR/CRi.

The data suggest that efficacy outcomes obtained with KTE-X19 in subjects who had received > 1 prior line of therapy are better than outcomes obtained with current SOC therapies. Furthermore, efficacy outcomes were numerically better in subjects who had received only 1 prior line of therapy before KTE-X19 infusion. Therefore, the applicant argues that subjects who have relapsed after only 1 treatment line should be included in KTE-X19 indication to provide the most optimal benefit-risk profile. This would be consistent with the subject population studied in ZUMA-3 where 18% of the subjects in the mITT analysis set, 15% in the FAS, and 19% in the combined Phase 1 + Phase 2 analysis set had received only 1 prior therapy.

The ZUMA-3 results, demonstrating that subjects with fewer lines of therapy have better outcomes, are consistent with published studies reporting that with each relapse, responses to subsequent lines of therapy deteriorate {Dombret 2019, Gokbuget 2016b, Kantarjian 2003, Kantarjian 2019, O'Brien 2013}.

In order to provide further context for the relationship between efficacy outcomes and the number of prior lines of therapy, the applicant analyzed baseline characteristics and the profile of treatment-emergent adverse events (TEAEs) between these 2 subgroups among subjects in the Phase 2 safety analysis set.

Compared with the subgroup comprising subjects who had received > 1 prior line of therapy, the subgroup comprising subjects who had received only 1 prior line of therapy had more subjects with ECOG performance status of 0 (40% versus 27%); fewer subjects who had received prior blinatumomab, inotuzumab, or an allo-SCT (10%, 0%, and 10% versus 53%, 27%, and 49%, respectively); fewer subjects with r/r disease after allo-SCT (20% versus 49%); more subjects with first remission lasting ≤ 12 months (50% versus 24%); and subjects had a lower tumor burden (median percentage of blasts in bone marrow at baseline of 47.4% [range: 0, 73%] and no subject with an extramedullary disease at screening versus median percentage of blasts in bone marrow at baseline of 65.0% [range: 2, 98%] and 13% of subjects with an extramedullary disease. Due to the imbalance regarding the number of subjects in these 2 subgroups (10 subjects who received 1 prior line versus 45 subjects who received > 1 prior line of therapy), these results should be interpreted with caution.

Table 23. Baseline Characteristics by Number of Prior Lines of Therapy (Phase 2, Safety Analysis Set, N = 55)

	1 Prior Therapy (N = 10)	>1 Prior Therapy (N = 45)
ECOG performance status, n (%)		
0	4 (40)	12 (27)
1	6 (60)	33 (73)
Philadelphia chromosome t(9;22) mutation, n (%)		
Yes	2 (20)	13 (29)
No	8 (80)	32 (71)
Prior blinatumomab, n (%)		
Yes	1 (10)	24 (53)
No	9 (90)	21 (47)
Blinatumomab as the last prior therapy, n (%)		
Yes	1 (10)	11 (24)
No	9 (90)	34 (76)
Prior inotuzumab, n (%)		
Yes	0	12 (27)
No	10 (100)	33 (73)
Prior allogeneic SCT, n (%)		
Yes	1 (10)	22 (49)
No	9 (90)	23 (51)
Primary refractory, n (%)		
Yes	4 (40)	14 (31)
No	6 (60)	31 (69)
Relapsed or refractory disease after allo-SCT, n (%)		
Yes	2 (20)	22 (49)
No	8 (80)	23 (51)
First relapse with first remission ≤ 12 months, n (%)		
Yes	5 (50)	11 (24)
No	5 (50)	34 (76)

	1 Prior Therapy (N = 10)	>1 Prior Therapy (N = 45)
Response to the last prior therapy, n (%)		
CR	5 (50)	11 (24)
CRi	1 (10)	0
PR	0	2 (4)
NR	3 (30)	17 (38)
PD	1 (10)	9 (20)
Not evaluated	0	6 (13)
% blasts in bone marrow at baseline		
Mean (STDEV)	40.9 (28.9)	56.9 (33.5)
Median	47.4	65.0
Min, Max	0, 73	2, 98
≤ 5%	1 (10)	4 (9)
> 5% to 25%	2 (20)	8 (18)
> 25%	7 (70)	33 (73)
Extramedullary disease at screening, n (%)		
Yes	0	6 (13)
No	10 (100)	39 (87)

Data cutoff date = 23Jul2021

An overall summary of TEAEs among subjects who had received only 1 prior line of therapy versus subjects who had received > 1 prior line of therapy is presented for the Phase 2 safety analysis set in Table . The incidence of AEs and SAEs were generally similar (< 10% difference) between the subgroups. Due to the imbalance regarding the number of subjects in these 2 subgroups (10 subjects who received 1 prior line versus 45 subjects who received > 1 prior line of therapy), these results should be interpreted with caution.

Table 24. Overall Summary of TEAEs by Number of Prior Lines of Therapy (Phase 2, Safety Analysis Set, N = 55)

	1 Prior Therapy (N = 10)	>1 Prior Therapy (N = 45)
Any TEAE	10 (100)	45 (100)
Worst Grade ≥ 3	9 (90)	43 (96)
Any serious TEAE	6 (60)	35 (78)
Worst Grade ≥ 3	6 (60)	34 (76)
Any KTE-X19 related TEAE	9 (90)	42 (93)
Worst Grade ≥ 3	9 (90)	40 (89)
Any serious KTE-X19 related TEAE	5 (50)	29 (64)
Worst Grade ≥ 3	5 (50)	26 (58)
Any TE CRS	9 (90)	40 (89)
Worst Grade ≥ 3	1 (10)	12 (27)
Any TE neurologic event [a]	6 (60)	27 (60)
Worst Grade ≥ 3	3 (30)	11 (24)
Any TE CRS or neurologic event [a]	10 (100)	40 (89)
Worst Grade ≥ 3	4 (40)	20 (44)
Any serious TE neurologic event [a]	4 (40)	10 (22)
Worst Grade ≥ 3	3 (30)	8 (18)
Any TE thrombocytopenia	6 (60)	21 (47)
Worst Grade ≥ 3	5 (50)	19 (42)
Any TE neutropenia	5 (50)	22 (49)
Worst Grade ≥ 3	5 (50)	22 (49)
Any TE anemia	5 (50)	24 (53)
Worst Grade ≥ 3	4 (40)	23 (51)
Any TE infection	2 (20)	18 (40)
Worst Grade ≥ 3	2 (20)	12 (27)
Any serious TE infection	1 (10)	10 (22)
Worst Grade ≥ 3	1 (10)	8 (18)
Any COVID-19 associated TE viral infection	0 (0)	0 (0)
Worst Grade ≥ 3	0 (0)	0 (0)
Any hypogammaglobulinemia	0 (0)	4 (9)
Worst Grade ≥ 3	0 (0)	0 (0)

	1 Prior Therapy (N = 10)	>1 Prior Therapy (N = 45)
Any tumor lysis syndrome	0 (0)	1 (2)
Worst Grade ≥ 3	0 (0)	1 (2)
Any graft-versus-host disease	0 (0)	2 (4)
Worst Grade ≥ 3	0 (0)	1 (2)

Data cutoff date = 23Jul2021.

Responses in Subjects Who Received a Subsequent Allo-SCT After KTE-X19 Infusion

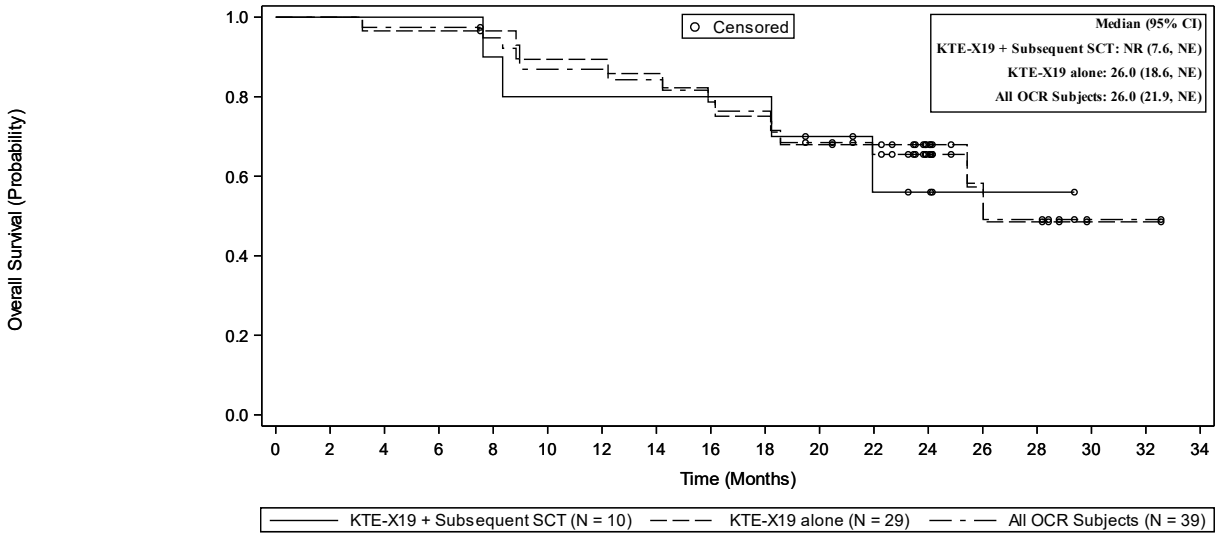
The applicant would like to provide additional data to emphasize the importance of allowing both SCT-naïve and subjects treated with a prior allo-SCT to receive KTE-X19. Prior exhaustion with an allo-SCT was not a mandatory inclusion criterion, and the majority of enrolled subjects in ZUMA-3 were allo-SCT-naïve; only 39% of subjects in Phase 2 FAS and 42% of the treated subjects in Phase 2 mITT analysis set had received a prior allo-SCT. The percentage of subjects with prior allo-SCT in ZUMA-3 is similar to that of published studies in r/r ALL with blinatumomab and inotuzumab where 35% of the subjects in the TOWER study and 18% of the subjects in the INO-VATE study had prior allo-SCT (**Error! Reference source not found.**).

Out of the 55 treated subjects, 11 (20%) in the ZUMA-3 mITT analysis set received an allo-SCT after KTE-X19 infusion; out of the 11 subjects, 10 (18%) had achieved a CR/CRi per central assessment. Out of the 11 subjects who received a subsequent allo-SCT, 1 subject died within 100 days, and the remaining subjects were in ongoing remission 100 days after allo-SCT.

Among the 10 subjects who achieved a CR/CRi after receiving KTE-X19 infusion and who received a subsequent allo-SCT, KM median OS was not reached (95% CI: 7.6 months, NE), even with the longer follow-up than previously reported for the primary analysis. Among the 29 subjects in the mITT analysis set who achieved a CR/CRi after receiving KTE-X19 alone without subsequent allo-SCT, the KM median OS was 26.0 months (95% CI: 18.6 months, NE)

Figure 4).

Figure 9. **Kaplan-Meier Plot of OS of OCR Subjects per Central Assessment by Subsequent Allogeneic SCT Group (Phase 2, mITT Analysis Set)**



KTE-X19 + Subsequent SCT at risk	10	10	10	10	9	8	8	8	8	8	6	4	3	1	1	0	0	0
(KTE-X19 + Subsequent SCT censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(3)	(5)	(5)	(6)	(6)	(6)
KTE-X19 alone at risk	29	29	28	28	27	25	25	24	22	21	19	18	11	6	5	1	1	0
(KTE-X19 alone censored)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(9)	(13)	(13)	(17)	(17)	(18)
All OCR Subjects at risk	39	39	38	38	36	33	33	32	30	29	25	22	14	7	6	1	1	0
(All OCR Subjects censored)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(4)	(12)	(18)	(18)	(23)	(23)	(24)

Data cutoff date = 23Jul2021

The percentage of subjects (20%) in ZUMA-3 who received KTE-X19 followed by a subsequent allo-SCT is consistent with the TOWER study where 24% of subjects in the blinatumomab arm underwent a subsequent allo-SCT. In contrast to the ZUMA-3 results, the mortality rate in the TOWER study was high following blinatumomab and allo-SCT; among the 38 subjects who achieved a CR/CRi/CRh to blinatumomab and underwent allo-SCT, 10 subjects (26%) died during a median follow-up period of 206 days {Kantarjian 2017}. In the INO-VATE study, a substantially higher percentage of subjects proceeded to SCT after receiving inotuzumab; 48.2% of the subjects in the ITT population and 53.7% of subjects who achieved a CR/CRi. Among the subjects who proceeded to SCT after receiving inotuzumab, 67.1% of the subjects died; the median OS for subjects treated with inotuzumab followed by SCT was 12.6 months (95% CI: 9.3, 27.7 months) {Kantarjian 2019}.

KTE-X19 Responses in SCT-naïve Versus SCT-pretreated Subjects

Efficacy outcomes in SCT-naïve subjects versus subjects who had received a prior allo-SCT before receiving KTE-X19 for the Phase 2 mITT analysis set (N = 55), for the Phase 2 FAS (N = 71), are displayed in Table for the combined Phase 1 + Phase 2 subjects treated with the pivotal dose of 1.0 x 10^6 CAR T cells/kg body weight (N = 78).

Table 25. Efficacy Outcomes in SCT-naïve Subjects Versus Subjects Who Had Received a Prior Allo-SCT (Phase 2, mITT Analysis Set)

	mITT (N=55)		
	Overall	**SCT-naïve, n=32**	**Prior Allo-SCT, n=23**
OCR rate (95% CI)	**71%** (57%, 82%)	**72%** (53%, 86%)	**70%** (47%, 87%)
CR rate (95% CI)	**56%** (42%, 70%)	**56%** (38%, 74%)	**57%** (34%, 77%)
OS rate at 24 months (95% CI)	**56%** (41%, 68%)	**52%** (33%, 68%)	**61%** (38%, 77%)
KM median OS (mos) (95% CI)	**25.4** (16.2, NE)	**NR** (9.0, NE)	**25.4** (14.2, NE)
RFS rate at 18 months (95% CI)	**35%** (21%, 51%)	**40%** (17%, 62%)	**32%** (14%, 52%)

Data cutoff date = 23Jul2021

Table 26. Efficacy Outcomes in SCT-naïve Subjects Versus Subjects Who Had Received a Prior Allo-SCT (Phase 2, Full Analysis Set)

	Full Analysis Set (N=71)		
	Overall	**SCT-naïve, n=43**	**Prior Allo-SCT, n=28**
OCR rate (95% CI)	**55%** (43%, 67%)	**53%** (38%, 69%)	**57%** (37%, 76%)
CR rate (95% CI)	**44%** (32%, 56%)	**42%** (27%, 58%)	**46%** (28%, 66%)
OS rate at 24 months (95% CI)	**49%** (36%, 61%)	**45%** (29%, 60%)	**55%** (35%, 72%)
KM median OS (mos) (95% CI)	**23.1** (10.4, NE)	**19.2** (8.5, NE)	**26.8** (10.4, NE)
RFS rate at 18 months (95% CI)	**29%** (17%, 42%)	**31%** (14%, 50%)	**28%** (12%, 46%)

Data cutoff date = 23Jul2021

Table 27. Efficacy Outcomes in SCT-naïve Subjects Versus Subjects Who Had Received a Prior Allo-SCT (Phase 1 + Phase 2 Subjects Dosed With 1.0 x 10^6 CAR T Cells/kg Body Weigh)

	Phase 2 + Phase 1 Subjects Dosed With 1.0 x 10^6 CAR T Cells/kg Body Weigh (N=78)		
	Overall	**SCT-naïve, n=49**	**Prior Allo-SCT, n=29**
OCR rate (95% CI)	**73%** (62%, 82%)	**71%** (57%, 83%)	**76%** (56%, 90%)
CR rate (95% CI)	**60%** (49%, 71%)	**61%** (46%, 75%)	**59%** (39%, 76%)
OS rate at 24 months (95% CI)	**52%** (40%, 63%)	**50%** (35%, 64%)	**54%** (34%, 70%)
KM median OS (mos) (95% CI)	**25.4** (16.2, NE)	**47.0** (10.9, NE)	**25.4** (14.2, NE)
RFS rate at 18 months (95% CI)	**38%** (25%, 51%)	**47%** (28%, 63%)	**33%** (16%, 51%)

Data cutoff date = 23Jul2021

For subjects who had already received a prior allo-SCT versus SCT-naïve subjects, the current ZUMA-3 data indicate that subjects greatly benefit from KTE-X19 irrespective of their previous transplant status. The already substantially improved outcomes achieved with KTE-X19 alone (median OS of 26.0 months) over current SOC (median OS of 7.7 months, can be further increased with a subsequent SCT (among subjects who achieved a CR/CRi after KTE-X19 infusion and received a subsequent allo-SCT, median OS was not reached.

The results presented with the more mature data set and a longer median study follow-up of 20.5 months are consistent with the data previously reported for the primary analysis with a median study follow-up of 12.4 months.

Thus, the applicant continues to recommend that subjects who are SCT naïve should also be eligible to receive KTE-X19. This is supported by ZUMA-3 data presented above and received by the applicant from healthcare providers representing real-world experience. Including allo-SCT naïve subjects in KTE-X19 label would reflect the subject population studied in ZUMA-3 where 58% of the enrolled subjects had not received a prior allo-SCT, and would be consistent with ZUMA-3 design, which allowed the use of a subsequent allo-SCT per investigator's choice for the studied population, as outlined in the ZUMA-3 clinical study protocol (Sections 7 and 10). Restricting the indication to only SCT-pretreated subjects would limit the subsequent treatment options for those subjects who achieve a CR/CRi after KTE X19 infusion; a second SCT, which is known to be associated with great risks and poor outcomes, if often not advised by current guidelines {Nagler 2019}.

Regarding safety, overall summaries of TEAEs for SCT-naïve subjects and subjects who had received a prior allo-SCT are presented for the Phase 2 safety analysis set in Table and for the combined Phase 1 + Phase 2 safety analysis set, comprising subjects treated with the pivotal dose, in Table 28. The incidence of AEs and SAEs were generally similar (< 10% difference) between the subgroups.

Table 28. Overall Summary of TEAEs by Prior SCT (Phase 2, Safety Analysis Set, N = 55)

	Prior SCT (N = 23)	**Naïve (N = 32)**
Any TEAE	23 (100)	32 (100)
Worst Grade ≥ 3	22 (96)	30 (94)
Any serious TEAE	19 (83)	22 (69)

	Prior SCT (N = 23)	Naïve (N = 32)
Worst Grade ≥ 3	19 (83)	21 (66)
Any KTE-X19 related TEAE	22 (96)	29 (91)
Worst Grade ≥ 3	21 (91)	28 (88)
Any serious KTE-X19 related TEAE	16 (70)	18 (56)
Worst Grade ≥ 3	14 (61)	17 (53)
Any TE CRS	20 (87)	29 (91)
Worst Grade ≥ 3	4 (17)	9 (28)
Any TE neurologic event [a]	12 (52)	21 (66)
Worst Grade ≥ 3	6 (26)	8 (25)
Any TE CRS or neurologic event [a]	20 (87)	30 (94)
Worst Grade ≥ 3	9 (39)	15 (47)
Any serious TE neurologic event [a]	6 (26)	8 (25)
Worst Grade ≥ 3	5 (22)	6 (19)
Any TE thrombocytopenia	13 (57)	14 (44)
Worst Grade ≥ 3	12 (52)	12 (38)
Any TE neutropenia	11 (48)	16 (50)
Worst Grade ≥ 3	11 (48)	16 (50)
Any TE anemia	13 (57)	16 (50)
Worst Grade ≥ 3	13 (57)	14 (44)
Any TE infection	11 (48)	9 (28)
Worst Grade ≥ 3	7 (30)	7 (22)
Any serious TE infection	7 (30)	4 (13)
Worst Grade ≥ 3	5 (22)	4 (13)
Any non-COVID-19 associated TE viral infection	2 (9)	0 (0)
Worst Grade ≥ 3	2 (9)	0 (0)
Any hypogammaglobulinemia	2 (9)	2 (6)
Worst Grade ≥ 3	0 (0)	0 (0)
Any tumor lysis syndrome	0 (0)	1 (3)
Worst Grade ≥ 3	0 (0)	1 (3)
Any graft-versus-host disease	2 (9)	0 (0)
Worst Grade ≥ 3	1 (4)	0 (0)

Data cutoff date = 23Jul2021.

Table 1. Overall Summary of TEAEs by Prior SCT ((Phase 1 + Phase 2 Subjects Dosed With 1.0 x 10^6 CAR T Cells/kg Body Weigh, Safety Analysis Set, N = 78)

	Prior SCT (N = 29)	Naïve (N = 49)
Any TEAE	29 (100)	49 (100)
Worst Grade ≥ 3	28 (97)	47 (96)
Any serious TEAE	25 (86)	37 (76)
Worst Grade ≥ 3	25 (86)	36 (73)
Any KTE-X19 related TEAE	28 (97)	46 (94)
Worst Grade ≥ 3	27 (93)	44 (90)
Any serious KTE-X19 related TEAE	22 (76)	31 (63)
Worst Grade ≥ 3	20 (69)	28 (57)
Any TE CRS	26 (90)	46 (94)
Worst Grade ≥ 3	5 (17)	15 (31)
Any TE neurologic event [a]	18 (62)	35 (71)
Worst Grade ≥ 3	8 (28)	17 (35)
Any TE CRS or neurologic event [a]	26 (90)	47 (96)
Worst Grade ≥ 3	12 (41)	27 (55)
Any serious TE neurologic event [a]	11 (38)	17 (35)
Worst Grade ≥ 3	7 (24)	15 (31)
Any TE thrombocytopenia	14 (48)	25 (51)
Worst Grade ≥ 3	13 (45)	22 (45)
Any TE neutropenia	16 (55)	29 (59)
Worst Grade ≥ 3	16 (55)	29 (59)
Any TE anemia	14 (48)	29 (59)
Worst Grade ≥ 3	14 (48)	25 (51)
Any TE infection	15 (52)	16 (33)
Worst Grade ≥ 3	9 (31)	14 (29)
Any serious TE infection	9 (31)	11 (22)
Worst Grade ≥ 3	7 (24)	11 (22)
Any non-COVID-19 associated TE viral infection	4 (14)	1 (2)
Worst Grade ≥ 3	3 (10)	0 (0)
Any hypogammaglobulinemia	4 (14)	3 (6)
Worst Grade ≥ 3	0 (0)	0 (0)
Any tumor lysis syndrome	0 (0)	1 (2)
Worst Grade ≥ 3	0 (0)	1 (2)
Any graft-versus-host disease	4 (14)	1 (2)
Worst Grade ≥ 3	1 (3)	0 (0)

Data cutoff date = 23Jul2021.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of efficacy of trial ZUMA-3

Title: Phase I/II multi-center study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r B-cell precursor ALL			
Study identifier	KTE-X19-103		
Design	Phase I/II single arm study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Actual follow-up time at DLP: mITT: 12.4 months (range. 0.3 to 22.1 months) FAS: 16.4 months not applicable not applicable
Hypothesis	Underlying OCR rate (in the absence of treatment with investigational therapy) is 40% and improvement in OCR to 65% would provide clinically meaningful benefit		
Treatments groups	KTE-X19		KTE-X19 single infusion N=71 enrolled and leukapheresed (FAS) N=55 treated (mITT)
Endpoints and definitions	Primary endpoint	Phase 1 Phase 2	Incidence of AEs and DLTs OCR rate (CR +Cri) per independent review (central assessment)
	Secondary endpoints Exploratory endpoints	- MRD rate - DOR - OCR - OS - RFS - Incidence of AEs - Incidence of presence of antibodies to the anti-CD19 CAR -Mortality rate -PR - BFBM rate -Anti-CD19 CAR T cells in blood -Cytokines in blood	Per investigator assessment
Database lock	09 September 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Modified Intent To Treat (mITT) : all treated subjects in phase 2 Full Analysis Set (FAS): all anrolled subjects in phase 2 (all received leukapheresis)			
Descriptive statistics and estimate variability	Treatment group	mITT	FAS	<group descriptor>
	Number of subject	N=55	N=71	<n>
	OCR (CR+CRi), n(%)	39 (70.9%)	39 (54.9%)	<point estimate>
	95% CI	(57%, 82%)	(43%, 67%)	<variability>
	CR, n(%)	31 (56.4%)	31 (43.7%)	<point estimate>
	95% CI	<variability>	(43%, 56%)	<variability>
	Cri, n(%)<endpoint> (<statistic>) 95% CI	8 (14.5%) (6%, 27%)	8 (11.3%) (5%, 21%)	<point estimate> <variability>

Supportive study

SCHOLAR-3 – A retrospective cohort study of adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia sampled from historical clinical trials (SCHOLAR-3)

Design

This is a non-interventional, retrospective cohort study utilizing data from the phase II ZUMA-3 investigational trial into KTE-X19 and patient level data from historical clinical trials in relapsed or refractory adult B precursor ALL contained within the Medidata Enterprise Data Store (MEDS) database.

Two matched cohorts were constructed to the ZUMA-3 trial, one in blin and ino naïve patients and one in blin experienced patients through the use of patient level data from trials selected from the Medidata MEDS database.

Study selection

Studies were selected through a literature search, with a search for all trials in the sub-indication of interest regardless of the availability of the trial to Medidata through data sharing agreements (Figure below). All trials in the indication and meeting basic project criteria were identified by searching across major trial repositories (NIH, clinicaltrials.gov, EudraCT and UMIN-CTR) and publication databases (PubMed, MEDLINE).

Trials represented in the Figure below met the following basic requirements for this study:

- Targeted condition of Acute Lymphoblastic Leukaemia (ALL)
- Trial intervention contains therapies from one of the following comparator regimens:
    - Blinatumomab
    - Inotuzumab Ozogamicin
    - Standard of Care, defined here as HiDAC, FLAG, mitoxantrone, methotrexate or clofarabine regimens

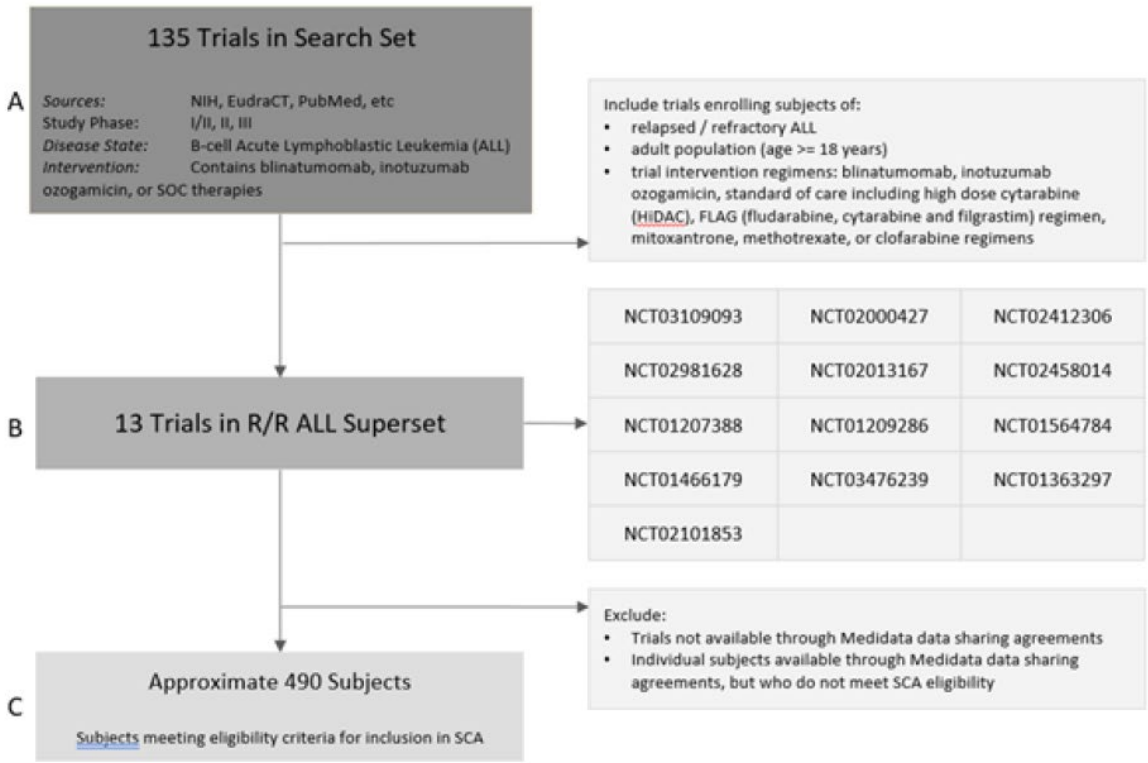
This search yielded 135 trials in the sub-indication of interest (Box A in Figure 1)

These studies were then narrowed according to the following scientific features of the trials or data that are required in order to address the research objective. (Box B)

- Relapsed / Refractory disease
- Adult population (enrolled patients aged >= 18 years)
- Trial intervention exact match to allowed comparator regimens

And only studies were used in the end which were available through Medidata data sharding agreement.

Figure 1. Trial Selection



SCA = Synthetic Control Arm

Matching

In order to create a matched cohort of patients to the phase II ZUMA-3 study a number of key considerations were made:

- The ZUMA-3 trial contains patients who initiate therapy with KTE-X19 after various numbers of previous regimens.
- Patients in the ZUMA-3 trial are heterogeneous in terms of prognostic factors.
- The ZUMA-3 trial consists of patients who are both allogenic stem cell transplant (allo-SCT) experienced and naïve.
- Some patients within the ZUMA-3 trial have been previously treated with the CD19 directed monoclonal antibody blinatumomab, prior to starting therapy with KTE-X19.

As there is evidence that prior treatment with blin may impact the efficacy of KTE-X19 due to CD19 modulation (Taraseviciute et al, two matched comparator cohorts are proposed; one comprising of patients who have been previously naïve to blin and ino treatment, the second cohort will comprise only blin experienced patients. These cohorts were thought to emulate a "physicians' choice" arm from a randomized trial with treatment exposures comprising of current standards of care (SOC).

Firstly, for each cohort (blin experienced and naïve) patients from the superset of trials were characterized into the following treatment exposures to create a potential pool of matches for each patient in ZUMA-3:

1. Patients who in the historical trial had previously failed an allo-SCT and been treated with either blin, ino or SOC chemotherapy; with or without a TKI dependent on Ph status.

2. Patients who in the historical trial had not previously failed an allo-SCT and been treated with blin, ino or SOC chemotherapy; with or without a TKI dependent on Ph status.

Each of these matching pools consisted of patients with varying previous lines of therapy, primary refractory status. age, sex, extra medullary disease status, Philadelphia chromosome status, ECOG performance status and varying percentage of bone marrow blasts.

The phase II ZUMA-3 trial consists of 55 patients who were treated with KTEX19, a matching approach was applied to select controls.

For the prognostic factors, line of therapy and prior allo-SCT, exact matching were used. For age, sex, ECOG performance status, Philadelphia chromosome status, percentage bone marrow blasts at baseline and extramedullary disease at baseline; propensity score matching was used.

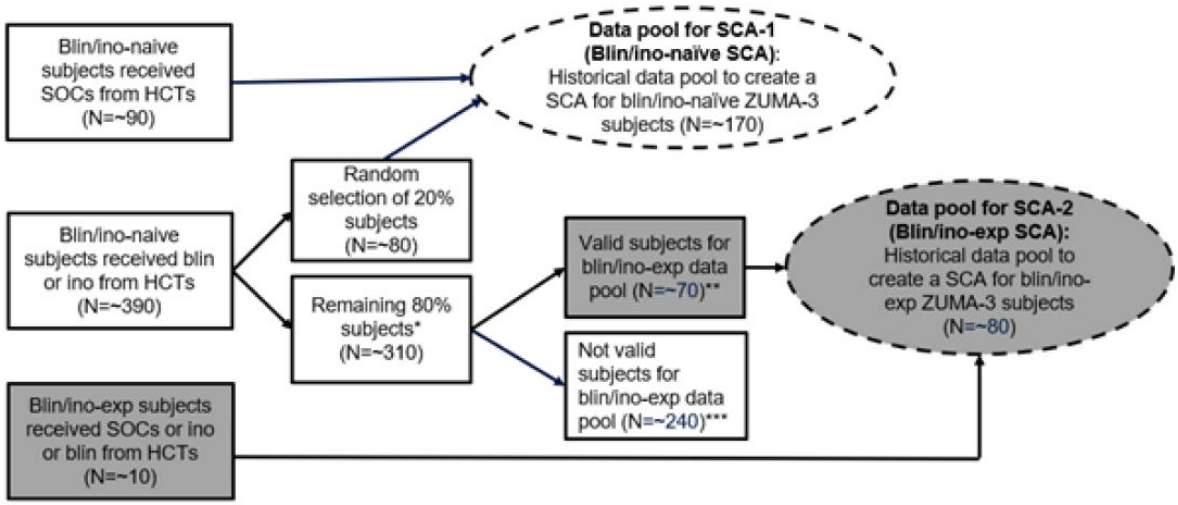
The propensity score was defined as the probability of patients being treated with KTE-X19 as a function of the above prognostic factors. It was derived using a multivariate model with a logit link function.

The greedy nearest-neighbor matching without replacement algorithm was used with a fixed 1-to-1 matching ratio which aligns with the commonly used 1:1 randomization ratio in clinical trials.

Either 1:1 optimal matching or variable ratio matching, with a maximum of a 1:3 ratio was planned to be used. Patients were matched within a specified caliper distance of 0.25 and balance between the ZUMA-3 and matched study arms was assessed through standardized mean differences (SMD).

Only baseline variables with limited or no missingness (e.g. < 15%) were included in the propensity score model. Missing values for baseline categorical variables were coded as an unknown category and can be used as a separate category or combined with one of the non-missing categories. Missing values for baseline continuous variables were imputed by a single regression imputation approach where the missing values were filled by predictions from regression models that are fitted using the mean and covariance matrix estimated by complete case analysis.

Figure 3. Sampling Approach Used in the Construction of Synthetic Control Arms



* The 80% subjects are the remainders of the subjects after 20% random selection for SCA-1 historical data pool
** Subjects had on-study treatment switch from blin or ino to other treatments, and the re-assessment dates of key prognostic factors were ≤ 60 days prior to treatment switch date
*** Subjects did not have on-study treatment switch from blin or ino to other treatments; or subjects had on-study treatment switch from blin or ino to other treatments, but the re-assessment dates of key prognostic factors were > 60 days prior to treatment switch date

Analysis

There is no formal hypothesis being tested as part of this study. Analyses were descriptive.

The balance of prognostic factors was assessed through the use of standardized mean differences (SMD) between the two treatment arms.

Fisher exact test was used to calculate rate difference, associated 95% confidence interval and p-value. For the comparative analysis, logistic regression was used to estimate an odds ratio.

The analysis was similar for other endpoints.

Results

Balance:

Balance is presented by matched subcohort and in all matched patients.

In SCA-2 9 patients were removed post-hoc, as it was discovered that they had protocol deviations.

Table 30. Subject Disposition and Balance Diagnostics of Matched ZUMA-3 and SCA-1 Patients

	Target Group (N=20)	SCA-1 (N=20)	Standardized Difference
Age at baseline (years)			-0.138
N	20	20	
Mean (STDEV)	42.5 (15.3)	44.8 (16.9)	
Median	42.5	44.5	
Min, Max	21.0, 68.0	20.0, 72.0	
Sex, n (%)			
Male	12 (60.0)	12 (60.0)	0.000
Female	8 (40.0)	8 (40.0)	
ECOG performance status, n (%)			
0	7 (35.0)	7 (35.0)	0.000
1	13 (65.0)	13 (65.0)	
Philadelphia chromosome status, n (%)			
Positive	4 (20.0)	3 (15.0)	0.135
Negative/Unknown	16 (80.0)	17 (85.0)	
Percentage bone marrow blasts			0.215
n	20	20	
Mean (STDEV)	48.2 (31.6)	41.6 (30.2)	
Median	50.0	37.5	
Min, Max	2.0, 96.0	0.3, 100.0	
Number of lines of prior therapy, n (%)			
≤ 2	16 (80.0)	16 (80.0)	0.000
> 2	4 (20.0)	4 (20.0)	
Presence of extramedullary disease (EMD), n (%)			
Yes	1 (5.0)	1 (5.0)	0.000
No/Unknown	19 (95.0)	19 (95.0)	
Prior allogeneic stem cell transplant (Allo-SCT), n (%)			
Yes	7 (35.0)	7 (35.0)	0.000
No/Unknown	13 (65.0)	13 (65.0)	
Primary refractory status, n (%)			
Yes	7 (35.0)	6 (30.0)	0.114
No/Unknown	13 (65.0)	14 (70.0)	

Table 31. Updated Subject Disposition and Balance Diagnostics of Matched ZUMA-3 and SCA-2 Patients

	Target Group (N=29)	SCA-2 (N=20)	Standardized Difference
Age at baseline (years)			-0.197
n	29	20	
Mean (STDEV)	40.9 (16.9)	44.2 (16.9)	
Median	40.0	45.5	
Min, Max	19.0, 84.0	19.0, 70.0	
Sex, n (%)			
Male	19 (65.5)	11 (55.0)	0.216
Female	10 (34.5)	9 (45.0)	
ECOG performance status, n (%)			
0	9 (31.0)	7 (35.0)	-0.084
1	20 (69.0)	13 (65.0)	
Philadelphia chromosome status, n (%)			
Positive	6 (20.7)	4 (20.0)	0.017
Negative/Unknown	23 (79.3)	16 (80.0)	
Percentage bone marrow blasts			-0.357
n	29	20	
Mean (STDEV)	59.3 (32.2)	69.9 (27.3)	
Median	70.0	77.9	
Min, Max	2.0, 98.0	0.0, 94.0	
Number of lines of prior therapy, n (%)			
≤ 2	11 (37.9)	5 (25.0)	0.281
> 2	18 (62.1)	15 (75.0)	
Presence of extramedullary disease (EMD), n (%)			
Yes	5 (17.2)	3 (15.0)	0.061
No/Unknown	24 (82.8)	17 (85.0)	
Prior allogeneic stem cell transplant (Allo-SCT), n (%)			
Yes	13 (44.8)	7 (35.0)	0.202
No/Unknown	16 (55.2)	13 (65.0)	
Primary refractory status, n (%)			
Yes	8 (27.6)	7 (35.0)	-0.160
No/Unknown	21 (72.4)	13 (65.0)	

Table 32. Subject Disposition and Matching Characteristics for All Matched Patients

	Target Group (N=49)	SCA (N=40)	Standardized Difference
Age at baseline (years)			-0.181
n	49	40	
Mean (STDEV)	41.5 (16.1)	44.5 (16.7)	
Median	40.0	44.5	
Min, Max	19.0, 84.0	19.0, 72.0	
Sex, n (%)			
Male	31 (63.3)	23 (57.5)	0.118
Female	18 (36.7)	17 (42.5)	
ECOG performance status, n (%)			
0	16 (32.7)	14 (35.0)	-0.050
1	33 (67.3)	26 (65.0)	
Philadelphia chromosome status, n (%)			
Positive	10 (20.4)	7 (17.5)	0.074
Negative/Unknown	39 (79.6)	33 (82.5)	
Percentage bone marrow blasts			-0.032
n	49	40	
Mean (STDEV)	54.8 (32.1)	55.8 (31.8)	
Median	60.0	63.0	
Min, Max	2.0, 98.0	0.0, 100.0	
Number of lines of prior therapy, n (%)			
≤ 2	27 (55.1)	21 (52.5)	0.052
> 2	22 (44.9)	19 (47.5)	
Presence of extramedullary disease (EMD), n (%)			
Yes	6 (12.2)	4 (10.0)	0.071
No/Unknown	43 (87.8)	36 (90.0)	
Prior allogeneic stem cell transplant (Allo-SCT), n (%)			
Yes	20 (40.8)	14 (35.0)	0.120
No/Unknown	29 (59.2)	26 (65.0)	
Primary refractory status, n (%)			
Yes	15 (30.6)	13 (32.5)	-0.041
No/Unknown	34 (69.4)	27 (67.5)	

OCR:

For the primary objective, it was estimated that 35% (95% CI 15.4%, 59.2%) of patients in SCA-1 achieved overall complete remission (OCR) inclusive of complete remission with incomplete hematological recovery at week 24.

Table 33. Complete Remission Rate Including Incomplete Hematological Recovery at Week 24 in SCA-1 Patients

	SCA-1 (N=20)	
Response Category	n	% (95% CI)
Overall complete remission (CR + CRi) rate at week 24	7	35.0 (15.4, 59.2)

In the comparison of OCR rate between matched ZUMA-3 and SCA-1 arms, matched patients from ZUMA-3 had an OCR rate of 85% (95% CI 62.1%, 96.8%). When compared to SCA-1 patients, matched ZUMA-3 patients had a higher odds of achieving OCR 10.5 (95% CI 2.3, 48.7) p-value 0.0031.

Table 34. Comparison of Complete Remission rate including incomplete hematological recovery at week 24 between matched ZUMA-3 and SCA-1 patients

	Target Group (N=20)		SCA-1 (N=20)		Treatment Difference (95% CI)		
Response Category	n	% (95% CI)	n	% (95% CI)	Rate Difference	Odds Ratio	P value
Overall complete remission (CR + CRi) rate at week 24	17	85.0 (62.1, 96.8)	7	35.0 (15.4, 59.2)	50.0 (17.9, 73.7)	10.5 (2.3, 48.7)	0.0031

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This application for extension of indication of Tecartus to include adults with B-cell precursor acute lymphoblastic leucemia (ALL) is based on the ZUMA-3 trial, a single-arm open-label phase I/II clinical trial, and on a historical control (Scholar-3), a retrospective cohort study, sampled from 135 historical phase I to III clinical trials in r/r B-cell ALL (appr. 490 subjects), where patients have been treated with blinatumomab or inotuzumab as SOC.

The pivotal part of the ZUMA-3 trial is the phase 2, where all subjects (n=55) had been treated with a target of 1×10^6 CAR-positive viable T cells per kg of body weight after completion of a conditioning chemotherapy (cyclophosphamide 900 mg/m2 on d-2, fludarabine 25 mg/m2 on d-4, d-3 and d-2).

Efficacy data and additional analyses

The median age among the subjects in the pivotal phase 2 of the ZUMA-3 trial (mITT analysis set, n=55) was 40.0 years of age. The majority of patients had relapsed or refractory disease after 2 or more lines of therapy. Subjects had a median of 2 lines of prior therapy (range: 1 to 8), 26 subjects (47%) had received 3 or more lines of prior therapy. Twenty-three subjects (42%) had previously received an allo-SCT. Twelve subjects (22%) had previously received inotuzumab, twenty-five subjects (45%) had

previously received blinatumomab. Altogether this population is regarded as heterogenous making subgroup analyses challenging and prone to spurious results.

Per DCO, the median OCR (CR + CRi) rate per central assessment was 70.9% (n=39) for all patients followed for a median of 12.4 months. The CR rate was 56% (n=31), and the MRD^- rate (assessed by central laboratory) was 76%. Among the 39 subjects who achieved CR or CRi, the KM median DOR was 12.8 months. None of the additional sixteen subjects included in the full analysis set (FAS, n=71) had achieved CR or CRi at DCO, therefore, results of DOR in FAS and mITT were identical. With regard to DOR (median 14.6 months) it is noticeable that 14/34 patients have been censored due to allo-SCT or due to start of a new treatment.

Overall the subgroup analyses for pertinent patient characteristics gave a consistent picture. The lowest response rates was observed in patients with the highest disease burden as defined by blast percentage in the bone marrow. Also patients with prior blinatumomab therapy, inotuzumab therapy or both achieved relevant response rates albeit numerically lower than patients naïve to either or both of these treatments.

Upon request additional data have been submitted for 23 subjects from ZUMA-3 phase 1, centrally assessed and treated with the pivotal dose of KTE-X19 with a recent DCO (23 July 2021), leading to a median follow-up of 20.5 months. Results for OCR (CR/CRi; 95% CI) in the updated analysis set Ph2 +Ph1 pivotal dose (n=78) were 73.1%. The MRD negative overall rate among OCR (CR/CRi; 95% CI) was 79%. These results support the primary analyses.

Additional expert consultation

The SAG-Oncology was consulted on 24 June 2022 to clarify the medical need for treatment options for adult patients, or subgroups of patients with r/r B-cell precursor ALL and to reflect on an appropriate positioning (if any) in the therapeutic armamentarium.

The following questions were asked to the SAG:

1. Is there a medical need for further treatment options in the indication relapsed/refractory B-cell precursor ALL in adults?

2. Can specific subgroups of patients with relapsed/refractory B-cell precursor adult ALL be identified that are currently not sufficiently treated with available treatment options also considering disease characteristics (resistant mutations, genomic alterations etc.)?

3. Besponsa and Blincyto are authorised in the indication relapsed/refractory B-cell precursor ALL in adults. Are there specific subgroups of patients where these authorized options are not appropriate for reasons such as the safety profile of the products or patient characteristics (e.g. co-morbidities)?

4. Would Tecartus be a treatment alternative in relapsed/refractory B-cell precursor adult ALL considering the strength of the evidence for Tecartus (derived from SAT, ORR) and for other treatment options /derived from RCT, OS)?

5. How would you judge the importance of Tecartus as a possible bridging to transplant and/or alternative to authorized products in the indication relapsed/refractory B-cell precursor adult ALL?

6. What type of data would be required to further characterize the remaining uncertainties regarding efficacy in the 2L or 3L+ population, respectively?

The outcome of the SAG is summarized below:

1. Is there a medical need for further treatment options in the indication relapsed/refractory (r/r) B-cell precursor acute lymphoblastic leukaemia (ALL) in adults?

The SAG agreed unanimously that there is a high unmet medical need in r/r B-cell precursor ALL, since, despite available treatments (including monoclonal antibodies blinatumomab and inotuzumab) the prognosis is dismal, with high degree of relapse, non-responder patients and with low PFS and low survival rates.

2. Can specific subgroups of patients with relapsed/refractory B-cell precursor ALL be identified that are currently not sufficiently treated with available treatment options also considering disease characteristics (resistant mutations, genomic alterations etc.)?

Due to the fact that the evidence presented for Tecartus in r/r B-cell precursor ALL is based on a small single arm phase 2 trial with a limited number of patients, the experts cannot identify any subgroups who are not sufficiently treated with available options.

There aren't any satisfactory treatments for R/R B-cell precursor ALL patients as a whole. Groups with the highest need include elderly patients, Philadelphia chromosome-negative (PH-), minimal residual disease positive (MRD+) and those ineligible for allogeneic stem cell transplantation (alloSCT) or those that have relapsed following alloSCT. The experts agreed that it is highly unlikely that these patients are salvaged by the current available treatments. Therefore, treating physicians need flexibility to select different optional treatments.

3. Besponsa and Blincyto are authorised in the indication r/r B-cell precursor ALL in adults. Are there specific subgroups of patients where these authorized options are not appropriate for reasons such as the safety profile of the products or patient characteristics (e.g. co-morbidities)?

The experts flagged that the landscape in ALL treatment is evolving, as Besponsa and Blincyto are moving forward in the line of treatment, leaving fewer alternatives in later lines of treatment.

There are no specific criteria which would render patients ineligible to Besponsa and Blincyto even though treatment duration may be limited due to liver function or occurrence of veno-occlusive disease (VOD). There might be severe adverse events (AEs), such as liver toxicity with inotuzumab, or pre-existing co-morbidities, in which cases certain treatments cannot be used and CAR-T cells might be preferred. However, the experts cannot define a treatment sequence for the different alternatives in ALL.

The experts agreed that the indication for Tecartus in r/r B-cell precursor ALL should reflect the population of patients with a positive balance of benefits and risks with the CAR-T treatment and not the unsuitability to other treatments. A broad indication would maximise the ability of physicians and patients to consider for which patients this treatment would be preferred. In addition, a broad indication would allow to collect more extensive and meaningful real-world data (RWD).

4. Would Tecartus be a treatment alternative in relapsed/refractory B-cell precursor ALL considering the strength of the evidence for Tecartus (derived from SAT, ORR) and for other treatment options (derived from RCT, OS)?

The SAG agreed that, despite the limited data, Tecartus can be a treatment alternative in r/r B-cell precursor ALL. However, the experts found that there is not enough evidence to define any optimal sequence and in which subpopulation Tecartus would be preferred.

5. How would you judge the importance of Tecartus as a possible bridge to transplant and/or as alternative to authorized products in the indication r/r B-cell precursor adult ALL?

Based on the high responses and high MRD negativity achieved with Tecartus, it is reasonable to expect that it is a good candidate for bridging therapy to transplantation, taking into account all limitations (e.g. the trial's small patient group). Tecartus can also be used as an alternative to authorized products in the same indication.

6. What type of data would be required to further characterize the remaining uncertainties regarding efficacy in the 2L or 3L+ population, respectively?

Data presented for Tecartus is sparse and lots of questions remain. The experts agreed that, ideally, a confirmatory RCT should be performed comparing Tecartus with actually available treatments. The experts acknowledge the difficulties to perform such a study, especially taking into account that the monoclonal antibodies are moving forward in the line of treatment in ALL.

The experts agreed that patients should be included in a post-authorization registry to better characterize efficacy and safety aspects and patient reported outcomes (PROs).

In particular, more data on the safety of Tecartus in this indication, more data in the elderly population who are not eligible to ASCT and on PH - patients and MRD - patients that cannot be transplanted would be very valuable.

Additional efficacy data needed in the context of a conditional MA

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2).

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry, according to an agreed protocol.

These post authorisation studies should provide longer term data as well as further efficacy and safety information on important subgroups (age groups from 18 to 25 years of age and older than 60 years, status MRD+ and PH-, patients that have relapsed following allo-SCT), which are not fully represented in the pivotal study submitted for this procedure. The provision of this data post authorisation will complement the dossier in order to have a comprehensive understanding of efficacy and safety and to confirm the positive benefit risk balance of the product in the new indication.

2.4.3. Conclusions on the clinical efficacy

Based on the submitted data and the recent update encompassing 78 patients, efficacy has been demonstrated in the ZUMA-3 trial. The included patient population is small and heterogeneous, however, subgroup analyses give a fairly consistent picture regardless of prior therapies. There is an indication for lower efficacy in patients with high disease burden (high blast percentage in the bone marrow), requiring further investigation in registry studies as a part of the conditional approval.

The following measures are considered necessary to address issues related to efficacy:

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2).

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry, according to an agreed protocol.

2.5. Clinical safety

Introduction

The important identified risks and the potential risks identified for KTE-X19 are similar to the AEs identified for this product class. No further risks and AEs could be identified which would be specific for KTE-X19 or for the MCL indication to be treated with KTE-X19. The important identified risks are CRS, neurotoxicity, cytopenias, infections, hypogammaglobulinemia.

The safety data for this extension to indication are based on the pivotal Phase 2 of ZUMA-3 trial, which is evaluating KTE-X19 for the treatment of adult subjects with r/r B-ALL. Additional safety data are provided from 4 studies of KTE-X19 in subjects with r/r MCL (ZUMA-2 and ZUMA-18, pooled as MCL), r/r pediatric and adolescent ALL (ZUMA-4), and r/r CLL (ZUMA-8).

Patient exposure

Exposure to Lymphodepleting Chemotherapy

In the main, ZUMA-3 study 71 patients were leukapheresed, and 55 patients were treated. All 55 subjects in Phase 2 safety analysis set received the planned total body-surface-area-adjusted dose of cyclophosphamide (900 mg/m^2). Subjects received a median total body-surface-area-adjusted dose of fludarabine of 75 mg/m^2 (range: 71 to 75 mg/m^2); all 55 subjects received within 10% of the planned total dose.

Table 35. Exposure to Lymphodepleting Chemotherapy in Study ZUMA-3 (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
Cyclophosphamide	
Total BSA-adjusted dose (mg/m^2) [a]	
n	55
Mean (STDEV)	900.0 (0.0)
Median (Q1, Q3)	900.0 (900.0, 900.0)
Min, max	900.0, 900.0
Subjects received +/- 10% planned total dose, n (%)	55 (100)
Fludarabine	
Total BSA-adjusted dose (mg/m^2) [a]	
n	55
Mean (STDEV)	74.9 (0.5)
Median (Q1, Q3)	75.0 (75.0, 75.0)
Min, max	71.0, 75.0
Subjects received +/- 10% planned total dose, n (%)	55 (100)

Data cutoff date = 09SEP2020.
Abbreviations: BSA, body surface area; max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
a. Total BSA-adjusted dose of cyclophosphamide/fludarabine received is calculated by (sum of nonmissing doses during lymphodepleting chemotherapy period).

According to the MAH, six patients did not receive KTE-X19 due to manufacturing failure. Eight other patients were not treated, primarily due to AEs following leukapheresis. Two patients who underwent leukapheresis and received lymphodepleting chemotherapy were not treated with KTE-X19; one patient experienced bacteremia and neutropenic fever and the other patient did not meet eligibility criteria after lymphodepleting chemotherapy.

In Phase 2, a total of 71 subjects were enrolled (ie, underwent leukapheresis); of these, 57 subjects (80%) received lymphodepleting chemotherapy. Fourteen subjects received neither lymphodepleting chemotherapy nor KTE-X19 after leukapheresis:

(I) Seven subjects were not treated due to AEs:

- One subject experienced various AEs following leukapheresis, including tumor lysis syndrome, lung infection, urinary tract infection, and sepsis. The subject died of sepsis, which was considered related to bridging therapy, before they could be treated with KTE-X19.

- One subject's product was not successfully manufactured from the initial leukapheresis material. Following the second leukapheresis, the subject developed a lung infection and respiratory failure and died of PD before they could be treated with KTE-X19.

- One subject's product was not successfully manufactured from the initial leukapheresis material. The subject developed fungal pneumonia and sepsis shortly after leukapheresis and ultimately died of PD without undergoing a second leukapheresis.

- One subject experienced an AE of deep vein thrombosis following leukapheresis, rendering this subject ineligible for the study. This subject was later determined to have had symptomatic deep vein thrombosis at the time of screening.

- One subject experienced various AEs following leukapheresis, including splenic rupture, neutropenic sepsis, aspiration pneumonia, and encephalopathy. The subject then died of cardiac arrest before they could be treated with KTE-X19.

- One subject experienced various AEs following leukapheresis, including Clostridium difficile infection, septic shock, colitis infection, and myositis. The subject was removed from study per the investigator's decision.

- One subject developed a hemiparesis due to air embolism following leukapheresis, rendering this subject ineligible for the study. The subject was subsequently treated under a compassionate use protocol.

(II) Three subjects were identified as not meeting eligibility criteria after leukapheresis:

- Two subjects were found to have CD19− blasts (both subjects had received prior blinatumomab). For 1 of these subjects, product was not successfully manufactured from the initial leukapheresis material.

- One subject was found to have < 5% blasts.

(III) Four subjects were not treated due to manufacturing failures:

- One subject's product was not successfully manufactured from the initial leukapheresis material. The subject developed a lung infection after leukapheresis and consequently was unable to undergo a second leukapheresis (reported as "product not available").

- One subject's product was not successfully manufactured from the initial leukapheresis material. Further leukapheresis attempts were delayed as the subject had developed febrile neutropenia after leukapheresis. The subject then partially withdrew consent from the study (which is the reason listed for this subject not having been treated) and died of febrile neutropenia in hospice care.

- One subject's product was not successfully manufactured from 3 sets of leukapheresis material. Further leukapheresis attempts were deferred indefinitely as the subject experienced clinical deterioration (reported as "other") and subsequently died of PD.

- One subject's product was not successfully manufactured from the initial leukapheresis material. A second leukapheresis was not attempted per the primary oncologist's decision that the subject was not clinically stable to proceed with CAR T-cell therapy (reported as "other").

Of the 57 subjects who received lymphodepleting chemotherapy, 55 subjects received KTE-X19. Two subjects were not treated with KTE-X19 after receiving lymphodepleting chemotherapy: 1 subject experienced AEs of bacteremia and neutropenic fever that precluded further treatment, and 1 subject deteriorated after lymphodepleting chemotherapy and no longer met eligibility criteria (the subject experienced fulminant progression of extramedullary disease and spinal cord compression, leading to ECOG performance status > 1).

Exposure to KTE-X19

In Phase 2, the median weight-adjusted dose of KTE-X19 was 1.0 x 10^6 anti-CD19 CAR T cells/kg (range: 0.5 x 10^6 to 1.0 x 10^6 cells/kg). The median total number of anti-CD19 CAR T cells in the KTE-X19 infusion was 75.7 x 10^6 cells (range: 39.3 x 10^6 to 101.0 x 10^6 cells), and the median total number of T cells infused was 128.4 x 10^6 cells (range: 65.5 x 10^6 to 277.8 x 10^6 cells).

Table 36. Exposure to KTE-X19 in ZUMA-3 (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
KTE-X19	
Weight-adjusted KTE-X19 dose received (x 10^6 anti-CD19 CAR T cells/kg)	
n	55
Mean (STDEV)	1.0 (0.1)
Median (Q1, Q3)	1.0 (1.0, 1.0)
Min, max	0.5, 1.0
Total number of CAR T cells (x 10^6)	
n	55
Mean (STDEV)	77.4 (16.8)
Median (Q1, Q3)	75.7 (64.9, 93.7)
Min, max	39.3, 101.0
Total number of T cells infused (x 10^6)	
n	55
Mean (STDEV)	138.9 (43.9)
Median (Q1, Q3)	128.4 (106.3, 170.0)
Min, max	65.5, 277.8
Subjects received +/- 10% planned total dose, n (%)	54 (98)[a]

Data cutoff date = 09Sep2020.
Abbreviations: CAR, chimeric antigen receptor; max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
a One subject weighed > 100 kg and received 0.81 x 10^8 anti-CD19 CAR T cells due to the product being out of specification (target dose of 1 x 10^8 anti-CD19 CAR T cells). See text for additional information.

In the supportive studies, patients were treated with KTE-X19 as follows:

Table 37. Exposure to KTE-X19 in Supporting Studies ZUMA-2, ZUMA-4, ZUMA-8, and ZUMA-18 (Safety Analysis Set)

	Adult MCL ZUMA-2 and ZUMA-18 (N = 103)	Adolescent/pediatric ALL ZUMA-4 (N = 36)	Adult CLL ZUMA-8 (N = 9)
KTE-X19			
Weight-adjusted KTE-X19 dose received (x 10^6 CAR T cell/kg)			
n	103	36	9
Mean (STDEV)	1.7 (0.53)	1.1 (0.33)	1.3 (0.47)
Median (Q1, Q3)	2.0 (1.9, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.7)
Min, max	0.5, 2.0	0.7, 2.0	0.9, 2.0
Subjects receiving +/- 10% planned total dose, n (%)	101 (98)	34 (94)	9 (100)
Total number of CAR T cells (x 10^6)			
n	103	36	9
Mean (STDEV)	144.8 (50.30)	47.7 (30.54)	110.3 (46.30)
Median (Q1, Q3)	155.0 (129.0, 181.0)	40.7 (25.0, 60.6)	89.8 (79.2, 149.0)
Min, max	29.2, 202.0	14.2, 157.0	65.4, 200.0
Total number of T cells infused (x 10^6)			
n	103	36	9
Mean (STDEV)	254.4 (114.87)	95.1 (86.33)	179.4 (65.86)
Median (Q1, Q3)	245.0 (193.9, 329.3)	72.4 (41.0, 121.5)	178.3 (119.8, 223.2)
Min, max	40.9, 579.4	18.3, 504.8	109.5, 275.9
Transduction ratio (%)			
n	103	36	9
Mean (STDEV)	60.6 (12.48)	57.0 (15.27)	61.7 (11.07)
Median (Q1, Q3)	61.0 (50.7, 70.0)	56.5 (46.1, 68.0)	58.0 (55.0, 69.0)
Min, max	32.0, 82.4	25.0, 87.8	46.0, 82.0

Data cutoff date = 09SEP2020.
Abbreviations: ALL, acute lymphoblastic leukemia; BSA, body surface area; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; max, maximum; MCL, mantle cell lymphoma; Min, minimum; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
Exposure during the retreatment period are excluded.
One subject in ZUMA-18 received 970 mg of cyclophosphamide and 58 mg of fludarabine treatments on Day -5, respectively. The BSA is 1.95 m^2.
One subject in ZUMA-18 received 870 mg of cyclophosphamide and 50 mg of fludarabine treatments on Day -5, -4 and -3, respectively. The BSA is 1.74 m^2.

Among the 55 subjects who received KTE-X19 in Phase 2, the median age was 40.0 years (range: 19 to 84 years), and 8 subjects (15%) were ≥ 65 years of age. Thirty-three subjects (60%) were male, and the majority was White (37 subjects, 67%).

Table 38. Demographics in Study ZUMA-3 (Phase 2, Safety Analysis Set)

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

Data cutoff date = 09SEP2020.
Abbreviations: Max, maximum; Min, minimum: STDEV, standard deviation.
Note: Percentages are based on the number of subjects treated with any dose of KTE-X19.

Among the 55 subjects treated with KTE-X19 in Phase 2, 18 subjects (33%) had primary refractory disease, 43 subjects (78%) had r/r disease after 2 or more lines of therapy, and 16 subjects (29%) had first relapse with first remission ≤ 12 months. Subjects had a median of 2 prior lines of therapy (range: 1 to 8 prior lines), and 26 subjects (47%) had received 3 or more lines of therapy. Twenty-three subjects (42%) had previously received an allo-SCT, and 12 subjects (22%) had previously received inotuzumab. Twenty-five subjects (45%) had previously received blinatumomab, and 12 subjects (22%) had received blinatumomab as the last prior therapy. Fifteen subjects (27%) were Ph^+. The median blast percentage in bone marrow at screening was 65.0% (range: 5.01% to 100%), and the median blast percentage at baseline (ie, the last assessment before lymphodepleting chemotherapy) was 60.0% (range: 0% to 98%). Forty subjects (73%) had a high disease burden (> 25% blasts) at baseline. Six subjects (11%) had extramedullary disease at screening

Table 39. Baseline Characteristics in Study ZUMA-3 (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
ECOG performance status, n (%)	
0	16 (29)
1	39 (71)
Philadelphia chromosome t(9;22) mutation, n (%)	
Yes	15 (27)
No	40 (73)
Prior blinatumomab, n (%)	
Yes	25 (45)
No	30 (55)
Blinatumomab as the last prior therapy, n (%)	
Yes	12 (22)
No	43 (78)
Prior inotuzumab, n (%)	
Yes	12 (22)
No	43 (78)
Prior allogeneic SCT, n (%)	
Yes	23 (42)
No	32 (58)
Prior autologous SCT, n (%)	
Yes	2 (4)
No	53 (96)
Number of lines of prior therapy, n (%)	
1	10 (18)
2	19 (35)
3	14 (25)
4	10 (18)
5	1 (2)
8	1 (2)
Median	2.0
Min, Max	1, 8
Primary refractory, n (%)	
Yes	18 (33)
No	37 (67)
Relapsed or refractory to 2nd or greater line therapy, n (%)	
Yes	43 (78)
No	12 (22)
Relapsed or refractory disease after allogeneic SCT, n (%)	
Yes	24 (44)
No	31 (56)
First relapse with first remission ≤ 12 months, n (%)	
Yes	16 (29)
No	39 (71)
Response to the last prior therapy, n (%)	
CR	16 (29)
CRi	1 (2)
PR	2 (4)
NR	20 (36)
PD	10 (18)
Not evaluated	6 (11)
Prior radiotherapy, n (%)	
Yes	13 (24)
No	42 (76)
% blasts in bone marrow at screening	
n	55
Mean (STDEV)	54.9 (31.9)
Median	65.0

Min, Max	5.01, 100
Category, n (%)	
> 5% to 25%	16 (29)
> 25%	39 (71)
% blasts in bone marrow at baseline	
n	55
Mean (STDEV)	54.0 (33.1)
Median	60.0
Min, Max	0, 98
Category, n (%)	
≤ 5%	5 (9)
> 5% to 25%	10 (18)
> 25%	40 (73)
% blasts in bone marrow after bridging chemotherapy	
n	46
Mean (STDEV)	53.3 (32.8)
Median	59.0
Min, Max	0, 98
Category, n (%)	
≤ 5%	5 (9)
> 5% to 25%	7 (13)
> 25%	34 (62)
Extramedullary disease at screening, n (%)	
Yes	6 (11)
No	49 (89)
CNS disease at baseline, n (%)	
CNS-1	55 (100)
CD19 % lymphoblast at baseline by central lab	
n	53
Mean (STDEV)	94.5 (12.0)
Median	100.0
Min, Max	45, 100
CD19 % lymphoblast baseline category based on central lab, n (%)	
≥ 95	41 (75)
< 95	12 (22)
Missing	2 (4)

Baseline extramedullary disease target lesion (SPD) (mm^2) [a]	
n	3
Mean (STDEV)	31853.7 (54169.8)
Median	1161.0
Min, Max	0, 94400
Baseline spleen measurement (LVD) (mm)	
n	1
Mean (STDEV)	140.0 (NA)
Median	140.0
Min, Max	140, 140
MLL translocation t(4;11) or Myc translocation t(8;14), n (%)	
Yes	2 (4)
No	53 (96)
Complex karyotype (≥ 5 chromosomal abnormalities), n (%)	
Yes	14 (25)
No	41 (75)
Low hypodiploidy (30-39 chromosomes), n (%)	
Yes	1 (2)
No	54 (98)
Near triploidy (60-78 chromosomes), n (%)	
Yes	1 (2)
No	54 (98)

Data cutoff date = 09Sep2020.
Abbreviations: CNS, central nervous system; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; ECOG, Eastern Cooperative Oncology Group; LVD, longest vertical dimension; Max, maximum; Min, minimum; MLL, mixed lineage leukemia; NA, not applicable; NR, no response; PD, progressive disease; PR, partial remission; SCT, stem cell transplant; SPD, sum of the products of diameters; STDEV, standard deviation.
Notes: Excludes information collected after retreatment. Baseline is defined as the last assessment prior to the start of lymphodepleting chemotherapy.
a. As measured by the SPD of all target lesions at baseline.

Adverse events

TEAEs were defined as AEs with an onset on or after the infusion of KTE-X19. AEs that occurred after retreatment are not included in this summary. The severity of AEs and serious adverse events (SAEs), with the exception of CRS, were graded by the investigator using the NCI CTCAE version 4.03. The severity of CRS was to be graded at the syndrome level according to a modification of the grading system proposed by Lee and colleagues {Lee 2014}. In the tables, CRS as a syndrome is not included as an AE preferred term (PT) and is reported separately. Also, CRS symptoms are presented twice, once in tables of AEs by PTs and once in tables of CRS and CRS symptoms. AEs were coded with the MedDRA version 23.0.

Among the 55 subjects treated in Phase 2, all subjects had at least 1 AE, 52 subjects (95%) had worst Grade 3 or higher AEs, and 41 subjects (75%) had SAEs. A total of 49 subjects (89%) had CRS, and 13 subjects (24%) had worst Grade 3 or higher CRS. No subject had Grade 5 CRS. Thirty-three subjects (60%) had at least 1 neurologic AE; 14 subjects (25%) had worst Grade 3 or higher neurologic AEs, and 14 subjects (25%) had serious neurologic AEs. One subject had a Grade 5 neurologic AE of brain herniation. As of the data cutoff date, 10 subjects (18%) in Phase 2 had died due to AEs, including 4 subjects (7%) who died due to disease progression within 3 months after the KTE-X19 infusion (reported as Grade 5 ALL) and 6 subjects (11%) who died due to AEs other than disease progression.

Table 40. Overall Summary of AEs in ZUMA-3 (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
Any TEAE	55 (100)
Worst Grade 5	10 (18)
Worst Grade ≥ 3	52 (95)
Any serious TEAE	41 (75)
Worst Grade 5	10 (18)
Worst Grade ≥ 3	40 (73)
Any KTE-X19 related TEAE	51 (93)
Worst Grade 5	2 (4)
Worst Grade ≥ 3	49 (89)
Any serious KTE-X19 related TEAE	34 (62)
Worst Grade 5	2 (4)
Worst Grade ≥ 3	31 (56)
Any TE CRS	49 (89)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	13 (24)
Any TE neurologic adverse event [a]	33 (60)
Worst Grade 5	1 (2)
Worst Grade ≥ 3	14 (25)
Any TE CRS or neurologic adverse event [a]	50 (91)
Worst Grade 5	1 (2)
Worst Grade ≥ 3	24 (44)
Any serious TE neurologic adverse event [a]	14 (25)
Worst Grade 5	1 (2)
Worst Grade ≥ 3	11 (20)
Any TE thrombocytopenia	27 (49)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	24 (44)
Any TE neutropenia	27 (49)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	27 (49)
Any TE anemia	29 (53)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	27 (49)
Any TE infection	20 (36)
Worst Grade 5	4 (7)
Worst Grade ≥ 3	14 (25)
Any serious TE infection	11 (20)
Worst Grade 5	4 (7)
Worst Grade ≥ 3	9 (16)
Any COVID-19 associated TE viral infection	0 (0)
Any non-COVID-19 associated TE viral infection	2 (4)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	2 (4)
Any hypogammaglobulinemia	4 (7)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	0 (0)
Any tumor lysis syndrome	1 (2)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	1 (2)
Any graft-versus-host disease	1 (2)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	0 (0)

Data cutoff date = 09Sep2020.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; TE, treatment emergent; TEAE, treatment-emergent adverse event.
TEAEs include all AEs with an onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with KTE-X19, the AEs occurring during the retreatment period are not included.
Subjects were summarized at their highest grade per CTCAE version 4.03. CRS is graded per the revised grading system proposed by Lee et al {Lee 2014}.
a. Neurologic adverse events are identified based on a modification of criteria proposed by Topp et al {Topp 2015}.

In Phase 2, the most common AEs by system organ class (SOC) were general disorders and administration site conditions (54 subjects, 98%), vascular disorders (42 subjects, 76%), and blood and lymphatic system disorders (41 subjects, 75%). The most common AEs by PT were pyrexia (52 subjects, 95%), hypotension (37 subjects, 67%), and anemia (29 subjects, 53%). The most common worst Grade 3 or higher AEs were anemia (27 subjects, 49%), pyrexia (20 subjects, 36%), and platelet count decreased (17 subjects, 31%).

The most common KTE-X19-related AEs of any grade were pyrexia (46 subjects, 84%), hypotension (34 subjects, 62%), and sinus tachycardia (19 subjects, 35%). The most common KTE-X19-related AEs that were worst Grade 3 or higher were pyrexia (20 subjects, 36%), hypotension (16 subjects, 29%), and hypoxia (11 subjects, 20%).

Serious adverse event/deaths/other significant events

Deaths

In Phase 2, the median potential follow-up time from the KTE-X19 infusion was 16.4 months (range: 10.3 to 22.1). Twenty of 55 subjects (36%) had died as of the data cutoff date. Brief descriptions are as follows:

Thirteen subjects died due to PD.

Six subjects died due to AEs other than Grade 5 ALL:

- One subject died on Day 8 due to a neurologic AE of brain herniation that was deemed related to KTE-X19.
- One subject died on Day 18 due to septic shock that was deemed related to lymphodepleting chemotherapy and KTE-X19.
- One subject died on Day 15 due to pneumonia that was deemed unrelated to KTE-X19.
- One subject died on Day 46 due to fungal pneumonia that was deemed unrelated to KTE-X19. This subject relapsed on Day 4 and received another anticancer therapy (inotuzumab from Day 10 to Day 39) prior to this fatal event.
- One subject died on Day 72 due to sepsis that was deemed unrelated to KTE-X19. This subject did not respond to KTE-X19 as of Day 16 and started another anticancer therapy (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine from Day 22 to Day 32) prior to this fatal event.
- One subject died on Day 491 due to respiratory failure that was deemed unrelated to KTE-X19. This subject relapsed on Day 314 after an initial response to KTE-X19 and had received 2 subsequent lines of therapy with tyrosine kinase inhibitors.

One subject died on Day 231 due to hemorrhagic shock secondary to a gastrointestinal bleed and disseminated intravascular coagulopathy, which were deemed as related to the underlying B-ALL. The cause of death was reported as "other."

Of the 20 subjects in Phase 2 who died, 4 subjects died within 30 days after the KTE-X19 infusion, 5 subjects died between 30 days and 3 months after the infusion, and 11 subjects died more than 3 months after the infusion.

Table 41. Deaths, Including Cause of Death in Study ZUMA-3 (Phase 2, Safety Analysis Set)

	Phase 2 (N = 55)
Subjects who died, n (%)	20 (36)
Deaths that occurred ≤ 30 days after KTE-X19 infusion, n (%)	4 (7)
Deaths that occurred > 30 days through 3 months (92 days) after KTE-X19 infusion, n (%)	5 (9)
Deaths that occurred > 3 months (92 days) after KTE-X19 infusion, n (%)	11 (20)
Primary cause of death, n (%)	
Adverse event[a]	6 (11)
Progressive disease[a]	13 (24)
Other	1 (2)

Data cutoff date = 09Sep2020.
a Subjects with Grade 5 acute lymphocytic leukemia are categorized as "progressive disease" and excluded from the "adverse event" category in this table.

Serious adverse events

In Phase 2, the most common SAEs were hypotension (16 subjects, 29%), pyrexia (15 subjects, 27%), and hypoxia (7 subjects, 13%). The most common worst Grade 3 or higher SAEs were hypotension (13 subjects, 24%), hypoxia (7 subjects, 13%), and pyrexia (6 subjects, 11%).

SAEs that occurred in ≥ 2 subjects and were deemed related to KTE-X19: thirty-four subjects (62%) had at least 1 SAE related to KTE-X19, the most frequently reported of which were hypotension (16 subjects, 29%), pyrexia (14 subjects, 25%), and hypoxia (7 subjects, 13%). The most common worst Grade 3 or higher SAEs related to KTE-X19 were hypotension (13 subjects, 24%), hypoxia (7 subjects, 13%) and pyrexia (6 subjects, 11%).

Important identified risks

CRS

In Phase 2, 49 subjects (89%) had CRS, and 13 subjects (24%) had CRS that was worst Grade 3 or higher. No subject had Grade 5 CRS.

Table 42. Subject incidence of CRS in Study Zuma-3 (Phase 2, Safety Analysis Set, N=55)

Event, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any CRS [a]	49 (89)	11 (20)	25 (45)	7 (13)	6 (11)	0 (0)

Among 49 subjects with CRS, the most common CRS symptoms of any grade were pyrexia (46 subjects, 94%), hypotension (33 subjects, 67%), and sinus tachycardia (18 subjects, 37%). The most common worst Grade 3 or higher CRS symptoms were pyrexia (19 subjects, 39%), hypotension (16 subjects, 33%), and hypoxia (11 subjects, 22%). Similarly, the most common serious CRS symptoms of any grade were hypotension (16 subjects, 29%), pyrexia (14 subjects, 25%), and hypoxia (7 subjects, 13%).

Among subjects who had CRS, the median time to onset was 5.0 days (range: 1 to 12 days) after KTE-X19 infusion. As of the data cutoff date, CRS had resolved in 46 of 49 subjects. For the remaining 3 subjects, CRS was ongoing at the time of death due to PD on Day 21 in 1 subject, brain herniation on Day 8 in 1 subject, and pneumonia on Day 15 in 1 subject. For subjects whose CRS had resolved, the median duration of CRS was 7.5 days (range: 2 to 48 days). Two subjects had CRS with a total duration > 28 days: 1 subject had CRS for 30 days with a prolonged CRS symptom of Grade 2 nonserious nausea for 30 days, and 1 subject had CRS for 48 days with a prolonged CRS symptom of Grade 1 nonserious increased C-reactive protein for 47.

Neurologic Adverse Events Including Cerebral Edema

In Phase 2, 33 subjects (60%) had at least 1 neurologic AE of any grade, including 14 subjects (25%) with worst Grade 3 or higher neurologic AEs. One subject had a Grade 5 neurologic AE of brain herniation. The most common neurologic AEs of any grade were tremor (15 subjects, 27%), confusional state (14 subjects, 25%), and encephalopathy (12 subjects, 22%). The most common worst Grade 3 or higher neurologic AEs were aphasia (5 subjects, 9%), encephalopathy (4 subjects, 7%), and confusional state, agitation, seizure, and paraparesis (2 subjects each, 4%).
Fourteen subjects (25%) had serious neurologic AEs of any grade, including 11 subjects (20%) with worst Grade 3 or higher serious neurologic AEs. The most common serious neurologic AEs of any grade were encephalopathy (4 subjects, 7%) and aphasia, confusional state, and seizure (3 subjects each, 5%).

Among subjects who had neurologic AEs, the median time to onset was 9.0 days (range: 2 to 16 days) after KTE-X19 infusion. As of the cutoff date, neurologic AEs had resolved in 29 of 33 subjects.

The duration of neurologic AEs for each subject was calculated as the last date of resolution for all qualifying neurologic AEs – the date of first onset of all qualifying neurologic AEs + 1. Among the 29 subjects whose neurologic AEs had resolved, the median duration of neurologic AEs was 7.0 days (range: 1 to 75 days).

Four subjects had unresolved neurologic AEs either at the data cutoff date or at the time of death:

One subject had Grade 4 serious encephalopathy, Grade 3 nonserious agitation, and Grade 1 nonserious confusion, which all started on Day 5; Grade 4 serious cerebral edema, which started on Day 6; and a fatal event of Grade 5 serious cerebral herniation on Day 8. All events were ongoing at the time of death and were deemed related to KTE-X19.

One subject had Grade 3 serious paralysis of the lower extremity, which started on Day 10 and was ongoing at the time of death due to PD on Day 553. The event was deemed related to KTE-X19.

One subject had Grade 3 serious paraparesis, which started on Day 9 and was ongoing at the time of death due to PD on Day 483. The event was deemed unrelated to KTE-X19. This subject had a history of bilateral lower extremity weakness, and spinal imaging performed after the onset of paraparesis demonstrated degenerative changes.

One subject had Grade 1 nonserious finger numbness, which started on Day 29 and was ongoing as of the data cutoff date. The event was deemed unrelated to KTE-X19.

Table 43. Subject incidence of Neurologic AEs in Study ZUMA-3 (Phase 2, Safety Analysis Set, N=55)

MedDRA Preferred Term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any neurologic AEs	33 (60)	6 (11)	13 (24)	13 (24)	0 (0)	1 (2)

Cytopenias

Twenty-seven subjects (49%) in Phase 2 had thrombocytopenia of any grade, including 24 subjects (44%) with worst Grade 3 or higher thrombocytopenia. Twenty-seven subjects (49%) had neutropenia, all of which were worst Grade 3 or higher. Twenty-nine subjects (53%) had anemia of any grade, including 27 subjects (49%) with worst Grade 3 or higher anemia.

The number of subjects who had worst Grade 3 or higher thrombocytopenia, neutropenia, or anemia that was present on or after Day 30 following the KTE-X19 infusion on Day 0 were 10 subjects (18%), 14 subjects (25%), and 4 subjects (7%), respectively.

Infections

Within the SOC of infections and infestations, 22 subjects (40%) in Phase 2 had AEs of any grade, and 14 subjects (25%) had AEs that were worst Grade 3 or higher. Four subjects (7%) had Grade 5 infections. The most common PT within this SOC was pneumonia (4 subjects, 7%); all other infections were reported in ≤ 2 subjects each.

Six subjects (11%) had bacterial infections of any grade, including 2 subjects (4%) with worst Grade 3 or higher bacterial infections. No subject had a Grade 5 bacterial infection. All bacterial infections were reported in 1 subject each.

Two subjects (4%) had viral infections, both of which were worst Grade 3. Four subjects (7%) had opportunistic infections, all of which were worst Grade 3 or higher. One subject (2%) had Grade 5 fungal pneumonia.

Fifteen subjects (27%) had unspecified pathogen infections, including 11 subjects (20%) with worst Grade 3 or higher infections. Three subjects (5%) had Grade 5 events (1 subject each with pneumonia, sepsis, and septic shock). The most common infections of any grade in this category were pneumonia (4 subjects, 7%) and bacteremia, sepsis, septic shock, and upper respiratory tract infection (2 subjects each, 4%); the remaining infections were reported in 1 subject each.

Hypogammaglobulinemia

In Phase 2, 4 subjects (7%) had hypogammaglobulinemia, all of which were worst Grade 1 or worst Grade 2 (2 subjects each, 4%).

Important Potential Risks

Secondary malignancies

The clinical database was reviewed for potential secondary malignancies by searching for AEs with MedDRA preferred terms in the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps). No new malignancies attributable to KTE-X19 have been found. Of particular note, prior chemotherapy confounded cases of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) where these have occurred. There is a significant latency between chemotherapy exposure and the appearance of treatment-related MDS or AML.

Immunogenicity

Subjects were tested for serum antibodies reactive to the anti-CD19 CAR.

In Phase 2, based on the initial screening enzyme-linked immunosorbent assay (ELISA), 3 subjects (5%) were antibody-positive at baseline, and 1 subject (2%) was antibody negative at baseline and antibody-positive at Day 28 after the KTE-X19 infusion. Samples from all 4 subjects were further assessed with a confirmatory cell-based flow cytometry assay. Results of the confirmatory assay demonstrated that all 4 subjects were antibody-negative at all time points tested.

In addition, based on the initial screening ELISA, 1 subject had a positive antibody result at Day 24 after retreatment with KTE-X19. Confirmatory results for this subject are not yet available.

Replication- competent Retrovirus

Of the 53 subjects in Phase 2 who had an evaluable sample for replication-competent retrovirus (RCR) testing at any time point, none were positive for RCR.

Tumor lysis syndrome

The clinical database was reviewed for cases of tumor lysis syndrome by using the MedDRA SMQ (narrow) for tumor lysis syndrome.

One subject in Phase 2 had Grade 3 nonserious tumor lysis syndrome, which was assessed as related to KTE-X19. The event started on Day 9 and resolved on Day 36. The tumor lysis syndrome occurred concurrently with evolving Grade 1, 2, and 4 CRS, which started on Day 5 and resolved on Day 28.

Aggravation of Graft-versus-host Disease

One subject (2%) who had undergone allo-SCT prior to enrollment in ZUMA-3 experienced worst Grade 2 GVHD. This subject had nonserious graft-versus-host syndrome that was assessed as related to KTE-X19. The event started as Grade 1 GVHD on Day 39, worsened to Grade 2 on Day 47, and was ongoing as of the data cutoff date.

Safety in the supporting studies

Deaths and SAEs in the supporting studies

Table 44. Deaths and Cause of Death in Supporting Studies ZUMA-2, ZUMA-4, ZUMA-8, and ZUMA-18(Safety Analysis Set)

	Adult MCL ZUMA-2 and ZUMA-18 (N = 103)	Adolescent/pediatric ALL ZUMA-4 (N = 36)	Adult CLL ZUMA-8 (N = 9)
Subjects who died on study[a], n (%)	33 (32)	16 (44)	3 (33)
Deaths that occurred between Day 0 and Day 30	2 (2)	2 (6)	0 (0)
Deaths that occurred between Day 31 and Day 92	5 (5)	1 (3)	1 (11)
Deaths that occurred ≥ Day 93	26 (25)	13 (36)	2 (22)
Primary cause of death			
Adverse event	7 (7)	2 (6)	0 (0)
Progressive disease	22 (21)	13 (36)	3 (33)
Secondary malignancy	1 (1)	0 (0)	0 (0)
Other	3 (3)	1 (3)	0 (0)
Subjects who had initiated new anti-cancer therapy or allogeneic stem cell transplant, n (%)	31 (30)	28 (78)	9 (100)
Subjects who died after the initiation of new anti-cancer therapy, n (%)	18 (17)	11 (31)	3 (33)
Primary cause of death			
Adverse event	0 (0)	1 (3)	0 (0)
Progressive disease	15 (15)	9 (25)	3 (33)
Secondary malignancy	0 (0)	0 (0)	0 (0)
Other	3 (3)	1 (3)	0 (0)

Data cutoff date = 09SEP2020.
Abbreviations: ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma.
a. Deaths occurred on or after the first KTE-X19 infusion through the data cutoff date.
Percentages are based on the number of subjects in the safety analysis set.
Where a cause of death is given as "Other", details can be found in m5.3.5.3, Listings 16.3.5.1, 16.3.5.2, 16.3.5.3, and 16.3.5.4.

In the combined studies ZUMA-2 and ZUMA-18 (adult MCL), 69 subjects (67%) had any SAE. The most common SAEs were pyrexia (18 subjects, 17%), encephalopathy (17 subjects, 17%), and hypotension (14 subjects, 14%). The most common worst Grade 3 or higher SAEs were encephalopathy (16 subjects, 16%), pneumonia (12 subjects, 12%), and hypotension (11 subjects, 11%).

In the combined studies ZUMA-2 and ZUMA-18, 55 subjects (53%) had an SAE related to KTE-X19. The most common SAEs deemed related to KTE-X19 were encephalopathy (17 subjects, 17%), pyrexia (16 subjects, 16%), and hypotension (12 subjects, 12%). The most common worst Grade 3 or higher related SAEs were encephalopathy (16 subjects, 16%), hypotension (10 subjects, 10%), confusional state, and pneumonia (both in 7 subjects, 7%).

In ZUMA-4 (adolescent/pediatric ALL), 26 subjects (72%) had any SAE. The most common SAEs in ZUMA-4 were pyrexia and hypotension (both with 12 subjects, 33%) and encephalopathy, confusional state, and tachycardia (all with 5 subjects, 14%). The most common worst Grade 3 or higher SAE was hypotension (11 subjects, 31%), encephalopathy (3 subjects, 8%), sepsis, and brain oedema (both in 2 subjects, 6%).

In ZUMA-4, 23 subjects (64%) had an SAE related to KTE-X19. The most common SAEs that occurred in ZUMA-4 and were deemed related to KTE-X19 were pyrexia and hypotension (both with 12 subjects,

33%) and encephalopathy, confusional state, and tachycardia (all with 5 subjects, 14%). The most common worst Grade 3 or higher related SAE were hypotension (11 subjects, 31%), encephalopathy (3 subjects, 8%), and brain oedema (2 subjects, 6%).

In ZUMA-8 (adult CLL), 6 subjects (67%) had any SAE. The only common SAE that occurred in more than 1 subject was pyrexia (3 subjects, 33%). No SAE with worst Grade 3 or higher occurred more than 1 subject.

In ZUMA-8 (adult CLL), 4 subjects (44%) had any SAE deemed related to KTE-X19. The only common SAE deemed related to KTE-X19 occurring in more than 1 subject was pyrexia (2 subjects, 22%). No SAE with worst Grade 3 or higher occurred in more than 1 subject.

Important identified risks in the supportive studies

CRS

In the combined studies ZUMA-2 and ZUMA-18 (adult MCL), 92 subjects (89%) had any grade of CRS. Among subjects who had CRS, the most common CRS symptoms of any grade were pyrexia (89 subjects, 97%), hypotension (51 subjects, 55%), and hypoxia (32 subjects, 35%). The most common worst Grade 3 or higher CRS symptoms were hypotension (22 subjects, 24%) and hypoxia (16 subjects, 17%).

Among subjects who had CRS, the median time to onset was 3 days (range: 1 to 13 days) following infusion. All but 1 cases of CRS had resolved as of the data cutoff date, and the median duration of CRS was 8 days (range: 1 to 50 days)

In ZUMA-4 (adolescent/pediatric ALL), 32 subjects (89%) had any grade of CRS. Among subjects who had CRS, the most common CRS symptoms of any grade were pyrexia (27 subjects, 84%) and hypotension (20 subjects, 63%). The most common worst Grade 3 or higher CRS symptoms were hypotension (15 subjects, 47%) and pyrexia (9 subjects, 28%).

Among subjects who had CRS, the median time to onset was 7 days (range: 1 to 14 days). All cases of CRS had resolved as of the data cutoff date, and the median duration of CRS was 7 days (range 1 to 16 days).

In ZUMA-8 (adult CLL), 7 subjects (78%) had any grade of CRS. Among subjects who had CRS, the most common CRS symptom of any grade was pyrexia (7 subjects, 100%). The only worst Grade 3 or higher CRS symptom was pyrexia (1 subject, 14%).

Among subjects who had CRS, the median time to onset was 10 days (range: 2 to 17 days). All cases of CRS had resolved as of the data cutoff date, and the median duration of CRS was 9 days (range: 1 to 19 days).

Table 45. Subject incidence of Treatment emergent CRS AE by Worst Grade in Supporting Studies (Safety Analysis Set)

	Adult MCL ZUMA-2 and ZUMA-18 (N = 103)		Adolescent/pediatric ALL ZUMA-4 (N = 36)		Adult CLL ZUMA-8 (N = 9)	
MedDRA Preferred Term, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any CRS[a], N (%)	92 (89)	13 (13)	32 (89)	12 (33)	7 (78)	0 (0)

Neurologic adverse events including cerebral edema

In the combined studies ZUMA-2 and ZUMA-18 (adult MCL), 70 subjects (68%) had at least 1 neurologic AE of any grade, and 33 subjects (32%) had a worst Grade 3 or higher neurologic AE. Nine subjects (9%) had a neurologic AE of Grade 4 and none had a neurologic AE of Grade 5. The most common neurologic AE of any grade were tremor (35 subjects, 34%), confusional state (29 subjects, 28%), and encephalopathy (28 subjects, 27%). The most common worst Grade 3 or higher neurologic AEs were encephalopathy (17 subjects, 17%), confusional state (12 subjects, 12%), and aphasia (5 subjects, 5%).

Among the 70 subjects who had neurologic AE, the median time to onset was 7 days (range: 1 to 262 days). Twelve subjects had unresolved neurologic AEs either at the data cutoff date or at the time of death.

Among subjects for whom neurologic AEs resolved, the median event duration was 12 days (range: 1 to 567 days, duration was calculated from the end date of the last event minus the onset date of the first event+1). The wide range was a result of a subject who experienced neurologic AEs starting on Study Day 5: Grade 3 serious aphasia and Grade 3 serious encephalopathy from Study Day 5 to 12, Grade 2 cognitive disorder from Study Day 13 to 16, Grade 1 confusional state from Study Day 17 to 58, Grade 3 serious confusional state from Study Day 59 to 72, Grade 1 agitation from Study Day 60 to 70, and memory impairment from Study Day 553 to 571. The last neurologic AE for this subject resolved on Study Day 572, but there were intermittent periods where no neurologic AE was recorded.

A total of 33 subjects (32%) had a serious neurologic AE and 27 subjects (26%) had a worst Grade 3 or higher neurologic AE. The most frequently reported serious neurologic AE as well as the worst Grade 3 or higher serious neurologic AE was encephalopathy (17 subjects, 17% and 16 subjects, 16%, respectively), confusional state (8 subjects, 8% and 7 subjects, 7%), and aphasia (4 subjects, 4% for both categories).

In ZUMA-4 (adolescent/pediatric ALL), 23 subjects (64%) had at least 1 neurologic AE of any grade, and 7 subjects (19%) had a worst Grade 3 or higher neurologic AE. Three subjects (8%) had a neurologic AE of Grade 4 and none had a neurologic AE of Grade 5. The most common neurologic AE of any grade were confusional state (9 subjects, 25%), encephalopathy (5 subjects, 14%), and aphasia, and lethargy (4 subjects, 11%). The only worst Grade 3 or higher neurologic AEs that occurred in more than 1 subject were encephalopathy (3 subjects, 8%) and brain oedema (2 subjects, 6%).

Among the 23 subjects who had neurologic AEs, the median time to onset was 10 days (range: 3 to 60 days). Two subjects had unresolved neurologic AEs (Grade 2 agitation, and Grade 2 dysphasia and encephalopathy) at the time of death.

Among subjects for whom neurologic AEs resolved, the median event duration was 5 days (range: 1 to 88 days).

A total of 13 subjects (36%) had serious neurologic AEs and 7 subjects (19%) had a worst Grade 3 or higher neurologic AE. The most frequently reported serious neurologic AEs were encephalopathy and confusional state (each in 5 subjects, 14%), and seizure (3 subjects, 8%). The only worst Grade 3 or higher neurologic AEs that occurred in more than 1 subject were encephalopathy (3 subjects, 8%) and brain oedema (2 subjects, 6%).

In ZUMA-8 (adult CLL), 7 subjects (78%) had at least 1 neurologic AE of any grade, and 1 subject (11%) had a worst Grade 3 neurologic AE (confusional state). No subject had a neurologic AE of Grade 4 or Grade 5. The most common neurologic AE of any grade were confusional state (3 subjects, 33%) and tremor and cognitive disorder (both in 2 subjects, 22%). Only 1 subject had a worst Grade 3 or higher neurologic AE (one event of confusional state).

Among the 7 subjects who had neurologic AEs, the median time to onset was 14 days (range: 3 to 28 days). One subject had an unresolved neurologic AE (Grade 1 amnesia) at the time of death.

Among subjects for whom neurologic AEs resolved, the median event duration was 12 days (range: 3 to 129 days).

A total of 2 subjects (22%) had serious neurologic AEs (one event each of confusional state and aphasia) and no subject had a worst Grade 3 or higher neurologic AE.

Table 46. Subject incidence of Treatment Emergent Neurologic AEs in Supporting Studies (Safety Analysis Set)

	Adult MCL ZUMA-2 and ZUMA-18 (N = 103)		Adolescent/pediatric ALL ZUMA-4 (N = 36)		Adult CLL ZUMA-8 (N = 9)	
MedDRA Preferred Term, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any neurologic AE	70 (68)	33 (32)	23 (64)	7 (19)	7 (78)	1 (11)

Cytopenias

In the combined studies ZUMA-2 and ZUMA-18 (adult MCL), 97 subjects (94%) had a cytopenia and 95 subjects (92%) had worst Grade 3 or higher cytopenic AEs. A total of 74 subjects (72%) had thrombocytopenia and 52 subjects (50%) had worst Grade 3 or higher thrombocytopenia with 35 subjects (34%) having Grade 4 events and no subject with a Grade 5 event. A total of 89 subjects (86%) had neutropenia and 88 subjects (85%) had worst Grade 3 or higher neutropenia with 73 subjects (71%) having Grade 4 events and no subject with a Grade 5 event. A total of 67 subjects (65%) had anemia of any grade, and 49 subjects (48%) had worst Grade 3 or higher anemia, with no subject having a Grade 4 or Grade 5 event.

A total of 74 subjects (72%) had a prolonged cytopenia and 58 subjects (56%) had worst Grade 3 or higher prolonged AEs in this category, with 41 subjects (40%) having Grade 4 events and no subject with a Grade 5 event.

In ZUMA-4, 28 subjects (75%) had a cytopenia and 27 subjects (75%) had worst Grade 3 or higher cytopenic AEs. A total of 14 subjects (39%) had thrombocytopenia and 13 subjects (36%) had worst Grade 3 or higher thrombocytopenia with 11 subjects (31%) having Grade 4 events and no subject with a Grade 5 event. Similarly, 21 subjects (58%) had neutropenia and 20 subjects (56%) had worst Grade 3 or higher neutropenia, with 16 subjects (44%) having Grade 4 events and no subject with a Grade 5 event. A total of 19 subjects (53%) had anemia of any grade, and 17 subjects (47%) had worst Grade 3 or higher anemia, with no subject having a Grade 4 or Grade 5 event.

A total of 21 subjects (58%) had a prolonged cytopenia and 19 subjects (53%) had worst Grade 3 or higher prolonged cytopenic AEs, with 12 subjects (33%) having Grade 4 events and no subject with a Grade 5 event.

In ZUMA-8 (adult CLL), 8 subjects (89%) had a cytopenia and 8 subjects (89%) had worst Grade 3 or higher cytopenia. A total of 4 subjects (44%) had thrombocytopenia and 3 subjects (33%) had worst Grade 3 or higher thrombocytopenia, with 3 subjects (33%) having Grade 4 events and no subject with a Grade 5 event. Similarly, 8 subjects (89%) had neutropenia and 8 subjects (89%) had worst Grade 3 or higher neutropenia, with 6 subjects (67%) having Grade 4 events and no subject with a Grade 5 event. A total of 4 subjects (44%) had anemia of any grade and 3 subjects (33%) had worst Grade 3 or higher anemia, with no subject having a Grade 4 or Grade 5 event.

A total of 6 subjects (67%) had a prolonged cytopenia and 5 subjects (56%) had worst Grade 3 or higher prolonged cytopenic AEs, with 4 subjects (44%) having Grade 4 events and no subject with a Grade 5 event.

Laboratory findings

The most common increased laboratory values observed in Phase 2 were creatinine (48 subjects, 87%), glucose (47 subjects, 85%), and aspartate aminotransferase (AST) (43 subjects, 78%). The most common worst Grade 3 or higher increased laboratory values were alanine aminotransferase (ALT) (17 subjects, 31%), AST (14 subjects, 25%), and glucose (13 subjects, 24%).

All 55 subjects in Phase 2 had decreases in hemoglobin, leukocytes, and calcium. The other most common decreased laboratory values were platelets (54 subjects, 98%), lymphocytes and neutrophils (53 subjects each, 96%), and albumin and phosphate (52 subjects each, 95%). The most common worst Grade 3 or higher decreased laboratory values were leukocytes (54 subjects, 98%), neutrophils (53 subjects, 96%), and lymphocytes (52 subjects, 95%).

Thirteen subjects met initial laboratory criteria for potential cases of Hy's law (6 subjects in Phase 2). Upon clinical review, however, an alternate explanation for the liver dysfunction was found for all 13 subjects. Thus, no subject was considered to have met criteria for Hy's law.

Safety in special populations

Age Category

The majority of subjects were < 65 years old, which limits the interpretation of these results.

Compared with subjects who were < 65 years old (N = 47), subjects who were ≥ 65 years old (N = 8) showed a numerically higher incidence of worst Grade 3 or higher KTE-X19-related AEs (100% versus 87%), CRS (100% versus 87%), worst Grade 3 or higher CRS (38% versus 21%), neutropenia (75% versus 45%), and hypogammaglobulinemia (25% versus 4%). Subjects who were < 65 years old showed a numerically higher incidence of SAEs (77% versus 63%), worst Grade 3 or higher SAEs (74% versus 63%), serious neurologic AEs (28% versus 13%), thrombocytopenia (51% versus 38%), anemia (55% versus 38%), and infections (40% versus 13%).

Sex

In Phase 2, compared with males (N = 33), females (N = 22) showed a numerically higher incidence of worst Grade 3 or higher KTE-X19-related SAEs (64% vs 52%), thrombocytopenia (59% vs 42%), worst Grade 3 or higher thrombocytopenia (50% vs 39%), anemia (59% vs 48%), and worst Grade 3 or higher anemia (55% vs 45%).

Males showed a numerically higher incidence of KTE-X19-related AEs (100% versus 82%), worst Grade 3 or higher KTE-X19-related AEs (94% versus 82%), CRS (94% versus 82%), serious neurologic AEs (30% versus 18%), worst Grade 3 or higher serious neurologic AEs (27% versus 9%), neutropenia (55% versus 41%), and worst Grade 3 or higher neutropenia (55% versus 41%).

Association of blast percentage in bone marrow with key safety outcomes

A numerically higher incidence of Grade 3 or higher CRS was observed among subjects in the highest interval of blast percentage (> 75% to 100% blasts) at screening (41%; 9 of 22 subjects) or baseline (37%; 7 of 19 subjects), compared with the incidence of 24% in the overall population. However, no

monotonic relationship was observed between the incidence of Grade 3 or higher neurologic AEs and blast percentage at screening or baseline.

Association of extramedullary disease with key safety outcomes

Compared to subjects who did not have extramedullary disease at screening, subjects with extramedullary disease at screening had a numerically higher incidence of Grade 3 or higher CRS (33% [2 of 6 subjects] vs 22% [11 of 49 subjects]) and Grade 3 or higher neurologic AEs (33% [2 of 6 subjects] vs 24% [12 of 49 subjects]). However, due to the small number of subjects with extramedullary disease at screening, these results should be interpreted with caution.

Use in pregnancy and lactation

There is no relevant clinical experience with KTE-X19 in pregnant women, and animal reproductive studies have not been performed. Once infused, CAR T cells may persist long-term, and women who plan a pregnancy should consult their physician. This therapy should not be administered to pregnant women. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Contraception must be used during treatment and for 6 months after receiving lymphodepleting chemotherapy and KTE-X19.

There is no clinical experience with KTE-X19 therapy in lactating women, and animal reproductive studies have not been performed. This therapy should not be administered to women who are breastfeeding.

No pregnancies were reported.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted.

2.5.1. Discussion on clinical safety

The safety database included 55 patients treated with KTE-X19 in the ZUMA-3 trial. For the patients included in this assessment, the median potential follow-up time from the KTE-X19 infusion was 16.4 months (range: 10.3 to 22.1), which is rather short.

Among the treated subjects, 95% had Grade 3 or higher AEs, 75% had SAEs.

49 subjects (89%) had CRS, and 13 subjects (24%) had CRS that was worst Grade 3 or higher. No subject had Grade 5 CRS. Among subjects who had CRS, the median time to onset was 5.0 days (range: 1 to 12 days) after KTE-X19 infusion. As of the data cutoff date, CRS had resolved in 46 of 49 subjects. For the remaining 3 subjects, CRS was ongoing at the time of death due to PD on Day 21 in 1 subject, brain herniation on Day 8 in 1 subject, and pneumonia on Day 15 in 1 subject.

33 subjects (60%) had at least 1 neurologic AE of any grade, including 14 subjects (25%) with worst Grade 3 or higher neurologic AEs. One subject had a Grade 5 neurologic AE of brain herniation. Among subjects who had neurologic AEs, the median time to onset was 9.0 days (range: 2 to 16 days) after KTE-X19 infusion. As of the cutoff date, neurologic AEs had resolved in 29 of 33 subjects.

Important identified risks (CRS, neurologic events, cytopenias, infections, and hypogammaglobulinemia) were largely reversible and manageable with supportive care and medical interventions.

No secondary malignancies were attributed to KTE-X19, no confirmed cases of immunogenicity were identified in Phase 2, and none of the tested subjects were positive for RCR. One subject in Phase 2 had Grade 3 nonserious tumor lysis syndrome assessed as related to KTE-X19. One subject in Phase 2 had Grade 2 nonserious GVHD assessed as related to KTE-X19; the subjects had undergone allo-SCT prior to enrollment in ZUMA-3.

No new safety signals were identified. Essentially, the AEs and risks are similar to what has been described for other CAR T cell therapies and for KTE-X19 in the MCL indication. No further risks and AEs could be identified which would be specific for KTE-X19 or for the indication to be treated with KTE-X19. The toxicity management plans are presented in the SmPC and are in line with the general management plans for this product class.

The relatively high number (8) of patients not treated due to AEs following leukapheresis is surprizing. It could be probably explained by the poor condition of patients and the natural course of the disease.

Upon request, additional safety data have been submitted with data cutoff July 23, 2021 regarding subgroup analysis for the SAS. There is no significant difference in TEAEs among subjects who had received only 1 prior line of therapy versus subjects who had received > 1 prior line of therapy, and the incidence of AEs and SAEs were generally similar (< 10% difference) between the subgroups. Similarly, no major differences were observed when comparing TEAEs for SCT-naïve subjects and subjects who had received a prior allo-SCT, when comparing age categories, or when comparing patients who received blinatumomab or inotuzumab versus their corresponding naïve subjects.

Additional safety data needed in the context of a conditional MA

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2).

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry, according to an agreed protocol.

These post authorisation studies should provide longer term data as well as further efficacy and safety information on important subgroups (age groups from 18 to 25 years of age and older than 60 years, status MRD+ and PH-, patients that have relapsed following allo-SCT), which are not fully represented in the pivotal study submitted for this procedure. The provision of this data post authorisation will complement the dossier in order to have a comprehensive understanding of efficacy and safety and to confirm the positive benefit risk balance of the product in the new indication.

2.5.2. Conclusions on clinical safety

The important identified risks for KTE-X19 in this indication are CRS, neurotoxicity, cytopenias, infections, hypogammaglobulinemia. There are some potential risks linked to the use of this product: secondary malignancy, immunogenicity, RCR, tumor lysis syndrome, and aggravation of GvHD.

No new safety signals were identified. Essentially, the AEs and risks are similar to what has been described for other CAR T cell therapies and for KTE-X19 in the MCL indication. No further risks and AEs could be identified which would be specific for KTE-X19 or for the indication to be treated with KTE-X19.

The following measures are considered necessary to address issues related to safety:

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the

MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2).

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry, according to an agreed protocol.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CAT received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.3 is acceptable.

The CAT endorsed this advice without changes.

Safety concerns

Important Identified Risks	Serious neurologic events, including cerebral edema
	CRS
	Cytopenias
	Infections
	Hypogammaglobulinemia
Important Potential Risks	Secondary malignancy
	Immunogenicity
	RCR
	TLS
	Aggravation of GvHD
Missing Information	New occurrence or exacerbation of an autoimmune disorder
	Long-term safety

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
KT-EU-472-5966 Tecartus Survey: Quantitative Testing of HCP Knowledge About Tecartus® Risk Minimization Measures Planned	Assess the prescribers' understanding of the risks of KTE-X19. Evaluate the effectiveness of risk minimization activities: HCP educational materials, and Patient Alert Card.	Serious neurologic events including cerebral edema CRS	Protocol submission	Protocol was submitted on 22 Apr 2021
			Final study report	Q3 2023
KTE-C19-108 (ZUMA-8) Phase 1 multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with relapsed/refractory CLL and SLL Ongoing	To evaluate the safety and tolerability of KTE-X19 in adult subjects with relapsed/refractory CLL and SLL	Serious neurologic events including cerebral edema CRS Cytopenias Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD New occurrence or exacerbation of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary	Annual
			Final study report	Dec 2036

In addition, the following studies imposed primarily for efficacy reasons will provide safety results relevant to the safety profile of the product:

Study/ Status	Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
KT-EU-472-6036 Long-term, non-interventional Study of recipients of Tecartus for treatment of adult patients in all indications	A prospective study to confirm the long-term efficacy and safety of Tecartus in adult patients with all indications and the Benefit/Risk in important subgroups: elderly, females, patients with severe disease	Overall response rate. Complete remission rate. Duration of response.	Protocol submission	Protocol submitted on 08 Mar 2021
			Annual report	TBD

Study/ Status	Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Planned		Time to relapse or progression. Effectiveness by gender and age. Effectiveness in special populations.	Final study report	MCL: Q2 2042 ALL: Q4 2042
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
KTE-C19-103 (ZUMA-3) Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with relapsed/refractory B-ALL) Ongoing	Primary objective of Phase 1: To evaluate the safety of KTE-C19. Primary objective of Phase 2: To evaluate the efficacy of KTE-C19, as measured by the overall complete remission rate defined as complete remission and complete remission with incomplete hematologic recovery in adult subjects with relapsed/refractory ALL. Secondary objectives: Assessing the safety and tolerability of KTE-X19, additional efficacy endpoints, and change in EQ-5D scores.		Specific obligation due date	31 Oct 2024*
			Final study report	Sep 2036
KTE-C19-102 (ZUMA-2) Completed	To confirm long term efficacy and safety in subjects treated with KTE-X19 in Cohort 1	Long term efficacy	Final study report	Q1 2022
Specific obligation for ALL Planned	Long-term efficacy and safety of Tecartus in adult patients with relapsed/refractory ALL.	Long term efficacy	Protocol submission	3 months following commission decision for the Extension of Indication in r/r ALL
			Final study report	31 December 2027

*5-year follow-up interim results

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Serious neurologic events including cerebral edema	**Routine risk minimization measures**: SmPC sections: 4.2, 4.4, 4.7, 4.8 PL section: 2, 4 Recommendations for monitoring and management of serious neurologic events, including treatment algorithms, are included in the SmPC sections 4.2, 4.4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: ▪ HCP educational material ▪ PAC ▪ Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire **Additional pharmacovigilance activities**: KT-EU-472-5966: Q3 2023 ZUMA-8: Dec 2036
CRS	**Routine risk minimization measures**: SmPC sections: 4.2, 4.4, 4.8 PL section: 2, 4 Recommendations for monitoring and management of CRS, including treatment algorithms, are included in the SmPC sections 4.2, 4.4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures**: ▪ HCP educational material ▪ PAC ▪ Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire **Additional pharmacovigilance activities**: KT-EU-472-5966: Q3 2023 ZUMA-8: Dec 2036
Cytopenias	**Routine risk minimization measures**: SmPC sections: 4.4, 4.8 PL section: 2, 4 Recommendation for blood count monitoring will be included in SmPC section 4.4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
Infections	**Routine risk minimization measures**: SmPC sections: 4.4, 4.8 PL section: 2, 4 Recommendation for monitoring the signs and symptoms of infection before, during	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	and after KTE-X19 infusion are included in SmPC section 4.4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
Hypogammaglobulinemia	**Routine risk minimization measures**: SmPC sections: 4.4, 4.8 PL section: 4 Recommendations for monitoring immunoglobulin levels and management using infection precautions, antibiotic prophylaxis and immunoglobulin replacement are included in SmPC section 4.4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
Important potential risk(s)		
Secondary malignancy	**Routine risk minimization measures**: SmPC section: 4.4 Recommendation for life-long monitoring for secondary malignancies is included in SmPC section 4.4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: Guide to handling, method of administration and sampling recommendations for secondary malignancies	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event Follow-up Questionnaire **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
Immunogenicity	**Routine risk minimization measures**: SmPC section: 4.8 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
RCR	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		ZUMA-8: Dec 2036
TLS	**Routine risk minimization measures**: SmPC section: 4.4 PL section: 2 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
Aggravation of GvHD	**Routine risk minimization measures**: SmPC section: 4.4 PL section: 2 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
Missing information		
New occurrence or exacerbation of an autoimmune disorder	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036
Long-term safety	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-8: Dec 2036

2.7. Update of the Product information

As a consequence of this new indication, sections 2.2, 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Annex II was updated to reflect the SOBs for the new indication. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Package leaflet has been updated with the proposed extension of an additional indication. As this does not lead to principle/significant changes relevant for user testing the MAH refers to the user testing in the context of the initial MAA.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applied indication is: Treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

3.1.2. Available therapies and unmet medical need

Patients in their second or later relapse may receive therapies typically utilized in the second line, such as allo- or auto-Stem Cell Transplantation (SCT). However, few patients in this setting are eligible for SCT. Novel therapies approved for the second line, such as blinatumomab or inotuzumab-ozogamicin, may also be utilized in the third line if not previously used, although outcomes with these treatments are typically not as favourable in patients being treated in the third line and beyond. Subjects receiving blinatumomab as a third or later line of therapy for B-ALL had a median OS of 5.1 months compared with 11.1 months for those receiving blinatumomab as their second line {Dombret 2019}. The combined CR/CRi/CRh rate was also lower for subjects receiving blinatumomab as a third or later line compared with those receiving blinatumomab as the second line (39.5% vs 51.0%, respectively). In the INO-VATE study, the CR/CRi rate was 77.8% for subjects receiving inotuzumab as the second line and 66.1% for those receiving inotuzumab as the third line {Kantarjian 2019}. Another study found that subjects who received inotuzumab combined with low-intensity chemotherapy as the third line or as a fourth or later line had 1-year OS rates of 26% and 39%, respectively, compared with a 57% 1-year OS rate in subjects receiving this combination as the second line {Jabbour 2018b}. Because of these poor outcomes with third-line and higher therapies, the National Comprehensive Cancer Network and European Society for Medical Oncology recommend that patients seeking treatment for r/r B-ALL participate in clinical trials {Hoelzer 2016, National Comprehensive Cancer Network 2020}.

Recently, Kymriah (tisagenlecleucel) was approved in the treatment of B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse in paediatrics and young adults up to and including 25 years of age.

3.1.3. Main clinical studies

Study KTE-C19-103 (ZUMA-3), a phase 1/2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in adult subjects with r/r B-ALL.

3.2. Favourable effects

Per DCO 09 September 2020, the median OCR (CR + CRi) rate per central assessment was 70.9% (n=39) for all treated patients followed for a median of 12.4 months. The CR rate was 56% (n=31), and the MRD- rate (assessed by central laboratory) was 76%. Among the 39 subjects who achieved CR

or CRi, the KM median DOR was 12.8 months. KM estimates of OS at Month 12 and Month 18 were 71.4% (95% CI: 57.0%, 81.7%) and 56.6% (95% CI: 41.8%, 72.1%), respectively. None of the additional sixteen subjects included in the full analysis set (FAS, n=71) had achieved CR or CRi at DCO, therefore, results of DOR in FAS and mITT were identical.

3.3. Uncertainties and limitations about favourable effects

Data are derived from a small trial without a concurrent randomised control. As with any other trials of this size in heterogeneous populations uncertainties are therefore related to the "true" estimate for efficacy and external validity. Most of the analyses are presented for the mITT population, i.e. the population that actually received study drug. This selection clearly biases the determined efficacy estimate.

From a methodological point of view the typical sequence of exploration and confirmation is difficult to distinguish with certainty.

The subgroup analyses for baseline population and disease characteristics generally give a fairly consistent picture. However, the small heterogeneous population and the multitudes of univariate analyses performed cannot exclude the possibility that subgroups are hidden that may not have the intended favourable effects. From subgroup analyses there is some indication that baseline characteristics related to higher disease burden are associated with a lower treatment response. Prior treatment with blinatumomab or inotuzumab ozogamicin is also associated with a lower response to the experimental treatment.

3.4. Unfavourable effects

The unfavourable effects for patients treated with KTE-X19 do not only occur as a consequence of KTE-X19 treatment, but the bridging therapy and conditioning chemotherapy may also induce such effects. Nonetheless, a list of unfavourable effects has crystallized which are expected and regarded as class effects for CAR-T cell based therapies.

Important identified unfavourable effects (CRS, neurologic events, cytopenias, infections, and hypogammaglobulinemia) were largely reversible and manageable with supportive care and medical interventions.

3.5. Uncertainties and limitations about unfavourable effects

The primary safety database included 55 patients treated with KTE-X19 in the ZUMA-3 trial, which is a rather low number. For the patients included in this assessment, the median potential follow-up time from the KTE-X19 infusion was 16.4 months (range: 10.3 to 22.1). While this period would be enough to identify the earlier and immediate AEs, there are certain potential risks for which conclusive data could not be obtained due to the limited follow-up time. Therefore, aspects regarding secondary malignancies, replication competent retrovirus analysis need to be appropriately assessed in the follow-up study.

3.6. Effects Table

Table 47: Effects Table for KTE-X19 (data cut-off efficacy: 23 July 2021, data cutoff safety: 09 September 2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OCR (per central assessment)	Primary EP, mITT Defined as CR or Cri (classification; *Table 5, clinical efficacy report*)	rate (%)	73.1 95% CI 62, 82	N.A.	Clear support by MRD data Small single arm trial Weaker evidence of OCR in patients with high blast percentage No high methodological standard	Response to RfSI
Unfavourable Effects						
Death/fatal AE	Death any time post-infusion	% (n/n)	35.08 (20/57)	N/A	13 deceased due to PD, 1 due to AE related to KTE-X19, 1 due to AE related to LD and KTE-X19, 5 deaths unrelated	
Cytokine Release Syndrome (CRS)	≥ Grade 3	% (n/n)	22.8 (13/57)	N/A	Strong evidence for relationship to the treatment with KTE-X19	
CART-related encephalopathy syndrome (CRES)	≥ Grade 3	% (n/n)	24.56 (14/57)	N/A	Strong evidence for relationship to the treatment with KTE-X19. One subject had Grade 5 AE of brain herniation.	
Infections	≥ Grade 3	% (n/n)	24.56 (14/57)	N/A	Possibly related to conditioning chemotherapy	

Abbreviations: N/A= not available

Notes: data in the unfavourable effects table part include all patients receiving conditioning chemotherapy (57). Of these patients, 55 received KTE-X19.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The final benefit-risk evaluation considers the initial clinical data set (n=55 subjects in the phase 2 portion of the ZUMA-3 study) and additional n=23 subjects from the phase 1 portion of the ZUMA-3 study, centrally assessed and treated with the pivotal dose.

Ultimately the benefit of a therapy in oncology is an improved survival. However, choosing OS as an endpoint requires a reliable comparison, preferably via a randomised control. For a number of reasons randomised controls are often not available in the later line setting in haemato-oncology generally and in the ATMP field specifically. Objective responses to therapy are accepted endpoints because they allow to estimate a favourable effect that is causally related to the therapy in a single arm trial. Consequently the demonstration of a high response rate (as determined by CR) to treatment with KTE-X19 that is also associated with the disappearance of measurable disease is regarded as highly relevant. This is particularly true for a population that has received multiple previous therapies. Even when taking into account the uncertainties as regards the selection of the population and the concerns on methodology and analyses of data the obtained response rates achieved are regarded as relevant on their own. The applicant has attempted to put the achieved results into context but further analyses of these datasets are necessary to come to a conclusion. Achieving CR is usually regarded as a prerequisite for additional therapeutic interventions but the follow-up is currently too short to determine the exact role of KTE-X19 in the overall treatment paradigm. It is noted that some patients went on to SCT as a potentially curative option, that the favourable effects appear lesser in a population with worse prognostic baseline characteristics and that the trial population was quite heterogeneous. As a second component to describe the favourable effects the duration of response is important to complement the results achieved for duration of response. The observed duration of response is in this case particularly remarkable, especially for individuals that achieved a complete response.

The most important unfavourable effects of KTE-X19 as a CAR T cell product in general are CRS, neurotoxicity, cytopenias, infections and hypogammaglobulinaemia. Generally these unfavourable effects are either treatable or have a self-limiting course and are reversible. The potential serious consequences of CRS have been recognised and treatment algorithms have been developed that are still being refined according to further experience. Overall considering the life-threatening disease the safety profile of KTE-X19 seems to be acceptable for the target population. Since the unfavourable effects are in line with the experience made with this drug class, the identified uncertainties and limitations are of limited relevance. No new safety signals were identified.

3.7.2. Balance of benefits and risks

Despite the described uncertainties on the favourable clinical effects, they appear to outweigh the identified unfavourable effects and limitations of the ZUMA-3 trial as a single arm trial with a small number of subjects treated. The benefit is regarded as sufficiently robust to conclude on a favourable B/R in the overall population in the context of a CMA.

The benefit risk balance of Tecartus in the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL), is positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

Tecartus was initially, and currently is, approved by a conditional marketing authorisation (CMA). As the underlying data supporting this new indication is regarded as not comprehensive and as it aims at the treatment of a life-threatening disease and is designated as an orphan condition, and in view of the foregoing, the legal requirements also apply for this extension of indication which falls within the scope of Article 14-a of Regulation (EC) No 726/2004.

The CAT considers that the new indication also fulfils the requirements under a conditional marketing authorisation framework:

- The benefit-risk balance is positive, as discussed above.
- It is likely that the applicant will be able to provide comprehensive data:

  - Long-term follow-up data from ZUMA-3: In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory ALL, the MAH will submit follow-up data from all treated patients with the pivotal dose in the ZUMA-3 trial Part 1 and Part 2.

  - A registry-based study: In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory ALL, the MAH will submit the results of a prospective, observational study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.

  These post authorisation studies will provide longer term data as well as further efficacy and safety information on important subgroups (age groups from 18 to 25 years of age and older than 60 years, status MRD+ and PH-, patients that have relapsed following allo-SCT , which are not fully represented in the pivotal study submitted for this procedure. The provision of this data post authorisation will complement the dossier in order to have a comprehensive understanding of efficacy and safety and to confirm the positive benefit risk balance of the product in the new indication.
- An unmet medical need will be addressed. With each subsequent relapse, the prognosis of adult patients with B-cell precursor ALL gets worse and there is a clear unmet medical need in this disease. Several medicinal products have been authorised in B-cell precursor ALL, most notably, blinatumumab and inotuzumab ozogamicin. When compared to blinatumomab and inotuzumab ozogamicin, the efficacy results in the ZUMA-3 trial indicate improved efficacy of Tecartus therefore offering a major therapeutic advantage over these two existing therapies. In addition, Kymriah (tisagenlecleucel) was approved in the treatment of B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse in paediatrics and young adults up to and including 25 years of age. Tecartus therefore addresses an unmet medical need via-a-vis Kymriah in the adult patient population aged 26 years and above

  In summary, Tecartus provides a treatment option for which a clinically meaningful benefit was demonstrated with respect to complete response, overall response rate and duration of response. Thus, the availability of Tecartus represents a major therapeutic advantage vis-à-vis existing treatments for adult patients 26 years of age and above.

- The benefits to public health of the immediate availability outweigh the risks inherent to the fact that additional data are still required. As benefit-risk balance on basis of the current data is regarded positive and in view of the medical need in the target population, an additional therapy option for for adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL) is considered beneficial.

In addition, the CAT considers the following measures necessary to ensure the follow up of safety and efficacy:

In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2).

In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory B-cell precursor ALL the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.

3.8. Conclusions

The overall B/R of Tecartus for the treatment of treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL), is positive subject to the specific obligations and conditions imposed in order to obtain further clinical data to generate a comprehensive clinical data set and inform the long-term efficacy and safety profile of the product in this new indication.

4. Recommendations

Outcome

Based on the review of the submitted data, the CAT considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.d.1.z	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	Type IB	I, II, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Group of variations including and extension of indication to include treatment of adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL) for Tecartus and a type IB variation to change the Drug Product Dose specification for the new indication. As a consequence, sections 2.2, 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II is updated to reflect the new Specific Obligations for the new indication. The Package Leaflet and Labelling are updated in accordance. Version 1.1 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following updated conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory (r/r) mantle cell Lymphoma (MCL) and adult patients with r/r acute lymphoblastic leukaemia (ALL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	MCL: 30 June 2042 ALL: 31 December 2042

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.	30 September 2025
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2).	31 October 2024
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry,according to an agreed protocol.	31 December 2027

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Tecartus is not similar to Kymriah, Besponsa, Iclusig and Blyncito within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Additional market protection

Furthermore, the CAT reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the

EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Product Name-H-C-Product Number-II-Var.No’