SUPPLEMENTARY APPENDIX

List of Investigators and Study Sites

Site	Lead Investigator	No. Patients Enrolled/Treated
Moffitt Cancer Center, Tampa, FL, USA	Bijal Shah	10/7
Hôpital Pontchaillou – CHU de Rennes, Rennes, France	Roch Houot	6/5
Vanderbilt University, Henry-Joyce Cancer Clinic, Nashville, TN, USA	Olalekan Oluwole	5/4
Washington University School of Medicine, Center for Advanced Medicine, St. Louis, MO, USA	Armin Ghobadi	5/4
University of California San Francisco, San Francisco, CA, USA	Aaron Logan	4/4
Hôpital Saint-Louis, Paris, France	Nicolas Boissel	4/3
University of Rochester, Rochester, NY, USA	Kristen O'Dwyer	2/2
UC San Diego Moores Cancer Center, La Jolla, CA, USA	Dimitrios Tzachanis	2/2
Mayo Clinic, Rochester, MN, USA	Yi Lin	2/2
UCLA Ronald Reagan Medical Center, Los Angeles, CA, USA	Gary Schiller	2/2
Emory University Hospital, Atlanta, GA, USA	Martha Arellano	4/2
University of Chicago, Chicago, IL, USA	Michael Bishop	2/2
University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA	Maria Baer	2/2
University of Washington Medical Center, Seattle, WA, USA	Ryan Cassaday	2/2
Hôpital Haut-Lévéque, Pessac, France	Edouard Forcade	2/2
Universitätsklinikum Würzburg Medizinische Klinik und Poliklinik, Würzburg, Germany	Max Topp	2/2
MD Anderson Cancer Center, Houston, TX, USA	William Wierda	1/1
Loyola University Medical Center, Maywood, IL, USA	Patrick Stiff	1/1
Dana Farber Cancer Institute, Boston, MA, USA	Daniel DeAngelo	1/1
UC Irvine Medical Center, Orange, CA, USA	Deepa Jeyakumar	1/1

University of California Davis, Sacramento, CA, USA	Mehrdad Abedi	2/1
Memorial Sloan Kettering Cancer Center, New York, NY, USA	Jae Park	4/1
Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands	Monique Minnema	1/1
Klinikum der Universität München Medizinische Klinik II, Munich, Germany	Marion Subklewe	3/1
Princess Margaret Cancer Center, Toronto, Canada	Andre Schuh	1/0

Supplementary Methods

Eligibility Criteria[1]

Additional inclusion criteria:

- Patients with Philadelphia chromosome (Ph)+ disease were eligible if they had disease intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they had relapsed/refractory disease despite treatment with ≥2 different TKIs
- Absolute neutrophil count ≥500/μL unless in the opinion of the investigator cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy
- Platelet count ≥50,000/μL unless in the opinion of the investigator cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy
- Absolute lymphocyte count ≥100/μL
- Adequate renal, hepatic, pulmonary, and cardiac function were defined as
    - Creatinine clearance (as estimated by Cockcroft Gault) ≥60 cc/min
    - Serum alanine aminotransferase/aspartate aminotransferase ≤2.5 × upper limit of normal
    - Total bilirubin ≤1.5 mg/dL, except in patients with Gilbert's syndrome
    - Left ventricular ejection fraction ≥50%, no evidence of pericardial effusion as determined by an echocardiogram, no New York Heart Association class III or class IV functional classification, and no clinically significant arrhythmias
    - No clinically significant pleural effusion
    - Baseline oxygen saturation >92% on room air
- Females of childbearing potential must have had a negative serum or urine pregnancy test
- Patients with central nervous system (CNS)-2 disease (cerebrospinal fluid [CSF] blast cells with <5 white blood cells/mm^3) without neurological changes were eligible
- In patients 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.

Additional exclusion criteria:

- Diagnosis of Burkitt's leukemia/lymphoma according to World Health Organization classification or chronic myelogenous leukemia lymphoid blast crisis
- History of malignancy other than non-melanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease-free for ≥3 years
- History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study
- CNS abnormalities
    - Presence of CNS-3 disease defined as detectable cerebrospinal blast cells in a sample of CSF with ≥5 white blood cells (WBCs) per mm^3 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 mm^3 with neurological changes. Note: Patients with CNS-1 (no detectable leukemia in the

CSF) and those with CNS-2 without clinically evident neurological changes are eligible to participate in the study
    - History or presence of any CNS disorder, such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome, or cerebral edema
- History of concomitant genetic syndrome associated with bone marrow failure
- History of clinically significant cardiac disease within 12 months of enrollment
- History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment
- Primary immunodeficiency
- Known infection with HIV, hepatitis B, or hepatitis C virus. A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative polymerase chain reaction and/or nucleic acid testing
- Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite Medical Monitor
- Acute graft-vs-host disease (GVHD) grade II-IV by Glucksberg criteria or severity B-D by International Bone Marrow Transplant Registry index; acute or chronic GVHD requiring systemic treatment within 4 weeks prior to enrollment
- Prior medication:
    - Salvage systemic therapy (including chemotherapy, TKIs for Ph+ disease, and blinatumomab) ≤1 week or 5 half-lives (whichever is shorter) prior to enrollment
    - Prior CD19-directed therapy other than blinatumomab
    - History of Common Terminology Criteria for Adverse Events grade 4 neurologic event or grade 4 cytokine release syndrome with prior CD19-directed therapy
    - Treatment with alemtuzumab ≤6 months prior to enrollment, clofarabine or cladribine ≤3 months prior to enrollment, or PEG-asparaginase ≤3 weeks prior to enrollment
    - Donor lymphocyte infusion ≤4 weeks prior to enrollment
    - Treatment with any drug for GVHD and any immunosuppressive antibody ≤4 weeks prior to enrollment
    - At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecular therapy prior to enrollment
    - Corticosteroid therapy at a pharmacologic dose (>5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 1 week prior to enrollment
- Presence of any indwelling line or drain. Ommaya reservoirs and dedicated central venous access catheters are permitted
- Live vaccine ≤4 weeks prior to enrollment
- Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant

- Patients of both genders of childbearing potential who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-X19
- Patients who, in the investigator's judgment, are unlikely to complete all protocol-required study visits or procedures or comply with the study requirements for participation
- History of autoimmune disease resulting in end organ injury or requiring systemic immunosuppression or systemic disease modifying agents within the last 2 years

Study Design

The study was designed in a collaboration between the study sponsor (Kite, a Gilead Company) and the authors. The institutional review board at each site approved the protocol. All authors contributed to the conduct of the study, analysis and interpretation of data, and writing of the manuscript, with medical writing support funded by the study sponsor.

Bridging Chemotherapy

After leukapheresis and before conditioning chemotherapy, bridging chemotherapy was allowed at the discretion of the treating physician, and was recommended particularly for patients with high disease burden at baseline (>25% leukemic blasts in BM or ≥1000 blasts/mm^3 in peripheral circulation by local review). After bridging chemotherapy, a BM aspirate was required by day −4. Allowed bridging chemotherapy regimens are shown below.

Bridging Chemotherapy Regimens	
Attenuated VAD	Vincristine non-liposomal (1-2 mg IV weekly) or liposomal (2·25 mg/m^2 IV weekly), and dexamethasone 20-40 mg IV or PO daily x 3-4 days per week. Optional doxorubicin 50 mg/m^2 IV x 1 (first week only)
Mercaptopurine (6-MP)	50-75 mg/m^2/day by mouth (administer at bedtime on an empty stomach to improve absorption)
Hydroxyurea	Doses titrated between 15-50 mg/kg/day (rounded to the nearest 500 mg capsule and given as a single daily oral dose on a continuous basis)
DOMP	Dexamethasone 6 mg/m^2/day PO (or IV) divided BID days 1-5, vincristine 1·5 mg/m^2 (maximum dose 2 mg) IV on day 1, methotrexate 20 mg/m^2 PO weekly, 6-MP 50-75 mg/m^2/day PO daily
Attenuated FLAG/FLAG-IDA	Fludarabine 30 mg/m^2 IV days 1-2, cytarabine 2 g/m^2 IV days 1-2, G-CSF 5 µg/kg SC or IV starts on day 3 and can continue until day before the start of conditioning chemotherapy. With or without idarubicin 6 mg/m^2 IV days 1-2
Mini-hyper CVAD (courses A and/or B)	Course A: Cyclophosphamide 150 mg/m^2 every 12 h x 3 days, dexamethasone 20 mg/d IV or PO daily days 1-4 and 11-14, vincristine 2 mg IV x 1

	Course B: methotrexate 250 mg/m^2 IV over 24 hours on day 1, cytarabine 0·5 g/m^2 IV every 12 hours x 4 doses on days 2 and 3

Use of a TKI in combination with any of the above regimens was allowed for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia and Philadelphia chromosome-like acute lymphoblastic leukemia.

BID, twice daily; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; DOMP, dexamethasone, 6-mercaptopurine, methotrexate, and vincristine; FLAG, fludarabine, high-dose cytarabine, and G-CSF; G-CSF, granulocyte-colony stimulating factor; IDA, idarubicin; IV, intravenous; MP, 6-mercaptopurine; PO, oral; SC, subcutaneous; TKI, tyrosine kinase inhibitor; VAD, vincristine, doxorubicin, and dexamethasone.

Toxicity Management

CRS and neurotoxicity management guidelines were previously published in the Phase 1 portion of this trial.[1] Briefly, tocilizumab was administered for patients beginning with Grade 2 CRS or Grade 2 neurologic events with concurrent CRS; corticosteroids were recommended for patients beginning with Grade 2 neurologic events without concurrent CRS or for patients with concurrent CRS after 24 hours

Disease Assessments

Overall disease response was classified as shown below.

Response	**BM**		**Peripheral Blood***		**CNS EMD**		**Non-CNS EMD†**
CR	≤5%‡	*and*	ANC ≥1000 and Plt ≥100,000	*and*	CNS-1	*and*	CR§
CRi			ANC ≥1000 and Plt <100,000 OR ANC <1000 and Plt ≥100,000				
CRh			ANC ≥500 and Plt ≥50,000 but not CR				
Blast-free hypoplastic or aplastic BM			Any values not meeting criteria for CR, CRi, or CRh				
PR	All criteria for CR, CRi, CRh, or blast-free hypoplastic or aplastic bone marrow are met					*and*	PR
Relapse	>5%‡	*or*	Circulating leukemia present¶	*or*	CNS-2 or CNS-3	*or*	PD
No response	All required assessments are performed with failure to attain the criteria needed for any response category						
Unknown	Assessment is not done, incomplete, or indeterminate Note: Overall disease response can be assessed as 'relapsed disease' if any single element of disease response assessment shows relapse; other unknown elements of disease response assessment do not need to be evaluated						

*The units for Plt and ANC are per µL. ANC and Plt values should be evaluated every time a BM evaluation is performed. If not done, ANC and Plt values used for response assessment can be from any time 7 days prior to the

BM result to any time after the BM result.

†See next table below for disease assessment in patients with known baseline EMD. In patients evaluated for non-CNS EMD, imaging and BM results used for assessment of overall disease response must be within 30 days of each other.

‡Blasts by morphology in BM.

§If baseline EMD is present, then images must show CR. If no baseline EMD, then images are not required, but if performed, must show CR per next table below.

¶No circulating leukemia is <1% circulating blasts by morphology. Circulating leukemia is ≥1% circulating blasts by morphology. If ≥1% blast by morphology and there is no other evidence of leukemia, then flow or molecular studies should be conducted to confirm that blasts are leukemia.

ANC, absolute neutrophil count; BM, bone marrow; CNS, central nervous system; CR, complete remission; CRh, complete remission response with partial hematologic recovery; CRi, complete remission response with incomplete hematologic recovery; EMD, extramedullary disease; PD, progressive disease; Plt, platelets; PR, partial response.

As previously reported, for patients with extramedullary disease at baseline, response was assessed according to the response criteria for extramedullary and central nervous system (CNS) disease in the revised International Working Group Criteria for malignant lymphoma.[1,2]

Response was assessed by the investigator per the table below at baseline and post-baseline with an imaging modality appropriate for the anatomical site and clinical scenario (eg, magnetic resonance imaging for central nervous system lesion, ultrasound for testicular lesion, computed tomography for intra-abdominal or thoracic lesion) and with the same imaging modality throughout.

Response*	**PET Baseline, On-study**		**Baseline Lesion(s) by CT or MRI**		**New Lesion(s)**
CR	Neg, N/A	*and*	All of: • Disappearance of measurable and non-measurable nodal lesions: o Nodal masses >1·5 cm in GTD at baseline must have regressed to ≤1·5 cm in GTD o Nodes that were 1·1 to 1·5 cm in their long axis and more than 1·0 cm in their short axis before treatment must have decreased to 1·0 cm in their short axis after treatment • If testes, spleen, and/or liver involvement, they must be normal size by imaging or physical examination	*and*	No
	Pos, Neg	*and*	Any	*and*	No
PR	Any	*and*	All of: • ≥50% decrease in SPD of up to 6 of the largest dominant masses. Dominant masses should be clearly measurable in at least 2 perpendicular dimensions, and	*and*	No

			should be from different regions of the body if possible • No increase in size of liver or spleen by imaging or physical exam • If multiple splenic and hepatic nodules are present, they must regress by ≥50% in SPD. There must be a >50% decrease in GTD for a single nodule		
SD	Does not meet the criteria for CR, PR, or PD				
PD	Any	*and*	At least one of the following: • ≥50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node • At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis • ≥50% increase in size of splenic, hepatic or any other non-nodal lesion	*or*	Yes

*Modified revised International Working Group criteria.[2]

CR, complete remission; CT, computed tomography; GTD, greatest transverse diameter; MRI, magnetic resonance imaging; N/A, not applicable; Neg, Negative; PD, progressive disease; Pos, Positive; PR, partial response; SD, stable disease; SPD, sum of the product of the diameters.

Biomarker Analyses

Analysis of pharmacokinetics and pharmacodynamic markers for KTE-X19 were conducted on pre-infusion product, blood and serum samples. Products were evaluated for IFN-γ in co-culture and phenotypes, including CAR expression by flow cytometry. The presence, expansion, and persistence of gene-marked CD19 CAR+ T cells in blood were assessed using droplet digital polymerase chain reaction as previously described.[1,3,4] Cytokines, chemokines, immune effector molecules, and markers of macrophage-activating syndrome in serum, and their associations with clinical outcomes, were assessed as previously reported.[1,3]

Detection of minimal residual disease (MRD) in ZUMA-3 was performed in a CAP/CLIA certified central laboratory (NeoGenomics USA and EU) using a validated test method based on the Children's Oncology Group (COG) B-ALL MRD multiparametric flow cytometry assay.[5] The B-ALL MRD flow cytometry assay contained the following markers and was designed to identify and enumerate CD19+ B-ALL blasts in fresh bone marrow: CD3, CD9, CD10, CD13, CD19, CD20, CD33, CD34, CD38, CD45, CD58, CD71. The assay was suitable for detection of malignant B-ALL blasts at 10^{-4} sensitivity at both testing sites. This assay was also used to determine CD19 expression at baseline, or day −4 in patients who received bridging chemotherapy. CD19 expression at relapse was assessed locally by the investigators using tumor samples.

The presence and percentage of CD19+, CD20+, or CD19+CD20+ B cells in cryopreserved peripheral blood mononuclear cells were evaluated by a flow cytometry assay (Primity Bio, a Caprion Company; Fremont, CA, USA).

Reactivity against KTE-X19 was tested via an ELISA-based screening assay, followed by a cell-based flow cytometry confirmatory assay for samples that tested positive in the screening assay.

Hospitalization for KTE-X19 Infusion

Patients were hospitalized to receive infusion of KTE-X19 followed by a minimum 7-day observation period. Patients remained in the hospital through day 7 after infusion of KTE-X19. For German patients, the post-infusion monitoring of patients was extended by monitoring on Days 8, 9, and 10; these patients could stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

Patient-Reported Outcome Analyses

For all treated patients in phase 2 (safety analysis set), patient-reported outcome data were collected and descriptively summarized using the 5-level version of the European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaire at screening, day 0, day 28, month 3, and every 3 months during the long-term follow-up. The EQ-5D questionnaire is a 2-part self-reported instrument. In the first part, 5 domains were evaluated: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain was divided into 5 levels of severity: “No problem”, “Slight problems”, “Moderate problems”, “Severe problems”, and “Extreme problems”. In the second part, patients were shown a 20-cm visual analogue scale (VAS) and asked to make a global assessment of their current state of health (on the day that the questionnaire was administered), with 0 indicating the worst and 100 indicating the best perceived health. An absolute value of 7 was used to identify meaningful change (stable, improved, deteriorated) over time in VAS as frequently used in previous research.[6]

Statistical Analysis

Wilcoxon rank sum test was used for 2-group comparisons and Kruskal-Wallis test with post hoc Dunn test was used for 3-group comparisons to evaluate associations among CAR T-cell and cytokine levels, and clinical outcomes, without adjustment for multiplicity.

Analysis sets:

- Phase 2
    - Full analysis set (Intention-to-treat analysis set; N=71): Consisted of all patients enrolled in phase 2 and was used for the summary of patient disposition
    - Safety analysis set (N=55): Consisted of all patients treated with any dose of KTE-X19
    - All treated patients (modified intention-to-treat analysis set; N=55): Consisted of all patients enrolled in phase 2 and treated with KTE-X19. This analysis set was used for the hypothesis testing of the primary endpoint of overall complete remission (CR)/CR with incomplete

hematologic recovery rate at the time of primary analysis, as well as all other efficacy analyses unless otherwise specified

- Phase 1 and Phase 2 combined (N=78): Consisted of all patients treated in phase 1 (n=23) and phase 2 (n=55) at the recommended phase 2 dose of KTE-X19 (1×10^6 CAR T cells/kg)
- Phase 1 long-term population (N=45): Consisted of all patients treated with any dose of KTE-X19

An independent Data Safety Monitoring Board reviewed safety data through one interim analysis during the phase 2 portion of the study after 20 patients in phase 2 had been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion.

Supplementary Results

Patients

The majority of treated patients were White (67%); 5% of patients were Asian, 2% Black or African American, and 2% American Indian or Alaska Native. Race demographic was missing for 7% of patients and reported as other for 16% of patients.

Efficacy

Ten patients (18%) received allo-SCT post-KTE-X19 infusion; 7 patients achieved CR and 2 CRi by central assessment in response to KTE-X19, and 1 patient achieved CRi by investigator assessment but blast-free hypoplastic or aplastic bone marrow by central assessment.

Safety

Median duration of hospitalization that occurred after infusion was 22 days (IQR, 17–35) and median duration of intensive care unit stays was 5 days (IQR, 4–10).

All cytokine release syndrome (CRS) events resolved except in 3 patients who had ongoing CRS at the time of death; these deaths were due to brain herniation (day 8; considered related to KTE-X19), pneumonia (day 15), or progressive disease (day 21). Neurologic events fully resolved for 29 of 33 patients as of this analysis: 1 patient had ongoing grade 1 finger numbness, 2 had ongoing grade 3 neurologic events at the time of death due to progressive disease (days 483 and 553), and 1 experienced grade 5 brain herniation as described above. Four patients had neurologic events in the absence of CRS.

Six patients (11%) died due to AEs other than Grade 5 ALL: 2 deemed related to KTE-X19 (brain herniation mentioned previously [day 8] and septic shock [day 18; also related to conditioning chemotherapy, with a positive culture of *Pseudomonas aeruginosa*]) and 4 deemed unrelated to treatment (pneumonia [day 15], fungal pneumonia [day 46, with a positive culture of *Rhizopus* on day 23], sepsis [day 72], and respiratory failure [day 491]; the latter 3 occurring after initiation of another anticancer therapy). One patient 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”.

Patient-Reported Outcome

Relative to screening, the proportion of evaluable patients reporting no problems in mobility, usual activities, and self-care decreased at day 28 after KTE-X19 administration. Starting at month 3, the proportion of patients reporting no problems rebounded (mobility and pain/discomfort) or reached higher levels (self-care, usual activities, and anxiety/depression) in EQ-5D-5L. By month 12, the proportions of evaluable patients reporting no problems were higher than those proportions at screening across all 5 dimensions. Additionally, the trend of functional improvement was pronounced as reported by visual analogue scale (VAS). The median VAS score of evaluable patients increased from 70·0 at screening to 87·5 by month 12. Most patients maintained stable VAS scores (absolute change of <7 points) or improved (increase of ≥7 points) over time (minimum: 79·5% stable or improved at day 28; maximum: 92·9% stable or improved at month 12).

Summary of Deviations From the Protocol

Relevant protocol deviations were not considered to impact the overall quality of the data and interpretation of the results. In the safety analysis set of Phase 2, important protocol deviations were reported for 18 patients (33%) during the study; of these, 2 patients (4%) had COVID-19–related important protocol deviations. Each category of important protocol deviations occurred in <10% of patients. The most frequent important protocol deviations were missed bone marrow aspirate (5 patients [9%]; this was COVID-19–related for 1 patient), and initial serious AE not reported within 24 hours (4 patients [7%]). All other protocol deviations occurred in ≤2 patients each.

Phase 1 and Phase 2 Pooled Analysis

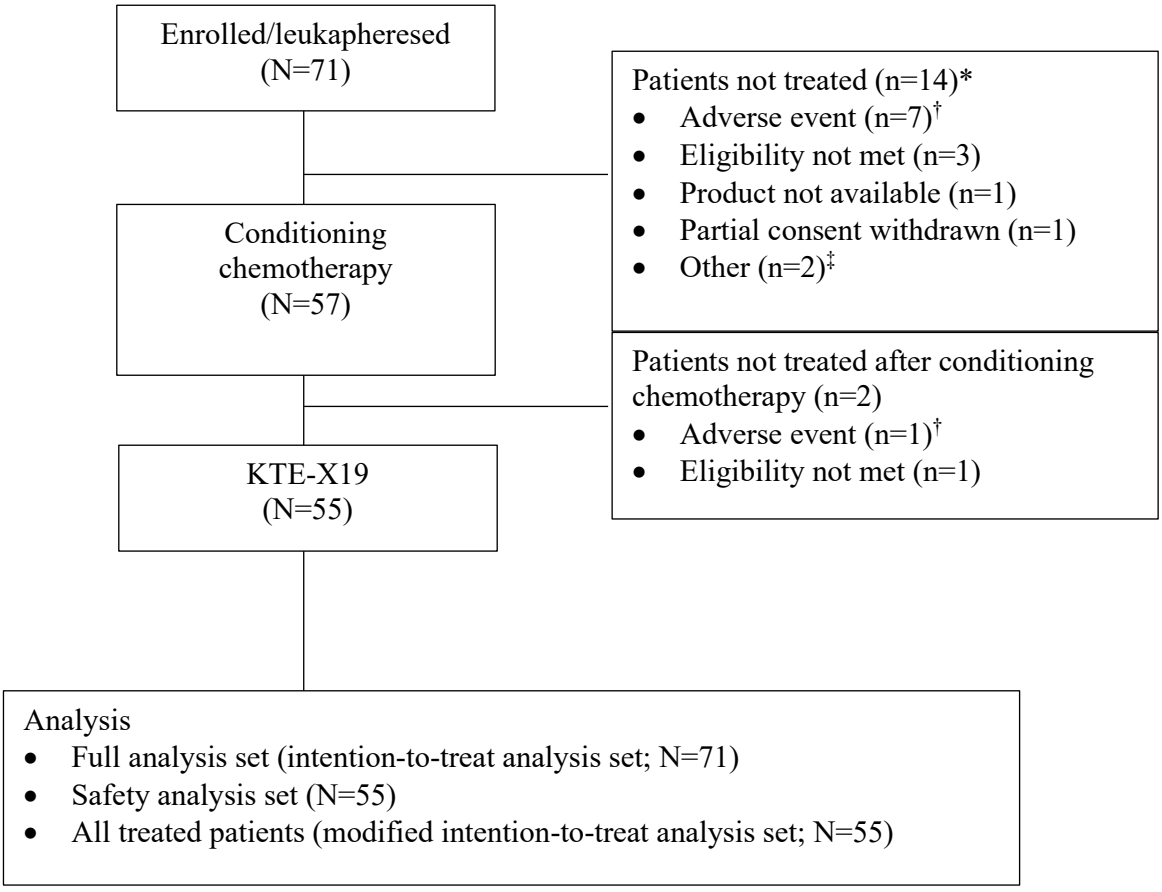
In an analysis of all patients treated at the 1×10^6 dose level in phases 1 and 2 combined (N=78), the CR/CRi rate was 74·4% (CR rate, 62·8%) by investigator assessment (**Table S11**). The median duration of remission (DOR) was 13·4 months, and as of the data cutoff, 33% of patients with CR/CRi (19/58) remained in ongoing response. The median relapse-free survival was 10·3 months. The median OS was 22·4 months. The median OS was not reached among patients with CR/CRi.

Phase 1 Long-Term Analysis

As of September 9, 2020, the CR/CRi rate among the 45 patients (2×10^6, n=6; 1×10^6, n=23; $0{\cdot}5\times10^6$, n=16) treated in phase 1[1] was 66·7% (55·6% CR), with a median follow-up of 39·4 months. The medians for DOR and OS were 14·2 and 12·1 months, respectively. Among patients treated at the 1×10^6 dose level, the CR/CRi rate was 78·3% (CR rate, 69·6%), and the medians for DOR and OS were 17·6 and 22·4 months, respectively; among patients with CR/CRi, the median OS was not reached.

All treated patients had ≥1 adverse event. Grade ≥3 cytopenias were present on or after 30 days post–KTE-X19 infusion in 44% of patients. Since the previous report, no new grade 5 events have occurred, and 2 patients have died due to disease progression. Two patients had secondary malignancies (myelodysplastic syndrome or leukemic retinopathy) considered unrelated to KTE-X19.

Figure S1. Consort Diagram.



*Products were not successfully manufactured for 6 patients. These patients were reported by the sites as not treated for the following reasons: adverse event (n=1), product not available (n=1), partial consent withdrawn (n=1), eligibility not met (n=1), and other (n=2).

†Adverse events leading to treatment discontinuation prior to conditioning chemotherapy included sepsis (n=1), acute lymphoblastic leukemia (n=1), fungal pneumonia and sepsis (both in the same patient, n=1), deep vein thrombosis (n=1), encephalopathy and cardiac arrest (both in the same patient, n=1), myositis (n=1), and hemiparesis due to air embolism (n=1). Following conditioning chemotherapy, one patient did not proceed to KTE-X19 infusion due to an adverse event of bacteremia. ‡One patient experienced clinical deterioration after product was not successfully manufactured from three leukapheresis attempts, and one patient was considered not clinically stable to proceed with CAR T-cell therapy after product was not successfully manufactured from the initial leukapheresis attempt.

Figure S2. Relapse-Free Survival Based on Central Assessment When Not Censoring at Allogeneic Stem Cell Transplant. The figure shows the Kaplan-Meier estimates of the relapse-free survival based on central assessment without censoring patients at subsequent allogeneic stem cell transplant. CR=complete remission; CRi=complete remission with incomplete hematologic recovery; RFS=relapse-free survival.

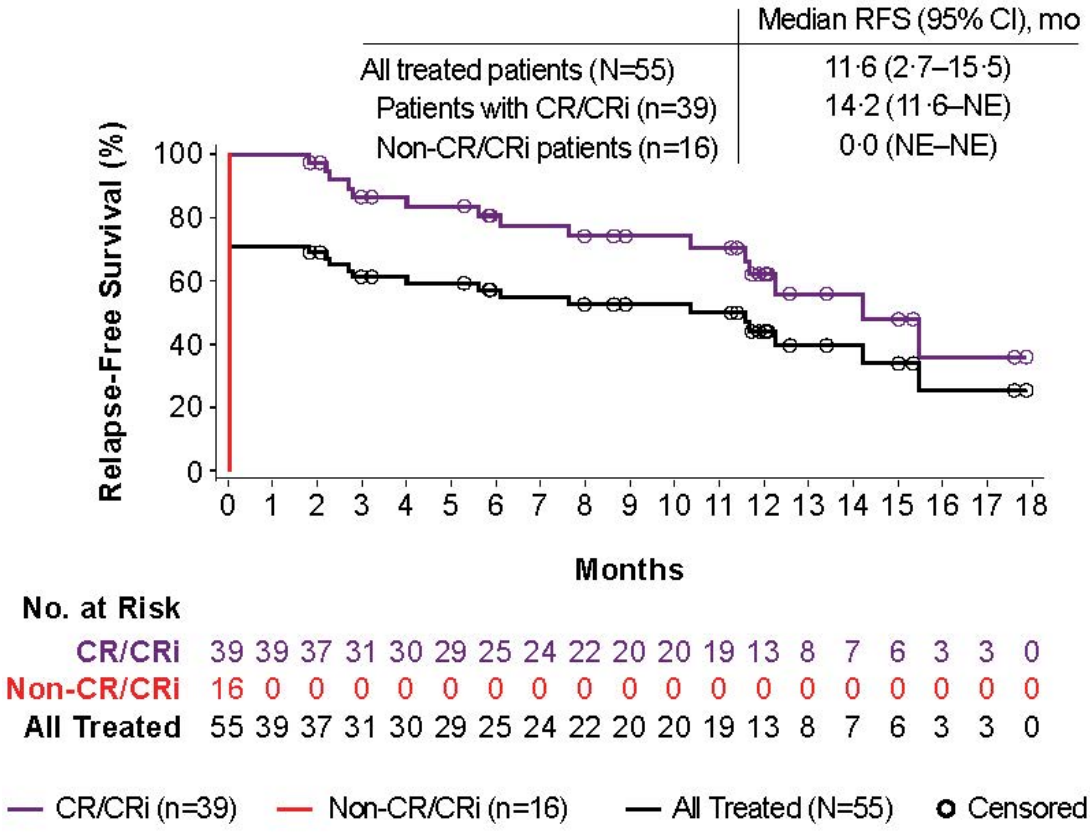


Figure S3. Subgroup Analysis of Relapse-Free Survival Rate at Month 6 Based on Central Assessment. The figure shows the analysis of relapse-free survival by baseline and clinical covariates. The Clopper-Pearson method was used to calculate the 95% confidence intervals (not adjusted for multiplicity). *Includes one patient who received autologous SCT. CNS=central nervous system; NE=not estimable; RFS=relapse-free survival; SCT=stem cell transplant.

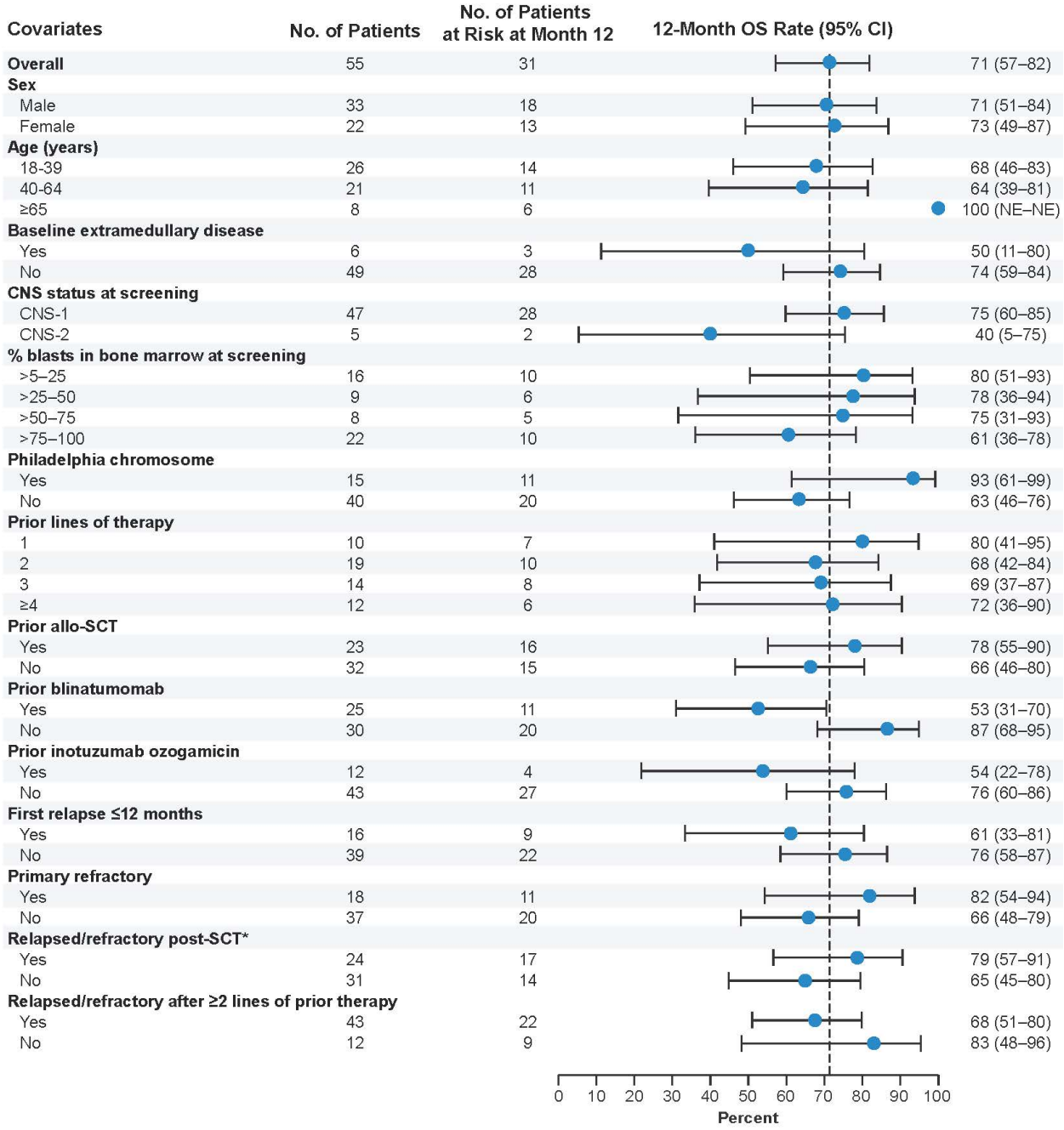


Figure S4. Subgroup Analysis of Overall Survival Rate at Month 12. The figure shows the analysis of overall survival by baseline and clinical covariates. The Clopper-Pearson method was used to calculate the 95% confidence intervals (not adjusted for multiplicity). *Includes one patient who received autologous SCT. CNS=central nervous system; NE= not estimable; OS=overall survival; SCT=stem cell transplant.

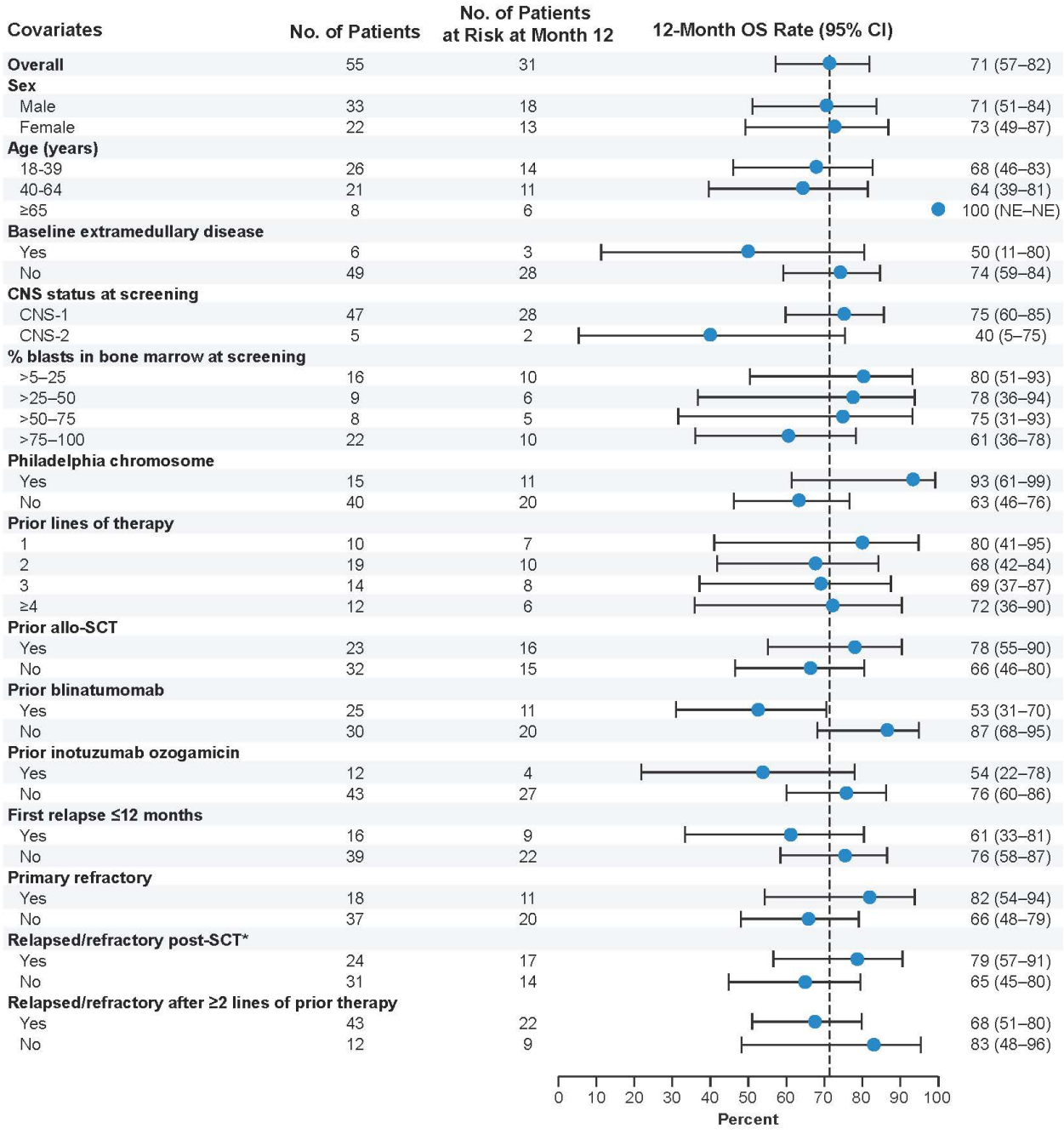


Figure S5. AUC of CAR T-Cell Levels and Associations With Response and Adverse Events. Panels A-E show the association between area under the curve from Days 0-28 of CAR T-cell levels in blood and ongoing response versus relapse or nonresponse (A), responders versus nonresponders (B), best minimal residual disease status overall (C), cytokine release syndrome (D), and neurologic events (E). Nominal P values were determined by the Wilcoxon rank sum test for 2-group comparisons and Kruskal-Wallis test with post hoc Dunn test for 3-group comparisons. CR=complete remission; CRi=complete remission with incomplete hematologic recovery; GM-CSF=granulocyte-macrophage colony-stimulating factor; Gr=grade; GzmB=Granzyme B; IFN=interferon; IL=interleukin; MRD=minimal residual disease; TNF=tumor necrosis factor.

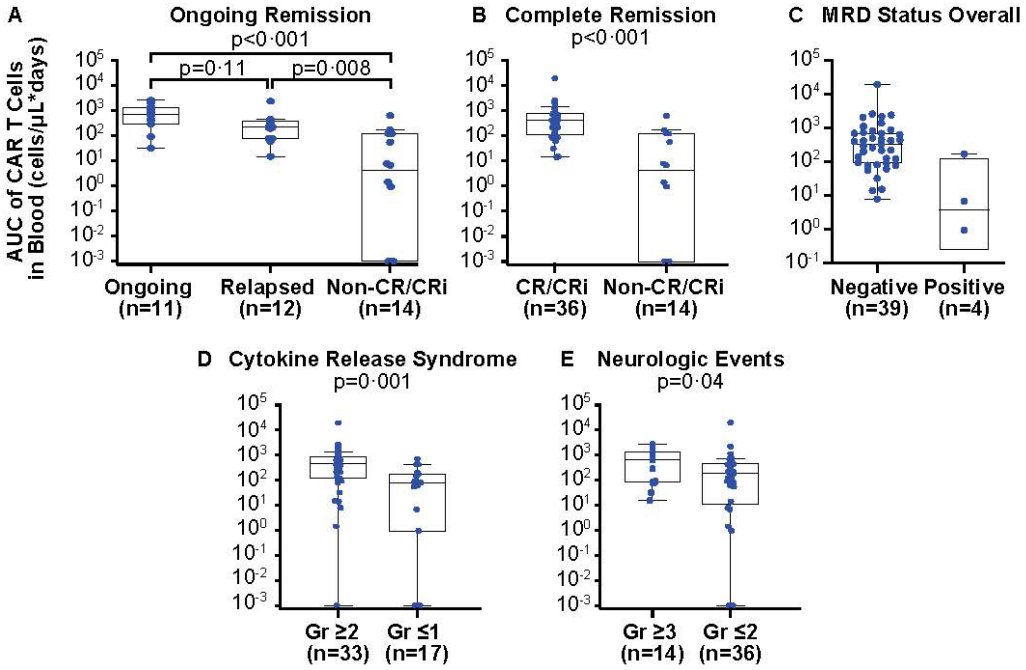


Figure S6. Longitudinal Profile of Cytokines. The figure shows the median fold change over baseline levels of cytokines. GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN=interferon; IL=interleukin; Rα=receptor alpha; RA=receptor agonist; TNF=tumor necrosis factor.

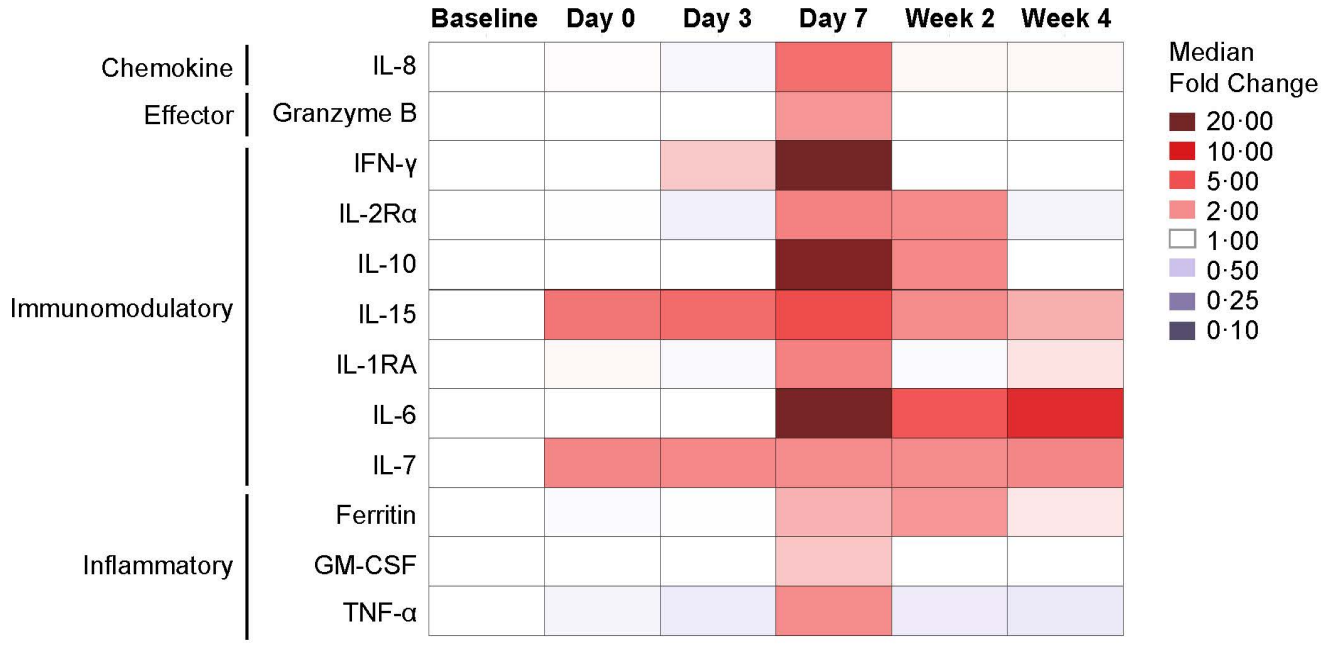


Table S1. Efficacy Endpoints in Treated Patients in Phase 2 Based on Investigator Assessment (Phase 2, Modified Intent-to-Treat Analysis Set).

Response, n (%)	**N=55**
Overall CR/CRi	40 (72·7)
CR	33 (60·0)
CRi	7 (12·7)
Blast-free hypoplastic or aplastic bone marrow	3 (5·5)
No response	9 (16·4)
Unknown or not evaluable	3 (5·5)
Overall concordance between central assessment and investigator assessment, %*	95
Kappa coefficient (95% CI)	0·87 (0·72–1·00)

*Overall concordance is the percentage of patients whose central assessment matches investigator assessment.
CR=complete remission; CRi=complete remission with incomplete hematologic recovery.

Table S2. Efficacy Endpoints in Enrolled Patients in Phase 2 Based on Central Assessment (Phase 2, Full Analysis Set).

n (%)	N=71
Overall CR/CRi	39 (54·9)
CR	31 (43·7)
CRi	8 (11·3)
Blast-free hypoplastic or aplastic bone marrow	4 (5·6)
No response	11 (15·5)
Unknown or not evaluable	17 (23·9)
Median DOR (95% CI), mo	12·8 (8·7–NE)
Median RFS (95% CI), mo	7·0 (0·0–13·2)
Median OS (95% CI), mo	19·2 (10·4–NE)

CR=complete remission; CRi=complete remission with incomplete hematologic recovery;
DOR=duration of remission; NE=not estimable; OS=overall survival; RFS=relapse-free survival.

Table S3. Adverse Events of Cytopenia Occurring in Treated Patients in Phase 2 (Phase 2, Safety Analysis Set).

	N=55					
n (%)	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Any thrombocytopenia, neutropenia, or anemia	42 (76)	0	0	11 (20)	31 (56)	0
Any thrombocytopenia	27 (49)	1 (2)	2 (4)	3 (5)	21 (38)	0
Platelet count decreased	18 (33)	1 (2)	0	3 (5)	14 (25)	0
Thrombocytopenia	9 (16)	0	2 (4)	0	7 (13)	0
Any neutropenia	27 (49)	0	0	7 (13)	20 (36)	0
Neutrophil count decreased	15 (27)	0	0	1 (2)	14 (25)	0
Neutropenia	8 (15)	0	0	2 (4)	6 (11)	0
Febrile neutropenia	7 (13)	0	0	7 (13)	0	0
Any anemia	29 (53)	0	2 (4)	25 (45)	2 (4)	0

Table S4. Adverse Events of Cytopenia Occurring on or After 30 Days Post-KTE-X19 Infusion in Treated Patients in Phase 2 (Phase 2, Safety Analysis Set).

	N=55			
n (%)	**Any grade**	**Grade ≥3**	**Grade 3**	**Grade 4**
Any thrombocytopenia, neutropenia, or anemia on or after 30 days post–KTE-X19	22 (40)	20 (36)	2 (4)	18 (33)
Any thrombocytopenia	10 (18)	10 (18)	0	10 (18)
Platelet count decreased	8 (15)	8 (15)	0	8 (15)
Thrombocytopenia	2 (4)	2 (4)	0	2 (4)
Any neutropenia	14 (25)	14 (25)	2 (4)	12 (22)
Neutrophil count decreased	9 (16)	9 (16)	1 (2)	8 (15)
Neutropenia	4 (7)	4 (7)	0	4 (7)
Febrile neutropenia	1 (2)	1 (2)	1 (2)	0
Any anemia	8 (15)	4 (7)	3 (5)	1 (2)

Table S5. CAR T-Cell Levels in Blood Over Time in All Treated Patients in Phase 2 (Phase 2, Safety Analysis Set).

Parameter	N=55
Peak (cells/µL)	(n=50)
Median	20·62
IQR	4·58–62·97
AUC_{0-28} (cells/µL•days)	(n=50)
Median	220·60
IQR	56·25–676·94
Time-to-Peak (days)	(n=50)
Median	15
IQR	11–16
Baseline (cells/µL)	(n=52)
Median	0
IQR	0–0
Day 7 (cells/µL)	(n=43)
Median	0·77
IQR	0·06–15·99
Week 2 (cells/µL)	(n=42)
Median	17·28
IQR	4·58–59·75
Week 4 (cells/µL)	(n=41)
Median	1·62
IQR	0·12–5·87
Week 8 (cells/µL)	(n=37)
Median	0·24
IQR	0–0·94
Month 3 (cells/µL)	(n=31)
Median	0·02
IQR	0–0·49
Month 6 (cells/µL)	(n=28)
Median	0
IQR	0–0
Month 9 (cells/µL)	(n=22)
Median	0
IQR	0–0

Month 12 (cells/µL)	(n=20)
Median	0
IQR	0–0
Month 15 (cells/µL)	(n=9)
Median	0
IQR	0–0·43
Month 18 (cells/µL)	(n=3)
Median	0
IQR	0–0·79

AUC_{0-28}=area under the curve from day 0 to day 28; CAR=chimeric antigen receptor; IQR=interquartile range.

Table S6. 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 at Screening	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

AUC_{0-28}, area under the curve from day 0 to day 28; CAR, chimeric antigen receptor.

Table S7. B-Cell and CAR T-Cell Levels in Blood by Ongoing Response Based on Central Assessment (Phase 2, Modified Intent-to-Treat Analysis Set).

	Ongoing CR/CRi* n=12			Relapsed n=13			Non-CR/CRi n=16		
	n (%)	B cell ,% Median (IQR)	CAR T, cells/µL Median (IQR)	n (%)	B cell ,% Median (IQR)	CAR T, cells/µL Median (IQR)	n (%)	B cell ,% Median (IQR)	CAR T, cells/µL Median (IQR)
B cells tested at baseline	12 (100)	18·00 (4·93–33·95)	0·00 (0·00–0·00)	13 (100)	55·73 (39·29–77·46)	0·00 (0·00–0·00)	11 (68·8)	50·84 (14·67–63·36)	0·00 (0·00–0·00)
No B cells									
With B cells	12 (100)	18·00 (4·93–33·95)	0·00 (0·00–0·00)	13 (100)	55·73 (39·29–77·46)	0·00 (0·00–0·00)	11 (100)	50·84 (14·67–63·36)	0·00 (0·00–0·00)
B cells tested at day 28	9 (75·0)	0·02 (0·02–0·02)	11·58 (2·31–30·32)	11 (84·6)	0·04 (0·03–0·05)	0·48 (0·00–2·18)	4 (25·0)	16·97 (0·04–56·70)	4·48 (0·00–15·69)
No B cells	7 (77·8)		19·18 (3·28–32·22)	9 (81·8)		0·88 (0·00–2·39)	1 (25·0)		8·96 (8·96–8·96)
With B cells	2 (22·2)	0·02 (0·02–0·02)	0·12 (0·12–0·12)	2 (18·2)	0·04 (0·03–0·05)	0·14 (0·00–0·28)	3 (75·0)	16·97 (0·04–56·70)	0·00 (0·00–22·43)
B cells tested at month 3	10 (83·3)	0·96 (0·06–17·71)	0·51 (0·18–0·97)	8 (61·5)	4·68 (0·16–24·47)	0·00 (0·00–0·11)	2 (12·5)	0·06 (0·04, 0·08)	0·26 (0·02–0·49)
No B cells	4 (40·0)		0·82 (0·18–1·25)	2 (25·0)		0·06 (0·00–0·11)			
With B cells	6 (60·0)	0·96 (0·06–17·71)	0·47 (0·00–0·97)	6 (75·0)	4·68 (0·16–24·47)	0·00 (0·00–0·00)	2 (100)	0·06 (0·04–0·08)	0·26 (0·02–0·49)
B cells tested at month 6	10 (83·3)	14·08 (0·05–22·00)	0·08 (0·00–0·71)	7 (53·8)	30·93 (10·60–69·58)	0·00 (0·00–0·00)	1 (6·3)	1·18 (1·18–1·18)	0·00 (0·00–0·00)

No B cells	2 (20·0)		0·70 (0·30–1·10)						
With B cells	8 (80·0)	14·08 (0·05–22·00)	0·00 (0·00–0·44)	7 (100)	30·93 (10·60–69·58)	0·00 (0·00–0·00)	1 (100)	1·18 (1·18–1·18)	0·00 (0·00–0·00)
B cells tested at month 12	10 (83·3)	12·60 (0·57–29·66)	0·00 (0·00–0·00)	5 (38·5)	38·56 (35·00–69·18)	0·00 (0·00–0·00)	2 (12·5)	11·81 (2·19–21·43)	0·22 (0·00–0·44)
No B cells									
With B cells	10 (100)	12·60 (0·57–29·66)	0·00 (0·00–0·00)	5 (100)	38·56 (35·00–69·18)	0·00 (0·00–0·00)	2 (100)	11·81 (2·19–21·43)	0·22 (0·00–0·44)
B cells tested at month 15	4 (33·3)	14·25 (0·37–28·14)	0·28 (0·00–0·65)	3 (23·1)	37·11 (19·48–57·15)	0·00 (0·00–0·00)	1 (6·3)	20·03 (20·03–20·03)	0·00 (0·00–0·00)
No B cells	2 (50·0)		0·65 (0·55–0·76)						
With B cells	2 (50·0)	14·25 (0·37–28·14)	0·00 (0·00–0·00)	3 (100)	37·11 (19·48–57·15)	0·00 (0·00–0·00)	1 (100)	20·03 (20·03–20·03)	0·00 (0·00–0·00)

*Ongoing CR/CRi is defined as patients with CR or CRi at the primary analysis data cutoff.
CAR=chimeric antigen receptor; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; IQR=interquartile range.

Table S8. CAR T-Cell Levels in Blood by Overall MRD Status in All Treated Patients in Phase 2 (Phase 2, Modified Intent-to-Treat Analysis Set).

	MRD Status Overall in Bone Marrow Sample	
	Positive	**Negative**
	n=4	**n=42**
Peak (cells/µL)	n=4	n=39
Median	0·49	31·00
IQR	0·05–11·65	6·04–65·85
AUC_{0-28} (cells/µL•days)	n=4	n=39
Median	3·87	329·81
IQR	0·48–90·05	90·53–731·14

AUC_{0-28}=area under the curve from day 0 to day 28; CAR=chimeric antigen receptor; IQR=interquartile range.

Table S9. Selected Inflammatory Soluble Serum Biomarkers at Baseline and at Post-Infusion Peak in All Treated Patients in Phase 2 (Phase 2, Safety Analysis Set).

	N=55		
Biomarker, median (IQR)	**Baseline**	**Peak**	**AUC**
Ferritin, ng/mL	2113·1 (1223·5–3590·5)	8029·3 ($3854·3–1·9\times10^4$)	$1·2\times10^5$ ($5·4\times10^4$–$2·1\times10^5$)
IL-8, pg/mL	24·8 (15·2–60·5)	255·6 (68·5–750·0†)	1859·8 (928·3–4443·2)
Granzyme B, pg/mL	1·0* (1·0*–5·5)	33·7 (1·0*–230·6)	152·2 (32·0–1253·2)
IFN-γ, pg/mL	7·5* (7·5*–19·3)	598·7 (160·2–1876·0†)	2465·3 ($1102·4–1·1\times10^4$)
GM-CSF, pg/mL	1·9* (1·9*–1·9*)	3·9 (1·9*–17·4)	60·8 (60·8–129·0)
IL-10, pg/mL	0·7* (0·7*–5·0)	45·7 (14·7–239·0)	259·6 (130·8–1165·0)
IL-1RA, pg/mL	313·5 (198·4–555·0)	1657·8 (844·0–4195·9)	$2·1\times10^4$ ($1·1\times10^4$–$3·6\times10^4$)
IL-2Rα, ng/mL	3·7 (2·2–9·5)	19·4 (8·8–36·1)	232·4 (152·2–481·7)
IL-6, pg/mL	1·6* (1·6*–6·0)	336·7 (36·8–976·0†)	1251·9 (365·8–5728·3)
TNF-α, pg/mL	3·4 (2·2–6·0)	8·0 (4·9–14·6)	110·5 (78·1–160·3)
IL-15, pg/mL	5·2 (3·2–9·2)	33·6 (25·4–50·9)	548·0 (327·7–667·1)
IL-7, pg/mL	6·3 (3·2–10·9)	20·2 (11·9–27·8)	392·4 (235·4–599·1)

*Assigned below the limit of quantification value for cytokine analyses in serum.
†Assigned upper limit of quantification value for cytokine analyses in serum.
AUC=area under the curve from baseline (day −4) to day 28; GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN=interferon; IL=interleukin; IQR=interquartile range; Rα=receptor alpha; RA=receptor agonist; TNF=tumor necrosis factor.

Table S10. Association of Selected Soluble Serum Biomarkers With Cytokine Release Syndrome and Neurologic Events in All Treated Patients in Phase 2 (Phase 2, Safety Analysis Set).

		Cytokine Release Syndrome			Neurologic Events		
Function	Biomarker Median Levels (IQR)	Grade ≥3 (n=13)	Grade 0–2 (n=42)	p value	Grade ≥3 (n=14)	Grade 0–2 (n=41)	p value
Inflammatory	**Ferritin, ng/mL**						
	Baseline	2596·7 (1864·0–4075·2)	1914·3 (1195·2–3466·3)	0·2307	1739·3 (531·6–2864·5)	2402·5 (1617·9–3590·5)	0·1394
	Peak	$1·8\times10^4$ ($9518·9–3·2\times10^{4\dagger}$)	6041·8 ($2309·0–1·4\times10^4$)	0·0027	7464·8 ($3854·3–2·0\times10^{4\dagger}$)	8029·3 ($4021·4–1·8\times10^4$)	0·9923
	AUC	$2·6\times10^5$ ($5·6\times10^4–3·0\times10^5$)	$1·2\times10^5$ ($4·6\times10^4–1·8\times10^5$)	0·1108	$1·3\times10^5$ ($3·6\times10^4–1·8\times10^5$)	$1·2\times10^5$ ($5·6\times10^4–2·3\times10^5$)	0·4807
	TNF-α, pg/mL						
	Baseline	4·5 (2·6–6·7)	3·0 (2·2–5·2)	0·4278	3·1 (1·9–4·1)	3·5 (2·3–6·0)	0·5949
	Peak	15·5 (9·5–38·9)	7·3 (4·7–12·3)	0·0023	12·1 (6·1–13·4)	7·7 (4·9–15·4)	0·6778
	AUC	152·9 (90·5–353·5)	108·7 (78·1–141·2)	0·2630	106·7 (93·4–149·7)	116·2 (77·6–169·9)	0·9923
	GM-CSF, pg/mL						
	Baseline	1·9* (1·9*–1·9*)	1·9* (1·9*–1·9*)	1·0000	1·9* (1·9*–1·9*)	1·9* (1·9*–1·9*)	1·0000
	Peak	10·8 (8·6–94·2)	1·9* (1·9*–13·7)	0·0312	9·0 (1·9*–17·7)	3·9 (1·9*–12·5)	0·6334
	AUC	109·8 (60·8–218·1)	60·8 (60·8–94·9)	0·1720	67·6 (60·8–130·8)	60·8 (60·8–119·1)	0·7353
Chemokine	**IL-8, pg/mL**						
	Baseline	36·0 (15·7–60·5)	24·4 (15·2–54·2)	0·5917	16·9 (11·2–24·8)	36·7 (16·0–75·4)	0·0220
	Peak	750·0† (540·5–750·0†)	139·6 (65·7–497·8)	0·0019	452·6 (77·7–750·0†)	211·8 (68·5–750·0†)	0·3640
	AUC	4280·9 (1264·5–7605·2)	1715·0 (825·8–3505·9)	0·0534	2389·8 (982·8–4469·1)	1859·8 (808·1–4227·8)	0·6086

Effector	**Granzyme B, pg/mL**						
	Baseline	1·0* (1·0*–6·2)	1·0* (1·0*–1·0)	0·2124	2·8 (1·0*–17·1)	1·0* (1·0*–1·0)	0·0418
	Peak	206·9 (51·4–898·7)	18·3 (1·0*–145·5)	0·0055	114·8 (1·0*–230·6)	21·0 (3·0–184·8)	0·6331
	AUC	456·8 (68·2–5277·0)	145·9 (32·0–790·5)	0·0988	324·0 (32·0–1262·5)	143·3 (32·0–1061.6)	0·6766
Immuno-modulatory	**IFN-γ, pg/mL**						
	Baseline	7·5* (7·5*–16·6)	7·5* (7·5*–20·0)	0·5943	7·5* (7·5*–26·4)	7·5* (7·5*–19·1)	0·8857
	Peak	1876·0† (1043·4–1876·0†)	303·5 (107·6–1876·0†)	0·0267	1876·0† (281·4–1876·0†)	312·9 (121·2–1876·0†)	0·0665
	AUC	7108·8 (2348·2–1·2×10^4)	2353·0 (1034·4–1·1×10^4)	0·0669	7321·1 (1996·1–1·1×10^4)	2361·0 (1034·4–9361·8)	0·1988
	IL-10, pg/mL						
	Baseline	0·7* (0·7*–2·5)	0·7* (0·7*–5·0)	0·9129	0·7* (0·7*–3·5)	0·7* (0·7*–5·0)	0·8897
	Peak	466·0† (120·9–466·0†)	33·9 (12·8–85·9)	0·0015	103·4 (45·7–466·0†)	33·4 (13·2–164·5)	0·0670
	AUC	1160·6 (132·5–2752·7)	227·4 (130·8–565·8)	0·1064	500·4 (221·7–2302·9)	222·5 (127·6–764·9)	0·1613
	IL-1RA, pg/mL						
	Baseline	249·0 (138·0–389·0)	330·5 (206·0–655·0)	0·1199	220·5 (184·7–588·8)	324·0 (211·0–459·0)	0·7208
	Peak	3318·0 (1297·0–5775·0)	1609·3 (844·0–3864·0)	0·3120	3721·0 (1657·8–4998·0)	1190·0 (687·7–3506·0)	0·0165
	AUC	2·0×10^4 (1·1×10^4–3·4×10^4)	2·1×10^4 (1·2×10^4–3·6×10^4)	0·8819	3·0×10^4 (2·1×10^4–5·9×10^4)	1·7×10^4 1·1×10^4–3·0×10^4)	0·0455
	IL-2Rα, ng/mL						
	Baseline	3·7 (2·4–15·1)	3·5 (2·2–8·7)	0·5457	2·7 (2·0–4·6)	4·5 (2·3–10·3)	0·1025
	Peak	52·0 (30·2–65·2)	16·2 (7·9–30·0)	0·0004	27·8 (11·4–46·6)	19·2 (8·1–33·5)	0·3587
	AUC	495·3 (250·6–686·1)	200·7 (128·3–366·4)	0·0082	260·7 (188·4–366·4)	209·2 (139·9–495·3)	0·9769
	IL-6, pg/mL						
	Baseline	1·6* (1·6*–10·3)	1·6* (1·6*–5·1)	0·8337	1·6* (1·6*–3·8)	1·6* (1·6*–6·6)	0·3652

	Peak	976·0† (667·9–976·0†)	141·0 (28·1*–949·6)	0·0154	912·7 (72·3–976·0†)	255·9 (28·1*–949·6)	0·0444
	AUC	4030·0 (365·8–7929·5)	826·3 (396·6–5205·6)	0·1400	3488·5 (616·3–6791·2)	1097·7 (276·4–5586·0)	0·1988
Homeostatic	**IL-15, pg/mL**						
	Baseline	6·9 (6·0–9·3)	5·0 (3·2–7·8)	0·0864	4·4 (2·8–6·9)	5·9 (3·6–9·3)	0·1043
	Peak	50·0 (36·2–64·7)	30·5 (22·1–41·3)	0·0023	38·5 (36·2–50·9)	30·9 (23·0–50·0)	0·1153
	AUC	675·4 (480·3–765·2)	423·1 (311·0–634·0)	0·0316	625·4 (420·0–675·4)	480·3 (303·5–639·1)	0·1199
	IL-7, pg/mL						
	Baseline	4·1 (1·4*–6·6)	7·8 (3·5–11·6)	0·0552	7·2 (2·9–13·1)	5·6 (3·5–9·4)	0·6911
	Peak	18·3 (12·7–22·1)	21·3 (11·9–29·2)	0·2424	24·0 (11·9–32·7)	20·0 (12·7–25·6)	0·4282
	AUC	237·3 (207·9–360·3)	416·9 (291·6–607·6)	0·0366	515·2 (237·3–632·9)	390·0 (235·4–536·6)	0·3587

P values were calculated using Wilcoxon rank sum test. Baseline values were the last measured value prior to conditioning chemotherapy.
*Assigned below the limit of quantification value for cytokine analysis in serum.
†Assigned upper limit of quantification value for cytokine analysis in serum.
AUC=area under the curve from baseline (day −4) to day 28; CCL=C-C motif chemokine ligand; CRP=C-reactive protein; CXCL=C-X-C motif chemokine ligand; GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN=interferon; IL=interleukin; IP=interferon γ-induced protein; IQR=interquartile range; MCP=monocyte attractant protein; MDC=macrophage-derived chemokine; MIP=macrophage inflammatory protein; PD-L1=programmed death-ligand 1; Rα=receptor alpha; RA= receptor agonist; SAA=serum amyloid A; TARC=thymus and activation regulated chemokine; TNF=tumor necrosis factor.

Table S11. Product Characteristics in All Treated Patients in Phase 2 (Phase 2, Safety Analysis Set).

Characteristic, median (IQR)	N=55
Percent transduction	57·0 (49·0–68·0)
Percent viability	90·2 (86·0–93·0)
CD4/CD8 ratio	1·3 (0·8–2·5)
IFN-γ in coculture (pg/mL)	7242·0 (3527·0–$1·17\times10^4$)
T cell subsets (%)	
CCR7+CD45RA+ (Tnaïve)*	54·9 (43·5–77·3)
CCR7+CD45RA- (Tcm)*	8·8 (5·8–13·3)
CCR7-CD45RA- (Tem)*	4·4 (2·7–9·6)
CCR7-CD45RA+ (Teff)*	25·2 (13·7–34·9)

*Percent of viable CD3 cells.
IFN=interferon; IQR=interquartile range; Tcm=central memory T cells; Teff=effector T cells; Tem=effector memory T cells; Tnaïve=naïve T cells.

Table S12. Efficacy Endpoints in All Patients Treated at the 1×10^6 Dose Level in Phase 1 and Phase 2 Based on Investigator Assessment (Phase 1: 1×10^6 Dose Level and Phase 2, All Dosed Patients).

n (%)	N=78
Overall CR/CRi	58 (74·4)
CR	49 (62·8)
CRi	9 (11·5)
Blast-free hypoplastic or aplastic bone marrow	4 (5·1)
No response	12 (15·4)
Unknown or not evaluable	3 (3·8)
Median DOR (95% CI), mo	13·4 (9·4–NE)
Median RFS (95% CI), mo	10·3 (5·6–14·4)
Median OS (95% CI), mo	22·4 (15·9–NE)

CR=complete remission; CRi=complete remission with incomplete hematologic recovery;
DOR=duration of remission; NE=not estimable; OS=overall survival; RFS=relapse-free survival.

Supplementary References

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Redacted Clinical Trial Protocol for Journal Use

A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)

NCT02614066
EudraCT Number: 2015-005009-35
Phase 1/2
FINAL AMENDED PROTOCOL
KTE-C19-103

Final Protocol Date:	31 October 2018
Original Protocol Date:	07 May 2015
Amendment 1 Date:	04 October 2015
Amendment 2 Date:	09 November 2015
Amendment 3 Date:	28 July 2016
Amendment 4 Date:	10 March 2017
Amendment 5 Date:	25 October 2017
Prepared by:	Kite Pharma, Inc., 2400 Broadway, Santa Monica, CA 90404

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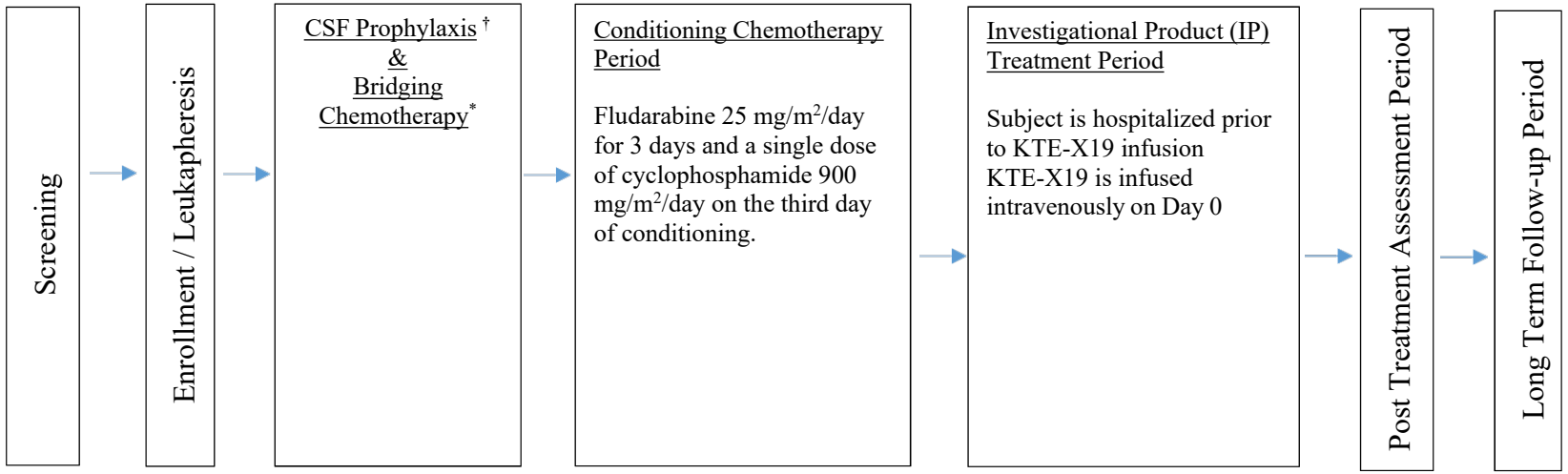
STUDY GLOSSARY

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALL	acute lymphoblastic leukemia
CAR	chimeric antigen receptor
CAR+	chimeric antigen receptor positive
CBC	complete blood count
CNS	central nervous system
CPF	cell processing facility
CR	complete remission
CRh	complete remission response with partial hematologic recovery
CRi	complete remission response with incomplete hematologic recovery
CRF	case report form
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	common terminology criteria for adverse events
ddPCR	droplet digital polymerase chain reaction
DLT	dose-limiting toxicity
DOR	duration of remission
DSMB	data safety monitoring board
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life-5 Dimensions
GVHD	graft-versus-host disease
HEENT	head, eyes, ears, nose, and throat
IB	Investigator's Brochure
ICF	informed consent form
IHC	immunohistochemistry
IP	investigational product
IPM	Investigational product manual
IRB/IEC	institutional review board/independent ethics committee
IV	intravenous
mITT	modified intention-to-treat
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI	National Cancer Institute
OS	overall survival
PCR	polymerase chain reaction
Ph^+	Philadelphia chromosome positive
PR	partial response

qPCR	quantitative polymerase chain reaction
RFS	relapse-free survival
r/r	relapsed/refractory
SAE	serious adverse event
SCT	stem cell transplant
SRT	safety review team
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
VAS	visual analogue scale
WBC	white blood cell

Figure 1. Study Schema



† CSF Prophylaxis (administered any time during screening through 7 days prior to KTE-X19 infusion):
All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines must be administered. CSF prophylaxis may be administered with the screening lumbar puncture. See Section 5.4 for additional details.

* Bridging Chemotherapy (administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy)
Bridging chemotherapy is recommended for all subjects particularly those subjects with high disease burden at screening [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation]. See Section 5.3 for details.

1. STUDY OBJECTIVES and ENDPOINTS

1.1 Study Objectives

The primary objective of Phase 1 is to evaluate the safety of KTE-X19.

The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission rate defined as complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). Secondary objectives will include assessing the safety and tolerability of KTE-X19, additional efficacy endpoints, and change in European Quality of Life-5 Dimensions (EQ-5D) scores.

1.1. Study Endpoints

1.1.1. Primary

Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT)

Phase 2: Overall complete remission rate (CR + CRi) per independent review (Appendix 1). All subjects that do not meet the criteria for CR or CRi by the analysis data cutoff date will be considered non-responders for the overall complete remission rate evaluation.

1.1.2. Secondary

- Duration of Remission (DOR): for subjects who experience CR or CRi per independent review, DOR is defined as the time between their first complete response per indepedent review to relapse or any death in the absence of documented relapse. Relapse is defined in Appendix 1. Subjects who do not meet the criteria for relapse and who have not died will be censored at the last evaluable disease assessment or disease status follow up assessment. A sensitivity analysis will be conducted in which non-disease mortality will be considered a competing risk. Disease assessments obtained after new anti-cancer therapies (including allogeneic stem cell transplant [SCT]) will not contribute to the derivation of duration of remission. The DOR for subjects that undergo allogeneic SCT while in remission is censored at the date of the allogeneic SCT; the DOR for subjects that undergo other new anti-cancer therapies in the absence of documented relapse is censored at the last evaluable disease assessment prior to the new anti-cancer therapies.

- In subjects who achieve CR, a tyrosine kinase inhibitor (TKI) may be resumed 2 months after KTE-X19 infusion. In such subjects who resume TKI therapy, disease assessments obtained after resumption of TKI therapy will contribute to the derivation of the duration of remission. A sensitivity analysis will be conducted in which the duration of remission in such subjects is censored atthe first date of the resumption of TKI therapy.

- Minimum Residual Disease (MRD) Negative Rate: The incidence of a minimal residual disease response (MRD-). MRD- is defined as MRD < 10^{-4} per the standard assessment (see Section 6.8).

- Overall complete remission rate (CR + CRi) per investigator assessment (Appendix 1).

- Allogeneic SCT Rate

- Overall Survival (OS): OS is defined as the time from KTE-X19 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censoredat their last contact date.

- Relapse-free Survival (RFS): RFS is defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause. Subjects not meeting the criteria for relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who have not achieved a complete remission (CR or CRi) at the analysis data cutoff will be evaluated as having an RFS event at Day 0.

- Incidence of adverse events and common terminology criteria for adverse events (CTCAE) grade changes in safety laboratory values.

- Incidence of anti-KTE-X19 antibodies.

- Changes over time in the EQ-5D scale score and EQ-5D visual analogue scale (VAS) score

1.1.3. Exploratory Endpoints

- Treatment related mortality rate 100 days post allogeneic stem cell transplant (TRM-Allogeneic SCT 100 day survival)Overall survival from the time of allogeneic stem cell transplant (OS-Allogeneic SCT): OS-Allogeneic SCT is evaluated in subjects who undergo allogeneic SCT and is defined as the time from allogeneic SCT to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

- Complete Remission with partial Hematological Recovery (CRh). The incidence of a CRh (see Appendix 1 for definition). All subjects that do not meet the criteria for CRh by the analysis data cutoff date will not be considered to have CRh.

- Blast-free hypoplastic or aplastic bone marrow rate: The incidence of blast-free hypoplastic or aplastic bone marrow (see Appendix 1 for definition). All subjects who do not meet the criteria for blast-free hypoplastic or aplastic bone marrow by the analysis date cutoff date will not be considered to have blast-free hypoplastic or aplastic bone marrow.

- Partial remission (PR) rate: The incidence of PR (see Appendix 1 for definition). All subjects that do not meet the criteria for PR by the analysis data cutoff date will not be considered to have PR.

- The overall complete remission rate (CR and CRi), MRD-negative rate, and DOR among subjects retreated with KTE-X19 (Section 6.9.9)

- Level and activity of chimeric antigen receptor positive (CAR^+) T cells, as well presence $CD19^+$ cells in blood and bone marrow.

- Levels of cytokines in serum and cerebrospinal fluid (CSF).

2. STUDY DESIGN

2.1. General Study Design

ZUMA-3 is a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with relapsed or refractory B-precursor ALL. In this study, relapsed or refractory is defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogenic SCT (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment).

During Phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or ≥1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and makerecommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on theincidence of DLTs and overall safety profile of KTE-X19. Additionally, approximately 40 subjects with high or low burden disease may be enrolled to further assess safety (see Figure 2).

During Phase 2, approximately 50 subjects in the modified-intention to treat (mITT) set will be assessed to evaluate theefficacy and safety of KTE-X19.

In total, up to approximately 100 subjects may be enrolled and treated with KTE-X19 in the study in Phase 1 and 2 combined.

During Phase 2, one interim and one primary analysis will be performed. The interim analysis is for safety only and will be performed by an independent data safety monitoring board (DSMB) after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion (see Section 9.6). Additional interim analyses for safety may be requestedby the DSMB.

The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT set has had the opportunity to complete the month 6 disease assessment (see Section 9.7).

Each subject will provide consent and be evaluated for study participation. Once deemed eligible and enrolled into the study, each subject will follow the same study treatment schedule

and procedural requirements, independent of the phase of the study, and proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period
- Bridging chemotherapy and CSF prophylaxis period
- Conditioning chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long term follow-up period

2.2. Participating Sites

Approximately 35 centers located in North America, Europe, and potentially other regions will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

Sites that do not enroll a subject within 4 months of site activation may be considered for closure.

2.3. Number of Subjects

Participants in this trial will be referred to as "subjects". Up to approximately 100 subjects may be enrolled into the entire study in order to obtain 3-12 subjects evaluable for DLT in the Phase 1 portion, up to approximately 40 additional Phase 1 subjects, and approximately 50 subjects in the mITT set in the Phase 2 portion of the study.

It should be noted that Kite Pharma may choose to close enrollment at any time. Refer to the statistical considerations section of the protocol for sample size estimations.

2.4. Study Duration

2.4.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the long term follow-up period, the duration of the study will take approximately 15 years to complete. However, individual study duration will vary depending on a subject's screening requirements, response to treatment and survival.

The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects.

2.4.2. Completion of Study

Completion of the study is defined as the time at which all enrolled subjects complete the long term follow-up period visit, is considered lost to follow-up, withdraws consent, or dies.

3. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved consent form before initiating any studyspecific procedures or activities that are not part of a subject's routine care.

Each subject who enters the screening period will receive a unique subject identification number at the time of consent [refer to the Investigational Product Manual (IPM)]. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated (see Section 6.9.9 for details regarding retreatment).

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

4. SUBJECT ELIGIBILITY

4.1. Inclusion Criteria

101) 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

102) Morphological disease in the bone marrow (> 5% blasts)

103) Subjects with Ph^+ disease are eligible if they are intolerant to TKI therapy, or if they have relapsed/refractory disease despite treatment with at least2 different TKIs

104) Age 18 or older

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

106) Absolute neutrophil count ≥ 500/μL unless in the opinion of the PI cytopenia is due to underlying leukemiaand is potentially reversible with leukemia therapy

107) 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

108) Absolute lymphocyte count ≥ 100/μL

109) Adequate renal, hepatic, pulmonary and cardiac function defined as:

- Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min
- Serum alanine aminotransferase /aspartate aminotransferase ≤ 2.5 x upper limit normal
- Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome.
- Left ventricular ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram, no NYHA class III or class IV functional classification,and no clinically significant arrhythmias
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air

110) Females of childbearing potential must have a negative serum or urine pregnancy test

111) 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.

4.2. Exclusion Criteria

201) Diagnosis of Burkitt's leukemia/lymphoma according to World Health Organization classification or chronicmyelogenous leukemia lymphoid blast crisis

202) History of malignancy other than non-melanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease free for at least 3 years

203) History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study

204) Central nervous system (CNS) abnormalities

- Presence of CNS-3 disease defined as detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 white blood cell (WBCs) per mm^3 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 mm^3 with neurological changes
  Note: Subjects with CNS-1 (no detectable leukemia in the CSF) and those with CNS-2 without clinically evident neurological changes are eligible to participate in the study.

- History or presence of any CNS disorder such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome, or cerebraledema

205) History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, Shwachman-Diamond syndrome

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

207) History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment.

208) Primary immunodeficiency

209) Known infection with HIV, hepatitis B or hepatitis C virus. A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative polymerase chain reaction (qPCR) and/or nucleic acid testing.

210) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis arepermitted if responding to active treatment and after consultation with the Kite Medical Monitor

211) Prior medication:

- Salvage systemic therapy (including chemotherapy, TKIs for Philadelphia chromosome-positive [Ph^+] ALL, andblinatumomab) within 1 week or 5 half-lives (whichever is shorter) prior toenrollment

- Prior CD19 directed therapy other than blinatumomab

- History of CTCAE grade 4 neurologic event or grade 4 cytokine release syndrome (CRS; Lee et al, 2014) withprior 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 prior to enrollment

- Donor lymphocyte infusion within 28 days prior to enrollment

- Any drug used for graft-versus-host disease (GVHD) within 4 weeks prior to enrollment (eg, calcineurin inhibitors, methotrexate, mycophenolyate, rapamycin,

thalidomide), or immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20,anti-tumor necrosis factor, anti-interleukin 6 or anti-interleukin 6 receptor)

- At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy prior to enrollment (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists etc)

- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to enrollment

212) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted

213) Acute GVHD grade II-IV by Glucksberg criteria or severity B-D by IBMTR index; acute or chronic GVHD requiring systemic treatment within 4 weeks prior to enrollment

214) Live vaccine ≤ 4 weeks prior to enrollment

215) Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

216) Subjects of both genders of child-bearing potential who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-X19

217) In the investigators judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

218) History of autoimmune disease (eg, Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

5. PROTOCOL TREATMENT

5.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- Bridging chemotherapy refers to treatment used to control a subject's disease prior to conditioning chemotherapy.

- CSF prophylaxis will be administered prior to infusion of conditioning chemotherapy.
- The Conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational product for this study is named KTE-X19.

5.2. Leukapheresis

Before leukapheresis commences, the criteria outlined in Section 6.9.2 must be met.

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacture of KTE-X19. Leukapheresed cells obtained from subjects at participating centers will be shipped to the Cell Processing Facility (CPF) overnight as described in the IPM.

Mononuclear cells will be obtained by leukapheresis. The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the IPM.

See Section 5.8 for excluded medications prior to leukapheresis.

5.3. Bridging Chemotherapy

Bridging therapy may be administered after leukapheresis and prior to conditioning chemotherapy at the investigators discretion. Bridging chemotherapy is recommended for allsubjects particularly those subjects with high disease burden at baseline [M3 marrow (>25% leukemic blasts) or ≥ 1000 blasts/mm^3 in the peripheral circulation]. If prescribed, bridging chemotherapy must be administered after leukapheresis and completed at least 7 days or 5 half- lives, whichever is shorter, prior to initiating conditioning chemotherapy.

5.4. CSF Prophylaxis

All subjects will receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines (eg, methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose).

CSF prophylaxis will be administered any time during screening (eg, at time of screening lumbar puncture) through 7 days prior to KTE-X19 infusion.

Subjects who are enrolled with CNS-2 disease at baseline must receive CSF prophylaxis after leukapheresis and at least 7 days prior to KTE-X19 infusion, unless otherwise approved by the Kite Medical Monitor.

Multiple doses of CSF prophylaxis can be given per investigator discretion in accordance with institutional guidelines, but at least 7 days must pass between the last dose of CSF prophylaxis and KTE-X19 infusion.

Additional CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after

KTE-X19 infusion if possible.

Should a subject have an Ommaya reservoir and there is no evidence of blockage of CSF flow from the spinal canal, administration of CSF prophylaxis through the reservoir is acceptable.

5.5. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of KTE-X19.

Conditioning chemotherapy will be supplied by the investigative site unless otherwisenoted.

Refer to the current product label for guidance on packaging, storage, preparation,administration and toxicity management associated with the administration of chemotherapy agents.

The investigational medicinal product (KTE-X19) must be available before initiation of conditioning chemotherapy.

See Section 6.9.5.1 for conditioning chemotherapy procedures.

5.5.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

5.5.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after intravenous (IV) administration rangesfrom 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

5.5.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient in mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$. Mesna will be administered around the cyclophosphamide dose according to institutional standards.

5.6. KTE-X19

The IP for this study is KTE-X19.

Refer to the most current Investigator's Brochure regarding KTE-X19 and clinical experience. This section contains general information and is not intended to provide specific instructions. Refer to the IPM for details and instruction on storage and administration of KTE-X19.

KTE-X19 is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of KTE-X19 infused, the thaw start/stop time, and KTE-X19 infusion start/stop time, will be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion.

To date, subjects have received doses of anti-CD19 CAR T cells ranging from 0.5 - 30 x 10^6 anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity (see Section 5.8 for more information related to corticosteroid use).

5.7. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study.

Investigators may additionally prescribe any other concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis and treatment except those medications listed in the excluded medication Section 5.8.

In subjects with Ph^+ disease and who achieve CR, a TKI may be resumed 2 months after KTE-X19 infusion at the investigator discretion and in accordance with institutional guidelines. See Section 5.3, for use of TKI's during bridging chemotherapy.

The investigator is responsible for reporting all concomitant medications as follows in Table 2:

Table 2. Reporting Requirements for Concomitant Medications

Subjects who are pre-screen or screen-fails	Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion

• Concomitant therapies related to serious adverse event(s) will be recorded from the date of the pre-screening informed consent or screening informed consent through 30 days after the last study-specific pre-screening or screening procedure, respectively.	• Concomitant therapies will be recorded from the date of the informed consent until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, conditioning chemotherapy) or until the initiation of new anti-cancer therapy, whichever occurs first.	• Concomitant therapies including medications, intubation, dialysis, oxygen, and blood products will be recorded from the date of the informed consent until 3 months after completing treatment with KTE-X19. (excluding allogeneic SCT) • After this 3-month follow-up period, targeted concomitant therapies will be recorded for either 24 months after KTE-X19 infusion or until disease progression, whichever occurs first. o Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations. o In subjects who received allogeneic SCT, only concomitant medications related to a KTE-X19-related serious adverse event (SAE) will be recorded. Reporting of these concomitant medications will commence at the time the SCT preparative regimen commences.

See Section 5.9 regarding documentation of subsequent anticancer therapy.

5.8. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 infusion.

Systemic corticosteroids should be avoided as premedication in subjects for whom computed tomography (CT) scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance).If possible, such subjects should undergo non-contrast CT scans or alternative imagine modality (such as magnetic resonance imaging [MRI]) instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KTE-X19 infusion, unless used to manage KTE-X19 related toxicities (Refer to the most current version of the IB; see Section 5.4). Other medications which may interfere with evaluation of KTE-X19, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, should be avoided anytime subjects are at risk of bleeding due to thrombocytopenia when possible. If a subject requires the initiation of therapeutic anticoagulant doses prior to initiation of conditioning chemotherapy or prior to KTE-X19 infusion, then conditioning chemotherapy/KTE-X19 infusion must be held and the case discussed with the Kite

Medical Monitor.

For subjects with Ph^+ ALL, all TKIs must be stopped at least 1 week prior to KTE-X19 infusion, including but not limited to imatinib, dasatinib, and ponatinib. In subjects who achieve CR, a TKI may be resumed 2 months after KTE-X19 infusion. See Section 5.3, Table 1 for use of TKIs during bridging chemotherapy.

CSF prophylaxis may be given post-KTE-X19 infusion per investigator discretion in accordance with institutional guidelines, but should be avoided for at least 8 weeks after KTE-X19 infusion if possible.

Treatment for the subject's leukemia such as chemotherapy, immunotherapy, targeted agents, radiation, high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression after KTE-X19 infusion. If permissibility of a specific medication/treatment is in question, contact the Kite Pharma medical monitor.

Medications with sedative properties should be avoided if possible in the setting of neurologic events (refer to the KTE-X19 IB).

5.9. Subsequent Therapy

Subsequent therapy administered after KTE-X19 infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy will be recorded for all enrolled subjects until one of the following occur: subject completes the long term follow up period, is considered lost to follow up, withdraws consent, or dies.

For subjects who are enrolled, but do not receive KTE-X19 infusion, any additional anti-cancer therapy will also be collected until subject completes the long term follow up period, is considered lost to follow up, withdraws consent, or dies.

5.10. Toxicity Management

To date, the following important risks have been identified with KTE-X19: CRS, neurological events, infections, and cytopenias. Refer to Section 6 of the current KTE-X19 Investigator's Brochure (IB) for details regarding these events and management guidance.

As the safety experience with KTE-X19 increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the KTE-X19 IB for guidance regarding managing KTE-X19 related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with KTE-X19 as well as possible complications associated with malignancy and cancer treatment.

6. STUDY PROCEDURES

The visit schedule is calculated from KTE-X19 infusion on Day 0.

An overview of study assessments/procedures is outlined below. Refer to the case report form (CRF) completion guidelines for data collection requirements and documentation of study procedures.

6.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current IRB/IEC approved Informed Consent form (ICF) prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

6.2. Demographic Data

Demographic data will be collected per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity and country of enrollment to study their possible association with subject safety and treatment effectiveness.

6.3. Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subject's chart should be obtained.

6.4. Physical Exam, Vital Signs, Performance Status, and European Quality of Life-5 Dimensions (EQ-5D)

Physical exams will be performed during screening and at times noted. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

During KTE-X19 infusion/hospitalization, vital signs including blood pressure, heart rate, oxygen saturation, and temperature will be monitored before and after the KTE-X19 infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3ºC or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

The EQ-5D will be completed only for subjects participating in phase 2. Subjects who are blind or illiterate may have the EQ-5D questions read to them bythe study staff. The study staff, however, cannot interpret any of the questions for the subject. Asubject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in one of the country languages available.

The EQ-5D is a 2 page generic patient questionnaire for assessing the overall health status of a subject. The EQ-5D consists of a 5 dimension descriptive system including questions on mobility, self-care, usual activities, pain/comfort, and anxiety/depression and a VAS which allows the respondent to record health on a vertical scale (eg, best healthto worst health) thus allowing a quantitative measure of health outcome.

6.5. Neurological Assessment

Subject's neurological status should be evaluated at screening to establish a baseline. After enrollment, subjects should be evaluated for any neurological symptoms. During the hospitalization period, evaluations of neurological status may need to be increased. Changes in neurological status should be reported as an adverseevent per Section 8.

6.6. Lumbar Puncture

Subjects with central nervous system malignancy will have a lumbar puncture performed at the screening visit for examination of cerebral spinal fluid. In addition, a lumbar puncture may be performed as applicable forsubjects with new onset of a Grade 2 or higher neurologic event after KTE-X19 infusion**.**

6.7. Disease Assessments

6.7.1. Bone Marrow Evaluation

Bone marrow aspirates and biopsies will be collected throughout the study.

- Screening bone marrow evaluation:

  ——If available, archival formalin-fixed paraffin embedded bone marrow blockand/or slides used for the original diagnosis of ALL will be submitted to the central laboratory along with the pathology report.

——A bone marrow aspirate and biopsy is required at screening and will be performed after the last dose of systemic chemotherapy and within approximately 14 days before enrollment to establish baseline disease.

- If there is a delay between when the screening bone marrow is performed and the apheresis, contact the Kite Medical Monitor for guidance on whether or not bone marrow evaluation needs to be repeated. If a fresh bone marrow aspirate and biopsy was recently collected and properly stored prior to consent, then contact the Kite Medical Monitor to confirm if this sample is adequate for screening.

——In subjects who receive bridging chemotherapy, an additional bone marrow sample is required between the end of bridging chemotherapy and Day -4. If bridging chemotherapy is not administered, then the additional bone marrow sample is not required, however, an assessment of peripheral circulating blasts is required.

- On study bone marrow evaluations:

——A bone marrow aspirate will be required at all time points to assesstreatment response.

- For subjects who undergo a SCT, bone marrow evaluations are not required during the first 100 days post-SCT. After 100 days, bone marrow evaluations should be performed at the next per protocol time point per the SOA. If a subject has a bone marrow evaluation earlier than the next per protocol time point, then the bone marrow samples should be processed and submitted to the central laboratory per the central laboratory manual.

——In addition to the bone marrow aspirate, a bone marrow biopsy is required at Day -4 and Day 28. A bone marrow biopsy at all other time points is recommended and should be performed if standard of care. Note: Anytime the bone marrow aspirate is a dry tap, then a bone marrow biopsy is required. In the case of a dry tap, the bone marrow biopsy will be used to determine disease burden by immunohistochemical (IHC) analyses. The following markers will be analyzed by IHC: CD10, CD19, CD20, CD34, Pax5 and TdT.

——For subjects who sign the optional portion of the consent form, a Day 7 bone marrow biopsy and aspirate will be performed. The optional day 7 bone marrow may be performed between day 7 and 14.

——Reminders:

- For subjects with a CR, collection and analysis of CSF is required to confirm CR (see Section 6.6)

- For subjects with progressive disease, a peripheral blood mononuclear cell sample should be collected at time of progression andprior to starting subsequent anticancer therapy

Locally evaluated % blasts from the bone marrow evaluation and if available local MRD will be entered to the CRF.

Overall response will be assessed by the investigator per Appendix 1. If bone marrow blasts are

≤ 5% and circulating blasts are ≥ 1%, then additional studies (eg, flow cytometry) should be performed to quantify the blasts.

Bone marrow aspirate and biopsy samples will be processed and submitted to the central laboratory as outlined in the central laboratory manual. Refer to the laboratory manual for collection, processing and shipment requirements; note some samples, eg, MRD, must be shipped on the same day of collection. Below is an overview of the sample types that will be required.

Samples from bone marrow aspirate may include:

- MRD assessment
- Stained slide smears
  - ——The same slides used to evaluate ALL disease status (eg, % blasts) locally will be submitted to the central laboratory and will then be returned back to the investigative site after the review is completed. If the same slides used to diagnose ALL cannot be submitted to the central laboratory per institutional policy, then slides from the same procedure should be submitted. See central laboratory manual for details.
- Bone marrow mononuclear cells

Samples from bone marrow biopsy may include:

- Touch prep slide
- Core biopsy in formalin, formalin-fixed paraffin embedded block, or unstained slides

The corresponding pathology report should be submitted to the central laboratory along with the archival and on-study bone marrow samples.

6.7.2. Imaging Requirements (Only Applies to Subjects with Known Non-CNS Extramedullary Disease at Baseline)

- Extramedullary disease will be assessed prior to baseline with an imaging modality appropriate for the anatomical site and clinical scenario (eg, MRI for CNS lesion, ultrasound for testicular lesion, CT for intra-abdominal or thoracic lesion).
  - ——For all subjects with known non-CNS extramedullary disease, images must be taken within 28 days before conditioning chemotherapy. In addition, for subjects receiving bridging chemotherapy, images must be taken after bridging chemotherapy has completed.
- Following KTE-X19 infusion, the first on study images will occur at the time of first presumed response (ie, bone marrow blasts ≤ 5%)
- Subsequent images will continue through Month 24 or disease progression, whichever occurs first. If the subject's disease has not progressed by Month 24, then images will be

performed per standard of care until disease progression.

- All on-study assessments of extramedullary disease detected through imaging should be made with the same imaging modality and of the same anatomical locations as imaged at baseline.
- Response is evaluated by the investigator (Appendix 1).
- For all subjects, images should be performed per standard of care anytime the subject presents with symptoms suggestive of disease progression.
- Images will be submitted to a central imaging vendor; central imaging vendor manual to be provided separately.

6.8. Biomarkers

Biomarker analysis will be performed on blood and bone marrow derived tumor samples to evaluate predictive and pharmacodynamic markers for KTE-X19. Prognostic markers specific for B-ALL and related to the tumor immune environment may also be evaluated**.**

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR T cells will be monitored in the blood and bone marrow by flow cytometry. Expansion and persistence in peripheral blood will also be monitored by a CD19 CAR specific droplet digital chain reaction assay (ddPCR).

Levels of serum cytokines and chemokines will be evaluated in the blood.

CSF as well as any additional subject samples (eg, pleural fluid) may be collected from subjects who develop neurologic events or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable lymphocyte populations residing inthe CSF or other additional subject samples may also be analyzed for the purpose of understanding the safety profile of KTE-X19.

6.9. Procedures by Study Period

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

6.9.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through enrollment. Informed consent must be obtained before completion of any study specific procedures. Procedures that are part of standard of care are not considered study specificprocedures and may be performed prior to obtaining consent and used to confirm eligibility.Confirmation of this data must occur within the time allowance as outlined below.

After written informed consent has been obtained, subjects will be screened to confirm study

eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 4 and who commence leukapheresis will be enrolled into the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

6.9.2. Enrollment/Leukapheresis

Before leukapheresis commences, the following criteria must be met:

- In general, all eligibility criteria confirmed during screening must not be known to be violated prior to leukapheresis. Additionally, the investigator must review and confirm that the last complete blood count (CBC) with differential and chemistry panel drawn prior to the start of leukapheresis must meet the eligibility criteria detailed in Inclusion criterion 105. If any screening assessments or procedures are repeated between screening and the start of leukapheresis andresults are outside the eligibility criteria (Section 4), contact the Kite medical monitor beforeproceeding with leukapheresis.

- Subjects must have no evidence of clinically significant infection prior to leukapheresis. Should a subject have clinically significant infection immediately prior to leukapheresis, cell collection must be delayed until the event resolves.

- If leukapheresis is delayed beyond 5 days, a CBC with differential and chemistry panel must be repeated.

- If WBC collected at time of leukapheresis is ≥ 50,000 cells/µL a contact must be made to the Kite Medical Monitor before proceeding with leukapheresis.

- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis (see Section 5.8).

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

Vitals, lab draws, adverse/serious adverse event reporting and concomitant medications documentation may be performed the day before leukapheresis, unless otherwise specified.

6.9.3. Bridging Chemotherapy Period

If prescribed, bridging chemotherapy will be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy (see Section 5.3).

Note: As appropriate, vitals and labs should be repeated each day bridging chemotherapy is administered.

6.9.4. CSF Prophylaxis Period

Intrathecal chemotherapy for CSF Prophylaxis will be administered any time during screening through 7 days prior to KTE-X19 infusion (see Section 5.4).

Note: As appropriate, vitals and labs should be repeated each day CSF prophylaxis is administered.

6.9.5. Conditioning Chemotherapy and KTE-X19 Infusion

Administration of KTE-X19 cells to subjects with ongoing infection or inflammation, evenif such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion.

Signs, symptoms or abnormal laboratory results attributed to the malignancy (elevated C-reactive protein [CRP]) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and KTE-X19 infusion should only be initiated afterit is reasonably assured that cell infusion can safely proceed.

The investigational medicinal product (KTE-X19) must be available before initiation of conditioning chemotherapy.

Refer to Section 6.9.6.5 for Requirements to Work-up Potential Infectious and/or Inflammatory States.

6.9.5.1. Conditioning Chemotherapy Period

6.9.5.1.1. Requirements for Initiating Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the work-up listed in Section 6.9.6.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38ºC within 72 hours before conditioning chemotherapy
- CRP > 100 mg/L any time between enrolment to start of conditioning chemotherapy
- WBC count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally,

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 4, then the condition must resolve prior to proceedingwith conditioning chemotherapy.
- Complete history and physical exam including head, ears, eyes, nose, and throat (HEENT), and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy

(prophylactic use of anti-microbials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determinedby the investigator in consultation with infectious disease service (if applicable).

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, polymerase chain reaction **[**PCR**]**, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungalinfection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with conditioning chemotherapy.

6.9.5.2. Conditioning Chemotherapy Administration

Subjects will receive a conditioning chemotherapy regimen consisting of cyclophosphamideand fludarabine. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

Conditioning chemotherapy (fludarabine and cyclophosphamide) will be supplied by the investigative site unless otherwise noted and should be administered per institutional guidelines. Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

Before conditioning chemotherapy commences, the criteria outlined in Section 6.9.5.1 must be met.

6.9.6. Investigational Product Treatment Period

6.9.6.1. Pre-KTE-X19 Infusion Criteria

If any of the following criteria are met prior to the initiation of KTE-X19, then the work-uplisted in Section 6.9.6.5 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of KTE-X19 infusion

- CRP > 100 mg/L any time between enrollment to start of KTE-X19 infusion

- WBC count or WBC differential concerning for infectious process between enrollment to start of KTE-X19infusion (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- All eligibility criteria of the protocol must be met. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of KTE-X19 infusion and results are outside the eligibility criteria listed in Section 4, then the condition must resolve prior to proceeding with KTE-X19 infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).

- Complete history and physical exam including HEENT, and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not revealevidence of infection/inflammation.

- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before KTE-X19 (prophylactic use ofanti-microbials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determinedby the investigator in consultation with infectious disease service (if applicable).

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungalinfection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with administration ofKTE-X19.

If the KTE-X19 infusion is delayed > 2 weeks, protocol guidelines should be followedregarding the need for repeat conditioning chemotherapy.

6.9.6.2. Hospitalization for KTE-X19 Infusion

Subjects will be hospitalized to receive infusion of KTE-X19 followed by a minimum 7 day observation period unless otherwise required by country regulatory agencies (refer to Appendix 3 for details).

Subjects will remain in the hospital through day 7 post infusion of KTE-X19. Subjects should not be discharged from the hospital until all KTE-X19-related non-hematological toxicities return to grade ≤ 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg, renal insufficiency) even if > grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > grade 1, or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurologic events in the outpatient setting after discharge, subjects and their family members/caregivers should be educated on potential symptoms of these syndromes such as fever, dyspnea, confusion, aphasia, dysphasia,

somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention.

See Section 5.8 for excluded medications prior to and after KTE-X19.

6.9.6.3. KTE-X19 Premedication Dosing

The following pre-KTE-X19 infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor

- Acetaminophen 650 mg PO or equivalent
- Diphenhydramine 12.5 mg administered either orally or via IV or equivalent

6.9.6.4. KTE-X19 Infusion

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of KTE-X19. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of KTE-X19 are outlined in the IPM. It is recommended that vital signs are recorded before KTE-X19 infusion and then routinely as clinically indicated (eg, fever ≥ 38.3°C).

The IPM must be reviewed prior to administration of KTE-X19.

Research sites should follow institutional guidelines for the infusion of cell products.

6.9.6.5. Requirements to Work-Up Potential Infectious and/or Inflammatory States Prior to KTE-X19 Infusion

In the absence of an identified source of infection (eg, line infection, pneumonia on chest x-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or KTE-X19 consists of:

- Call Kite medical monitor
- Infectious disease service consult (if applicable)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of anti-microbials if clinically feasible):

  ——Blood cultures (aerobic and anaerobic x2 bottles each) and UA and urine culture. Deep/induced sputum culture if clinically indicated.

  ——All indwelling lines, such as central venous catheters, should be examined for any signs of infection, and additional cultures should be drawn from the line.

——Nasopharyngeal-throat swab or equivalent assay for viral infection such asinfluenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus

——Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)

——Collection of appropriate serum viral studies (eg, cytomegalovirus)

- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR shouldbe performed.
- Any additional sign or symptom-directed investigation should be performed asclinically indicated.

Prior to proceeding with conditioning chemotherapy and/or KTE-X19 infusion, the above workup must not suggest the presence of an active infection, and all requirements for conditioning chemotherapy and/or KTE-X19 infusion must be satisfied. If the KTE-X19 infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

- If the above workup was triggered due to CRP > 100mg/L, CRP should be repeated, and if CRP continues to increase significantly, evaluation should be performed for any other potential infectious or inflammatory condition not previously evaluated.

6.9.7. Post-treatment Assessment Period

After completing KTE-X19 infusion and discharged from the hospital, all subjects will be followed in the post treatment assessment period. Counting from day 0 (KTE-X19 infusion), subjects will return to the clinic at the following intervals.

- Day 14 (± 2 days)
- Day 28 (+ 3 days)
- Week 8 (± 1 week)
- Month 3 (± 2 weeks)

Subject will allow key sponsor contacts to continue to access medical records so that information related to subjects health condition and initial treatment response may be obtained.

6.9.8. Long-term Follow-up Period

All enrolled subjects will be followed in the long term follow-up period for survival and disease status if applicable. Subjects will begin the long term follow-up period after they have completed the Month 3 visit of the post treatment assessment period (whether they have responded to treatment or went straight to the month 3 visit due to disease progression)

- Every 3 months (± 2 weeks) through Month 18
- Every 6 months (± 1 month) between Month 24 - Month 60
- Beginning with year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years after the last subject receives their KTE-X19 infusion.

Should the subject fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact the subject will be considered lost to follow-up and no additional contact will be required.

6.9.9. Retreatment

Subjects will be permitted to receive 1 additional KTE-X19 infusion provided the subject achieved remission of leukemia (CR, CRh, or CRi) after the initial KTE-X19 infusion at ≥ month3 disease assessment and subsequently progressed (>5% bone marrow blasts or progression of extramedullary disease per local assessment).

In addition, the subject must meet all of the following criteria:

- All inclusion criteria
  - Note: inclusion criteria 108 only applies if subject must undergo another leukapheresis in order to manufacture another dose of KTE-X19
- All exclusion criteria except for prior KTE-X19 use in this study
- Subject must not have had a grade ≥ 2 KTE-X19-related immediate hypersensitivity reaction
- CD19 tumor expression in bone marrow or peripheral blood must be documented after progression. If CD19 expression is quantified, then there must be ≥ 90% CD19 positive blasts.
- Subject did not experience grade 4 CRS, grade 4 neurologic events, or any grade of edema in the brain with the first KTE-X19 infusion
- Any CRS and neurologic events have fully resolved prior to the retreatment
- Any toxicity related to fludarabine or cyclophosphamide should be resolved to ≤ grade 1 or return to baseline, prior to retreatment, with the exception of clinically insignificant toxicities (eg, alopecia).
- The subject has not received subsequent therapy for the treatment of leukemia
- The subject does not have known anti-KTE-X19 antibodies
- In consultation with the Kite Medical Monitor there is agreement to give the additional KTE-X19 infusion

If the rate of grade ≥ 2 KTE-X19-related immediate hypersensitivity reaction to reinfusion of

KTE-X19 is > 33% after a minimum of 6 subjects, then no additional subjects will be permitted to receive an additional dose of KTE-X19. Incidences of grade ≥ 2 KTE-X19-related immediate hypersensitivity reaction will be monitored each time a subject is retreated. In the cases when 2 or more subjects with grade ≥ 2 KTE-X19-related immediate hypersensitivity reaction have been observed before the 6th subject is retreated, then no additional subjects will be permitted to receive an additional dose of KTE-X19.

A discussion regarding benefits and risks of any additional KTE-X19 dose, including the potential need to undergo leukapheresis a second time for the manufacturing of KTE-X19, should occur with the subject prior to performing any study related procedures or treatment. This conversation should also be recorded in the subject's source document.

Allowance for additional doses is based on clinical experience reported in studies conducted at the pediatric (Lee et al, 2015) and Surgery Branch (Kochenderfer et al, 2015) of the NCI where 6 subjects in total have been retreated upon progression.

Any subject who receives an additional dose will follow the same treatment schedule and procedural requirements per the initial treatment. This includes bridging chemotherapy, CSF prophylaxis and conditioning chemotherapy, unless discussed with the Kite Medical Monitor.

Subjects enrolled in Phase 1 will receive the KTE-X19 dose selected for Phase 2 if they are retreated in Phase 2. If the Phase 2 regimen has not yet been selected, subjects will receive the last KTE-X19 regimen that was determined safe by the SRT or the current dose being evaluated in the study. Subjects enrolled in Phase 2 will receive the KTE-X19 dose at the Phase 2 dose.

7. SUBJECT WITHDRAW

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

7.1. Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

- Adverse Event
- Subject request
- Product not available
- Lost to Follow-up
- Death
- Decision by sponsor

7.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

8. SAFETY REPORTING

8.1. Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered adverse events.

The term "disease progression" or any relapse after a remission should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms of underlying disease should be reported as the primary tumor type (eg, B-cell type acute leukemia).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the Month 3 visit.

8.1.1. Diagnosis Versus Signs and Symptoms

For adverse events, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the adverse event (AE) form. The exception is for CRS where both the diagnosis and signs and symptoms will be captured on the CRF AE form. For signs and symptoms ofthe underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

8.1.2. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an AE. A vital sign result must be reported as an AE

if it is a change from baseline and meets any of the followingcriteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an AE. However, if a clinically significant vital sign abnormality is asign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the CRF.

8.1.3. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significantchange from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an AE if it is a changefrom baseline and meets any of the following criteria:

- Associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia oriron replacement therapy for anemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

8.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject as follows in Table 3:

Table 3. Reporting Requirements for Adverse Events

Subjects who are enrolled, but do not receive KTE-X19 infusion	Subjects who are enrolled and receive KTE-X19 infusion
• Adverse events that occur from enrollment (ie, commencement of leukapheresis) through 30 days after the last study specific procedure (eg, leukapheresis, bridging chemotherapy, conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be reported	• Adverse events that occur from enrollment (ie, commencementof leukapheresis through 3 months after treatment with KTE-X19 infusion will be reported • After 3 months, only targeted AEs will be reported through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, will be reported o Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19-related SAEs.

Abbreviations: GVHD, graft-versus-host disease.
See Section 8.5 for reporting requirements.
See Section 5.7 for targeted concomitant medications and Section 8.5 for targeted SAEs reporting requirements.
See Section 8.5 for reporting requirement for non-serious CRS events Grade ≥ 3.

The investigator must address the below AEs:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, chemotherapy or study procedures
- Action taken

AE grading scale used will be the NCI CTCAE version 4.03. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov). CRS events will also be reported using the grading scale outlined in the KTE-X19 IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) leukapheresis, 2) bridging chemotherapy, 3) CSF prophylaxis, 4) Conditioning chemotherapy, 5) the investigational product (KTE-X19), or any protocol required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between thestudy treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.
The investigator is expected to follow reported AEs until stabilization or resolution. Ifa subject begins a new anti-cancer therapy, the AE reporting period for non-serious adverse events (SAEs) ends at the time the new treatment is started.

8.3. Definition of Serious Adverse Events

A SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization

  ——An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (eg, overnight stay).

  ——Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit or if that event resulted in a prolongation of the existing planned hospitalization.

- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

  ——If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

- The terms "severe" and "serious" are not synonymous. Severity refers to the intensityof an AE according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded on the CRF.
- Progression of the malignancy during the study should not be reported as a AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and indicated as being due to disease progression in the CRF. If the malignancy has a fataloutcome before the end of the SAE reporting period, the event leading to the death must be recorded as an SAE with the outcome of being fatal.

8.3.1. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should bedocumented and reported as a SAE as described in Section 8.5.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care

- Planned hospitalization required by the protocol (eg, for monitoring of the subject or toperform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

8.4. Reporting Deaths

Death must be reported if it occurs during the SAE reporting period, irrespective of anyintervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of KTE-X19 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the SAE reporting period requires expedited reporting within 24 hours only if it is consideredrelated to treatment.

Deaths that occur during the protocol-specified AE reporting period that are attributed bythe investigator solely to progression of underlying leukemia should be recorded as SAEs with the preferred term "chronic lymphocytic leukemia" and must be reported immediately to the sponsor.

Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. Every effort shouldbe made to capture the established cause of death, which may become available later on (eg, after autopsy).

8.5. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject. Unless otherwise indicated in Table 4 below, all SAEs will be reported within 24 hours and recorded in the CRF.

Table 4. Reporting Requirements for Serious Adverse Events

Subjects who are screen-fails or who are enrolled, but do not receive KITE-X19 infusion	Subjects who are enrolled and receive KITE-X19 infusion

• SAEs that occur from signing of the latest informed consent form through 30 days after the last study specific procedure (eg, screening procedure, leukapheresis, bridging therapy, conditioning chemotherapy) or until initiation of a new anti-cancer therapy, whichever occurs first, will be recorded in the CRF	• All SAEs that occur from signing of the screening informed consent form through 3 months after the KITE-X19 infusion or until initiation of another anti-cancer therapy, whichever occurs first • After 3 months, only targeted SAEs will be reported through 24 months after KITE-X19 infusion or disease progression, whichever occurs first o Targeted adverse events include central neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. • Subjects who receive an allogeneic SCT will only be followed for KTE-X19 related SAEs. Reporting of these SAEs will commence at the time the SCT preparative regimen commences through 24 months after KTE-X19 infusion or disease progression, whichever occurs first, within 24 hours using the SAE Report Form and in the CRF. • All SAEs deemed related to KITE-X19 infusion regardless of time period • All deaths that occur from signing of the ICF through the end of study will be recorded in the CRF

Abbreviations: SAE, serious adverse event; GVHD, graft-versus-host disease; CRF, case report form; ICF, informed consent form.
See Section 5.8 for concomitant medication and Section 8.2 for targeted AE reporting requirements.

All SAEs must be submitted to Kite via email to safety_fc@gilead.com within 24 hoursfollowing the investigator's knowledge of the event and using a SAE report form.

Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines.

8.6. Pregnancy and Lactation

There is no relevant clinical experience with KTE-X19 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of child bearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after conditioning chemotherapy dosing. Male subjects are recommended to notfather a child for 6 months after the conditioning chemotherapy dosing.

If a pregnancy occurs in a female subject enrolled into the study, or a female partner of a male subject within 6 months of completing the KTE-X19 infusion, the pregnancy must be reported to the key sponsor contact. Information regarding the pregnancy and/or the outcome may be requested by the key sponsor.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of conditioning chemotherapy through 6 months for female subjects and for 6 months for the female partner of the male subjects.

The pregnancy should be reported to the key sponsor contact within 24 hours of the investigators

knowledge of the pregnancy event.

If a lactation case occurs while the female subject is taking protocol required therapies report the lactation case to the key sponsor contact.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol required therapies through 6 months.

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

8.7. Safety Review Team and Dose-limiting Toxicity

The SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will be specifically chartered to review safety data from the first 3-12 subjects treated with KTE-X19 and make recommendations on further study conduct and progression of the study based on the incidence of KTE-X19 DLT and review of serious AEs.

Dose-limiting toxicity is defined as the following KTE-X19-related events with onset within the first 28 days following KTE-X19 infusion:

- Grade 4 hematologic toxicity lasting more than 30 days (except lymphopenia) if not attributable to underlying disease
- All KTE-X19-related grade 3 non-hematologic toxicities lasting for > 7 days and all KTE-X19-related grade 4 non-hematologic toxicities regardless of duration are considered DLTs, with the exception of the following which are not considered DLTs:

  ——Aphasia/dysphasia or confusion/cognitive disturbance which resolves to at least grade1 or baseline within 2 weeks and to at least baseline within 4 weeks.

  ——Fever grade 3 or 4

  ——Immediate hypersensitivity reactions occurring within 2 hours of KTE-X19 infusion (related to KTE-X19 infusion) that are reversible to a grade 2 or less within 24 hours of KTE-X19 infusion with standard therapy

  ——Renal toxicity which requires dialysis for ≤ 7 days

  ——Intubation for airway protection if ≤ 7 days

  ——Tumor lysis syndrome (TLS) including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal function, hyperuricemia)

  ——Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation, provided there is resolution to ≤ grade 2 within 14 days

  ——Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to ≤ grade 3 within < 72 hours

- ——Hypogammaglobulinemia grade 3 or 4

- ——Grade 3 nausea and/or anorexia

CRS will be graded according to a revised grading system (Lee et al, 2014). AEs attributed to CRS will be mapped to the overall CRS grading assessment for the determination ofDLT. Consistent with non-CRS toxicities, all occurrences of grade 3 CRS of duration > 7 days and all occurrences of grade 4 CRS are considered DLTs, other than occurrences of CRS due to the exceptions listed above.

Three subjects will initially be enrolled to evaluate the safety of the KTE-X19 regimen. Subjects will be evaluated for DLTs within the first 28 days following the completion of the KTE-X19 infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 9.4. The SRT will make recommendations based on the incidence of DLT and overall safety profile of the KTE-X19 regimen as outlined below**:**

- If the subject incidence of DLT is 0 of 3 subjects, the SRT may recommend either

  - ——proceeding to Phase 2 at 2 x 10^6 anti-CD19 CAR T cells/kg; or

  - ——accrual of additional subjects in Phase 1 to further characterize risk/benefit prior to Phase 2

- If the subject incidence of DLT is 1 of 3 subjects, the SRT may recommend either

  - ——accrual of an additional 3 subjects at the same cell dose with re-evaluation of the incidence of DLT after a total of 6 subjects in the DLT evaluable set have been assessed for DLT. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT in the 6 subjects is ≤ 1 of 6 subjects; or

  - ——evaluation of a lower dose of 1 x 10^6 anti-CD19 CAR T cells/kg in an additional set of 3-6 subjects. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT is < 33%.

- If the subject incidence of DLT is ≥ 2 of 3 subjects, a lower dose of 1 x 10^6 anti-CD19 CAR T cells/kg in an additional set of 3-6 subjects will be explored. In this case, the SRT may recommend accrual to Phase 2 if the cumulative incidence of DLT is < 33%.

If the conditioning chemotherapy regimen and KTE-X19 dose evaluated in Phase 1 is determined to be safe based on the incidence of DLT, up to approximately 40 additional subjects (high and non-high burden disease) may be enrolled at 2 x 10^6 anti-CD19 CAR T cells/kg, 1 x 10^6 anti-CD19 CAR T cells/kg, or 0.5 x 10^6 anti-CD19 CAR T cells/kg prior to commencing Phase 2. The data from these additional subjects will be reviewed by the SRT who will provide recommendations for dose for Phase 2. Further details to be outlined in the SRT Charter.

Based on the review of all available safety and efficacy data, the benefit/risk ratio was considered most favorable at the dose of 1 x 10^6 anti-CD19 CAR T cells/kg, therefore thedose of 1 x 10^6 anti-CD19 CAR T cells/kg was considered the recommended Phase 2 dose.

The final decision to commence Phase 2 and the dose selected for Phase 2 was formally

communicated to participating sites in a separate communication.

8.8. Data Safety Monitoring Board

An independent DSMB will be chartered to review safety datato make trial conduct recommendations. The DSMB will review safety data in an interim analysis during the Phase 2 portion of the study. For this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion. During Phase 2, Kite Pharma or delegate will submit SAEs or suspected unexpected serious adverse reactions (SUSARs) to the DSMB chair for risk benefit analysis. The DSMB Chair will review reportedSAEs at least monthly and SUSARs as soon as received.

8.9. Criteria to Pause Enrollment

Study enrollment will be paused in Phase 1 (DLT Evaluation Period) following any grade 5 AE that occurs within 30 days of KTE-X19 dosing regardless of attributions. The DLT evaluation period is now complete.

As part of its oversight of the study, the DSMB also will assess criteria to pause enrollment in Phase 2 after 10, 20, and 35 subjects enrolled in Phase 2 have been treated with KTE-X19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following is met:

Subject incidence of the following grade 4 KTE-X19-related AEs lasting more than 7 days is >33%:

- Neurologic events
- CRS (per Lee 2014 criteria)
- Other non-hematological serious AE
- Infection (treatment-related)

9. STATISTICAL CONSIDERATIONS

9.1. Hypothesis

This study is designed to differentiate between a treatment that has a true overall complete remission rate of 40% or less and a treatment with a true overall complete remission rate of 65% or more. The hypothesis is that the overall complete remission rate to KTE-X19 is significantly greater than 40%.

A secondary endpoint, MRD Negative Rate, will be tested againsta MRD-negative rate of 30% if the testing of the overall complete remission rate is significant. The hypothesis is that the MRD-negative rate to KTE-X19 is significantly greater than 30%.

9.1.1. Covariates

The primary endpoints and selected secondary endpoints will be evaluated in subgroup analysis by subjects with or without prior blinatumomab, and by subjects with or without prior inotuzumab. Such subgroup analyses may not be performed if too few (eg, n < 5) subjects in the mITT set have received prior blinatumomab or prior inotuzumab at the time of the analysis.

Additional covariates and subgroup analyses will be outlined in the Statistical Analysis Plan.

9.2. Sample Size Considerations

The anticipated enrollment in this study is approximately 100 subjects.

The primary efficacy endpoint and all analyses based on the response will be based on a mITT population consisting of all subjects who receive any dose of KTE-X19 in Phase 2.

This study uses a single-arm design to test for an improvement in overall complete remission rate. For the test of efficacy this study has 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. A step-down test of the secondary endpoint MRD-negative rate will be performed against a MRD-negative rate of 30% if the testing of the overall complete remission rate is significant.

In Phase 1, the SRT will review safety data after 3 subjects in the DLT evaluable set (see Section 9.4) have had the opportunity to be followed for 28 days after the KTE-X19 infusion.If the conditioning regimen and KTE-X19 dose evaluated in Phase 1 is determined to be safe based on the incidence of DLT, up to approximately 30 additional subjects may be enrolled to further evaluate safety prior to commencing Phase 2.

During Phase 2, one interim and one primary analyses will be performed. The interim analysis is for safety only and will occur after 20 subjects have been treated with KTE-X19 and have had the opportunity to be followed for 30 days after the KTE-X19 infusion. The primary analysis will occur when the overall study enrollment is complete and all subject in the mITT set have had the opportunity to complete the month 6 disease assessment. 65% Approximately

100 subjects may be enrolled into the entire study. At the time of the primary analysis, in the event that either less than or more than 50 subjects are eligible for the mITT set, all mITT eligible subjects will be included in the analysis.

9.3. Statistical Assumptions

This study assumes that the underlying overall complete remission rate (in the absence of treatment with investigational therapy) is 40%. For MRD-negative rate, it is assumed that the underlyingresponse rate (in the absence of treatment with investigational therapy) is 30%.

9.4. Analysis Subsets

KTE-X19 will be administered as a single infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg or 1×10^6 anti-CD19 CAR T cells/kg or 0.5×10^6 anti-CD19 CAR T cells/kg . For subjects weighing greater than 100 kg, a maximum flat dose of 2×10^8 or 1×10^8 or 0.5×10^8 anti-CD19 CAR T cells/kg may be administered. Full Analysis Set: the full analysis set will consist of all enrolled subjects and will be used for summaries of subject disposition.

mITT set: the modified intention-to-treat set will consist of all subjects enrolled in Phase 2 and treated with KTE-X19. The mITT analysis set will be used forall efficacy analyses unless otherwise specified.

DLT-evaluable set: All Phase 1 subjects treated with the target KTE-X19 dose and followed for at least 28 days, or received a dose of KTE-X19 lower than the target dose but experienced a DLT during the 28 day post infusion period, up to the time at which a dose level has been evaluated for DLT and deemed safe. Additional Phase 1 subjects enrolled and treated subsequently for the purpose of assessment of the overall safety in the same dose level or a lower dose level will not be considered as part of the DLT evaluable set, and DLT will not be assessed for such subjects.

Safety analysis set: the safety set is defined as all subjects treated with any dose of KTE-X19.

9.5. Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and Trial Integrity Document.

9.6. Interim Analysis

During Phase 1, the SRT will review safety data after 3 DLT evaluable subjects have had the opportunity to be followed for 28 days after the KTE-X19 infusion. The SRT will review the safety data and make recommendations on further study conduct and progression of the study.

During Phase 2, the DSMB will review safety data after 20 Phase 2 subjects have been treated and followed for 30 days. The DSMB will also review SAEs on a monthly basis prior to the primary analysis. The DSMB may request additional safety data or modifying the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may not have undergone completion of data cleaning procedures in

order to facilitate timelines for DSMB review.

9.7. Planned Method of Analysis

The primary efficacy analysis will be performed when all subject in the mITT set have had the opportunity to complete the month 6 disease assessment. Additional analyses may occur after the primary analysis has been completed. These additional analyses will be descriptive and will occur after inferential testing has been performed. The final analysis will occur when all subjects have completed the study.

9.7.1. Overall Complete Remission Rate

The incidence of response and exact 2-sided 95% confidence intervals will be generated. An exact binomial test will be used to compare the observed response rate to a response rate of 40%.

9.7.2. Duration of Remission

DOR: for subjects who experience CR or CRi per independent review, DOR is defined as the time between their first complete response per independent review to relapse or any death in the absence of documented relapse. Relapse is defined in Appendix 1. Subjects who do not meet the criteria for relapse and who have not died will be censored at the last evaluable disease assessment or disease status follow up assessment. Disease assessments obtained after new anti-cancer therapies (including allogeneic SCT) will not contribute to the derivation of duration of remission. The DOR for subjects that undergo allogeneic SCT while inremission is censored at the date of the allogeneic SCT; the DOR for subjects that undergo othernew anti-cancer therapies in the absence of relapse is censored at the last evaluable disease assessment prior to the new anti-cancer therapies. Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for DOR. Estimates of the proportion of subjects remained as in complete remission at 3-month intervals will be provided.

A sensitivity analysis of DOR will be conducted in which non-disease mortality will be considered a competing risk. A competing-risk analysis method (Klein and Moeschberger 2005; Putter et al, 2007) will be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence non-disease related mortality (the competing risk) will be estimated along with 2-sided 95% confidence intervals at 3-monthly time intervals.

9.7.3. MRD-negative rate

The incidence of MRD-negative rate and exact 2-sided 95% confidence intervals will be generated. If the statistical testing of the primary endpoint (overall complete remission rate) is significant, an exact binomial test will be used to compare the observed MRD-negative rate to a rate of 30% at a one-sided alpha level of 0.025.

9.7.4. CR Rate, CRi Rate, and DOR to Treatment Among Subjects Retreated with KTE-X19 for Progressive Disease after Initial Remission

The incidence of CR rate, and CRi rate, and exact 2-sided 95% confidence intervals will be generated.

DOR to retreatment is defined only for subjects who experience a CR or CRi to retreatment and is the time from the first complete remission after retreatment to relapse after retreatment or death due to disease relapse. The competing-risk analysis method will be used to estimate the cumulative incidence of relapse after retreatment.

9.7.5. Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

9.7.6. Allogeneic Stem Cell Transplant Rate

The incidence of Allogeneic SCT in the mITT set and 2-sided 95% confidence intervals will be generated.

9.7.7. Safety

Subject incidence rates of AEs including all, serious, fatal, CTCAE version 4.03 grade 3 or higher and treatment related AEs reported throughout the conduct of the study will betabulated by preferred term and/or system organ class. CTCAE grade changes in safety laboratory values will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths and treatment related SAEs will be provided.

9.7.8. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject receives their KTE-X19 infusion. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

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11. APPENDICES

Appendix 1. OVERALL DISEASE RESPONSE CLASSIFICATION

Response	BM		Peripheral Blood [d]		CNS EMD		Non-CNS EMD [b, e]
CR	≤ 5% [f]	*and*	ANC ≥ 1,000 and Plt ≥ 100,000	*and*	CNS-1	*and*	CR [c]
CRi			ANC ≥ 1000 and Plt < 100,000 OR ANC < 1000 and Plt ≥ 100,000				
CRh			ANC ≥ 500 and Plt ≥ 50,000 but not CR				
Blast-free hypoplastic or aplastic BM			Any values not meeting criteria for CR, CRi or CRh				
PR	All criteria for CR, CRi, CRh or blast-free hypoplastic or aplastic bone marrow are met					*and*	PR
Relapse	>5% [f]	*or*	Circulating leukemia present [a]	*or*	CNS-2 or CNS-3	*or*	PD
No response	All required assessments are performed with failure to attain the criteria needed for any response category						
Unknown	Assessment is not done, incomplete, or indeterminate Note: Overall disease response can be assessed as 'Relapsed disease' if any single element of disease response assessment shows relapse, other Unknown elements of disease response assessment do not need to be evaluated						

ANC = absolute neutrophil count; BM = bone marrow; EMD = extramedullary disease; Plt = platelets;

a No circulating leukemia is < 1% circulating blasts by morphology; Circulating leukemia is ≥ 1% circulating blasts by morphology; If ≥ 1% blast by morphology and there is no other evidence of leukemia, then flow or molecular studies should be conducted to confirm that blasts are leukemia.

b See Overall Non-CNS EMD table (Appendix 2)

c If baseline EMD is present, then images must show CR. If no baseline EMD, then images are not required, but if performed, must show CR per Appendix 2.

d ANC and Plt: The units for Plt and ANC are per uL. ANC and Plt values should be evaluated every time a BM evaluation is performed. If not done, ANC and Plt values used for response assessment can be from any time 7 days prior to the BM result to any time after the BM result.

e In subjects evaluated for non-CNS EMD, imaging and bone marrow results used for assessment of overall disease response must be within 30 days of each other

f Blasts by morphology in BM

Appendix 2. EXTRAMEDULLARY DISEASE RESPONSE

Subjects with known baseline extramedullary disease (EMD) should have disease assessed by the investigator per the Table below at baseline and post-baseline with an imaging modality appropriate for the anatomical site and clinical scenario (eg, MRI for CNS lesion, ultrasound for testicular lesion, CT for intra-abdominal or thoracic lesion) and with the same imaging modality throughout.

Response [a]	PET Baseline, On-study		Baseline lesion(s) (by CT or MRI) [b]		New Lesion(s)

CR	Neg, N/A	*and*	All of:
			• Disappearance of measurable and non-measurable nodal lesions:
			  ○ Nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD
			  ○ Nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0cm in their short axis after treatment
			• If testes, spleen and/or liver involvement, they must be normal size by imaging or physical examination.
				and	No

	Pos, Neg	*and*	Any	*and*	No
PR	Any	*and*	All of: • ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant masses. Dominant masses should be clearly measurable in at least 2 perpendicular dimensions, and should be from different regions of the body if possible. • No increase in size of liver or spleen by imaging or physical exam • If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for a single nodule.	*and*	No
SD	Does not meet the criteria for CR, PR, or PD				
PD	Any	*and*	At least one of the following: • ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node. • At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis • Greater than or equal to a 50% increase in size of splenic, hepatic or any other non-nodal lesion.	*or*	Yes

Neg = Negative; Pos = Positive; N/A = Not applicable
a Modified Revised IWG Criteria (Cheson et al, 2007)
b see Section 6.7.2 of protocol for details.

Appendix 3. HOSPITALIZATION FOR GERMAN SUBJECTS FOLLOWING KTE-X19 INFUSION

The post-infusion monitoring of subjects, described in section 6.9.6.2 in this protocol, willbe extended by monitoring on Day 8, Day 9, and Day 10. The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs, blood draw for chemistry panel with CRP, ferritin (and LDH if indicated), blood draw for CBC w/differential, and neurological assessment. Any observed toxicity will be managed according to this protocol.

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	KTE-X19
Protocol:	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)
Version Number:	Version 2.0
Release Date:	06 July 2020
Replaces Previous Version(s):	Version 1.0; dated 16 May 2018

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINTIONS OF TERMS

ADaM	Analysis data model
AE	Adverse event
ALL	Acute Lymphoblastic Leukemia
allo SCT	Allogeneic stem cell transplant
BFBM	Blast-free hypoplastic or aplastic bone marrow rate
CAR	Chimeric antigen receptor
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRh	CR with partial hematological recovery
CRi	CR with incomplete hematologic recovery
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DMP	Data management plan
DOR	Duration of response
DORR	Duration of response to retreatment
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EQ-5D-5L	European quality of life five dimensions five levels
FAS	Full analysis set
GVHD	Graft versus host disease
HDT	High-dose therapy
HLGT	High-level group term
IVIG	Intravenous immunoglobulin
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MLL	Mixed lineage leukemia
MRD	Minimal residue disease
NE	Neurologic event
OCR	Overall complete remission
OS	Overall survival

PFS	Progression-free survival
PR	Partial remission
PRO	Patient reported outcome
RCR	Replication-competent retrovirus
RFS	Relapse free survival
r/r	Relapsed/refractory
SAE	Serious adverse event
SCT	Stem cell transplant
SDTM	Study data tabulation model
SOC	System organ class
SOP	Standard operating procedures
SMQ	Standardized MedDRA query
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TFL	Tables, figures, and listings
TID	Trial integrity document
TKI	Tyrosine kinase inhibitor
VAS	Visual analog scale
WHO	Would health organization

1. INTRODUCTION

This statistical analysis plan provides the prespecification and details for the statistical analyses outlined within protocol KTE-C19-103 entitled “A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)”. The scope of this plan includes the interim, primary, and final analyses that are planned.

2. OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of KTE-X19 and determine the dosage for Phase 2.

The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission (OCR) rate defined as the proportion of subjects achieved either complete response (CR) or CR with incomplete hematologic recovery (CRi) in this study. Secondary objectives will include assessing the safety and tolerability of KTE-X19 and additional efficacy endpoints.

3. STUDY OVERVIEW

3.1. Study Design

Study KTE-C19-103 is a Phase 1/2 multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r ALL. The trial will be separated into 2 distinct phases designated as Phase 1 and Phase 2.

During Phase 1, approximately 3 to 12 subjects with high-burden [M3 marrow (> 25% leukemic blasts) or ≥ 1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for dose-limiting toxicity (DLT) will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review the safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. Up to approximately 40 additional subjects with high- or low-burden disease may be enrolled to further assess safety in Phase 1. The DLT definition and assessment is described in the study protocol.

During Phase 2, approximately 50 subjects with r/r ALL treated with KTE-X19 will be assessed to evaluate the efficacy and safety of KTE-X19. One interim and one primary analysis will be performed. A Data Safety Monitoring Board (DSMB) will review safety data after 20 subjects in Phase 2 have been treated and followed for 30 days.

The primary analysis will occur when the overall study enrollment is complete, and the last subject treated with KTE-X19 has had the opportunity to complete the 6-month disease assessment. The final analysis will occur when all subjects have completed the study.

3.2. Hypothesis

This study is designed to differentiate between a treatment that has a true OCR rate of 40% or less and a treatment with a true OCR rate of 65% or more. The hypothesis is that the OCR rate with KTE-X19 treatment is significantly greater than the historical control rate of 40%, ie,

$$H_0: p \leq 0.4 \; vs. \; H_1: p \; > 0.4$$

3.3. Sample Size Considerations

Three to 12 subjects will be enrolled to evaluate for DLT in Phase 1, and up to approximately 40 additional subjects will be enrolled into Phase 1 of this study.

If the study proceeds to Phase 2, approximately 50 subjects will be enrolled into Phase 2. Approximately 100 subjects may be enrolled and treated in the entire study (both Phase 1 and Phase 2).

KTE-X19 doses will range from 0.5 x 10^6 to 2 x 10^6 cells/kg. For the Phase 1 portion of the study and the evaluation of DLT, the doses are 2.0 x 10^6 anti-CD19 CAR T cells/kg, 1.0 x 10^6 anti-CD19 CAR T cells/kg, or 0.5 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8, 1 x 10^8, or 0.5 x 10^8 anti-CD19 CAR T cells will be administered.

Efficacy analyses will be based on a modified intent-to-treat (mITT) population consisting of all subjects enrolled in the Phase 2 portion of the study who receive KTE-X19 at any dose.

Efficacy analyses may also be based on a full analysis set (FAS) population consisting of all subjects enrolled in the Phase 2 portion of the study.

Safety analyses will be based on all subjects dosed with KTE-X19.

DLT analyses will be based on the DLT-evaluable analysis set, defined in Section 6.7.

This study uses a single-arm design to test for an improvement in OCR rate. A sample size of 50 KTE-X19 subjects in Phase 2 provides approximately 93% power to distinguish between an active therapy with a 65% true OCR rate from a therapy with a response rate of 40% or less, with the one-sided alpha level of 0.025. A step-down test of the secondary endpoint minimal residual disease negative (MRD−) rate will be performed against an MRD− rate of 30% if the testing of the OCR rate is significant. EAST version 6 was used to evaluate the operating characteristics of this design.

The hypothesis of MRD- will only be performed if the primary efficacy endpoint OCR rate reaches statistical significance, so that the family-wise type I error will be controlled at one-sided 2.5% level under this hierarchical testing scheme.

During Phase 2, 1 interim and 1 primary analysis will be performed.

- The interim analysis will occur after 20 subjects in the mITT analysis set have had the opportunity to be followed for 30 days; this analysis will be for the assessment of safety only. The DSMB will review the 20-patient interim analysis.

- The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT analysis set has had the opportunity to complete the 6-month disease assessment after KTE-X19 infusion.

At the time of the primary analysis, if either less than or more than 50 subjects are eligible for the mITT analysis set, all mITT-eligible subjects will be included in the analysis.

3.4. Statistical Assumptions

This study assumes that the underlying overall complete remission rate (in the absence of treatment with investigational therapy) is 40% and that an improvement in the overall complete remission rate to 65% provides clinically meaningful benefit. The responses from subjects in the study population are assumed to be independent and follow binomial distribution; therefore, an exact binomial test will be used to test the statistical hypothesis.

For MRD− rate, it is assumed that the underlying response rate (in the absence of treatment with investigational therapy) is 30%.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

Primary endpoint (Phase 1): The incidence of adverse events (AEs) defined as DLTs in the DLT-evaluable set

Primary endpoint (Phase 2): OCR (CR + CRi) rate per independent review

Secondary endpoints (Phase 2, unless noted):

- MRD− remission rate
- CR rate per independent review
- CRi rate per independent review
- Duration of Remission (DOR) per independent review
- OCR (CR + CRi) rate per investigator review
- Allogeneic stem cell transplant (allo-SCT) rate
- Rate of MRD− CR
- Rate of MRD− CRi
- Overall survival (OS)
- Relapse-free survival (RFS)
- Incidence of AEs and clinically significant changes in safety laboratory values
- Incidence of anti-CD19 CAR antibodies
- Changes over time in the EQ-5D scale score and EQ-5D visual analogue scale (VAS) score

Exploratory endpoint:

- The OCR (CR + CRi) rate, rate of MRD negative remission, and DOR among subjects retreated with KTE-X19
- Survival rate and non-relapse survival rate 100 days after allo-SCT
- CR with partial hematological recovery (CRh)
- Blast-free hypoplastic or aplastic bone marrow rate (BFBM)

- Rate of MRD− CRh
- Rate of MRD− BFBM
- Partial remission (PR) rate
- Level and activity of CAR T cells, as well as presence and status of CD19+ cells in blood and bone marrow
- Levels of cytokines in serum and cerebrospinal fluid (CSF)

Endpoints related to product characterization (level and activity of CAR T cells), presence and status of CD19+ cells in blood and bone marrow, as well as analyses related to these endpoints will be described in a supplemental statistical analysis plan.

4.2. Covariates

The following baseline covariates may be used to examine efficacy and/or safety in subgroups or covariate analyses:

- Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0, 1)
- Age at baseline (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race: white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other (categories may be collapsed or expanded based on accrual)
- Region (North America, Europe)
- Relapsed or refractory (r/r) Subgroup (primary refractory [refractory to first-line therapy], first relapse if duration of first remission was < 12 months, r/r to 2nd or greater line therapy, r/r after allo-SCT)
- Prior blinatumomab treatment (yes, no)
- Prior inotuzumab treatment (yes, no)
- Prior allo-SCT (yes, no)
- Extramedullary disease (yes, no)
- Lines of prior therapies (1, 2, > 2; categories may be modified based on accrual)
- % bone marrow blasts at screening (< 50%, ≥ 50%)

- Peripheral blasts (0, > 0 to 1000, > 1000 blasts/mm^3)
- Normal karyotype
- CD19 expression based on central read (positive, negative)
- Philadelphia chromosome t(9;22) (yes, no)
- Mixed lineage leukemia (MLL) translocation t(4;11) t(8;14) (yes, no)
- Complex karyotype (≥ 5 chromosomal abnormalities) (yes, no)
- Low hypodiploidy (30-39 chromosomes) (yes, no)
- Near triploidy (60-78 chromosomes) (yes, no)
- Bridging chemotherapy (yes, no)

Covariate levels that are sparse may be collapsed for purposes of statistical modeling.

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs when the subject commences leukapheresis.

Study Day 0: Study Day 0 is defined as the day the subject received the first KTE-X19 infusion. The day prior to Study Day 0 will be Study Day −1. Any days after enrollment and prior to Study Day −1 will be sequential and negative integer-valued.

Baseline: The baseline value is defined as the last value taken prior to conditioning chemotherapy.

Study therapy: Study therapy includes bridging chemotherapy, CSF prophylaxis, conditioning chemotherapy, and KTE-X19.

On-study: time from enrollment to the last date of contact or death

r/r subgroup: The r/r subgroups are defined as below:

- r/r disease after allo-SCT: A subject is considered to be r/r after allo-SCT if the subject experienced relapse or failed to achieve CR after allo-SCT
- Primary refractory: A subject is considered to be primary refractory if the subject failed to achieve CR to first-line therapy.
- r/r to 2nd- or greater-line therapy: A subject is considered to be r/r to 2nd- or greater-line therapy if the subject failed to achieve CR or relapsed after the 2nd- or greater-line therapy.
- First relapse with first remission ≤ 12 months: A subject is considered to be first relapse with first remission ≤ 12 months if the subject achieved CR but relapsed within 12 months.

Actual follow-up time: Actual follow-up time among all subjects treated with KTE-X19 is calculated as the time from the first dose of KTE-X19 to the date of death or last date known to be alive, whichever is later.

Potential follow-up time: Potential follow-up time is defined as the time from the KTE-X19 infusion to the data cutoff date for the analysis.

5.2. Safety

Treatment-emergent AE (TEAE): Any AE with an onset on or after the KTE-X19 infusion. For subjects who are retreated with KTE-X19, TEAEs during the retreatment period may be summarized separately.

KTE-X19 Retreatment period (defined only for subjects who undergo retreatment with KTE-X19): The KTE-X19 retreatment period begins on the day of the first dose of conditioning chemotherapy for retreatment or retreatment enrollment date, whichever is earlier.

Deaths: All deaths that occur after leukapheresis will be summarized. For subjects who undergo retreatment with KTE-X19, deaths that occur during the retreatment period may also be summarized separately.

AEs of special interest: AEs of interest for KTE-X19 treatment include the following categories:

Identified risks:

- Cytokine release syndrome (CRS)
- Neurologic events, including cerebral edema
- Cytopenias (thrombocytopenia, neutropenia, and anemia)
- Infections
- Hypogammaglobulinemia

Potential risks:

- Secondary malignancy
- Immunogenicity
- Replication-competent retrovirus (RCR)
- Tumor lysis syndrome
- Graft-versus-host disease (GVHD)

Time to onset and duration of the important identified risks CRS and neurologic events will be summarized.

CRS will be identified via collection of the syndrome on a case report form (CRF) specifically designed to record CRS. Specific individual symptoms of CRS (eg, fever) collected on the AE log will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and linked to the corresponding CRS episode. Individual symptoms of CRS will be graded per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, and CRS as a syndrome will be graded per modified Lee criteria {Lee 2014}. In the modified grading scale, neurologic AEs are not to be reported as part of the CRS syndrome and will be reported separately and summarized separately.

Neurologic events will be identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy {Topp 2015}. The search strategy focuses on central nervous system (CNS) toxicity, without regard to relatedness, temporal relationship, or concomitant conditions (eg, CRS). Additionally, the MedDRA system organ classes (SOCs) of Psychiatric Disorders and Nervous System Disorders will be reviewed for additional events; these events will then be evaluated for potential inclusion as neurologic AEs.

Immunogenicity will be identified by the development of antibodies against CAR-expressing cells using flow cytometry. In addition, a manual review of the AE terms indicative of autoimmunity will be performed, including infusion-related events and anaphylactic reactions among subjects who test positive for anti-CD19 CAR antibodies.

For other AEs of special interest, specific AEs may be mapped to these categories using dictionary-coded event terms and standardized MedDRA queries (SMQs) or other search strategies. Specific definitions of these events and the coded terms to which they correspond will be provided in the Program Safety Analysis Plan.

Duration of an AE of interest: The duration of an AE of interest may be derived only among subjects for whom all events of the class have resolved by the analysis data cutoff date. The duration is defined as the stop day of the last AE in the event class – the start day of the first AE in the event class + 1.

5.3. Efficacy

OCR (CR + CRi) rate: The proportion of subjects with either CR or CR with incomplete hematologic recovery (CRi) per independent review or investigator review prior to the subsequent anticancer therapy and allo-SCT.

CR rate: The proportion of subjects who experience CR, which will be analyzed per independent review and investigator review separately.

DOR: DOR is defined only for subjects who experience CR or CRi per independent review or investigator review and is the time from the first CR or CRi to relapse or death from any cause in the absence of documented relapse. Subjects not meeting the criteria for relapse and who have not died by the analysis data cutoff date will be censored at their last evaluable disease assessment date or disease status follow-up assessment. DOR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy and allo-SCT (excluding resumption of tyrosine kinase inhibitor (TKI)). Disease assessments obtained after new anticancer therapies including allo-SCT will not contribute to the derivation of DOR. The DOR for subjects who undergo allo-SCT while in remission will be censored at the last evaluable disease assessment prior to the allo-SCT; the DOR for subjects who undergo other new anticancer therapies in the absence of documented relapse is censored at the last evaluable disease assessment prior to the new anticancer therapies. A sensitivity analysis will be conducted in which the DOR in subjects who received subsequent allo-SCT will not censor at the last disease assessment prior to SCT, and instead, the response after SCT will contribute to the derivation of DOR.

In subjects who resume TKI therapy, disease assessments obtained after resumption of TKI therapy will contribute to the derivation of DOR. A sensitivity analysis will be conducted in which the DOR in such subjects is censored at the last evaluable disease assessment prior to the resumption of TKI therapy.

A sensitivity analysis may be conducted in which receiving allo-SCT or subsequent anti-cancer therapy are considered events.

Further details on the derivation of DOR are provided in Appendix 2.

DOR analysis will be conducted per independent review and investigator review separately. Both the mITT analysis set and the full analysis set (FAS) will be used.

MRD− remission rate: The incidence of an MRD− response. MRD− is defined as MRD < 10^{-4}. MRD− remission rate will be estimated for all dosed subjects, subjects with a CR, subjects with a CRi, and subjects with either a CR or a CRi combined. MRD− remission rate will also be estimated for subjects with CRh and blast-free hypoplastic or aplastic bone marrow.

Allo-SCT rate: the incidence of allo-SCT among subjects who have been treated with KTE-X19.

OS: OS for the mITT analysis set is defined as the time from the KTE-X19 infusion to the date of death from any cause.

OS for all enrolled subjects in the FAS is defined as the time from enrollment to the date of death from any case.

Subjects who have not died by the analysis data cutoff date will be censored at the last date known to be alive or the data cutoff date, whichever is earlier.

Further details on the derivation of OS and the specific data modules that will be used to derive the last date known to be alive are provided in Appendix 2.

Relapse-free Survival (RFS): RFS for the mITT analysis set is defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause. RFS for all enrolled subjects in the FAS is defined as the time from enrollment to the date of disease relapse or death from any cause. Subjects who have not achieved a CR or CRi at the analysis data cutoff will be evaluated as having an RFS event at Day 0 for RFS analysis on mITT set, or at the date of enrollment for RFS analysis on FAS set. Subjects not meeting the criteria for relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date or disease status follow up assessment. RFS will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy and allo-SCT (excluding resumption of a TKI). A sensitivity analysis will be conducted in which the RFS in subjects who received subsequent allo-SCT will not be censored at the last disease assessment prior to SCT, and instead, the response after SCT will contribute to the derivation of RFS.

In subjects who resume TKI therapy, disease assessments obtained after resumption of TKI therapy will contribute to the derivation of RFS. A sensitivity analysis will be conducted in which the RFS in such subjects is censored at the last evaluable disease assessment prior to the resumption of TKI therapy. Further details on the derivation of RFS are provided in Appendix 2.

OCR (CR + CRi) rate for retreatment: the incidence of OCR rate for subjects in the retreatment period.

DOR to retreatment (DORR): DORR is defined only for subjects who experience OCR to retreatment and is the time from the first OCR after retreatment to relapse after retreatment or death from any cause in the absence of documented relapse.

MRD− remission rate for subjects with CRh: The incidence of an MRD− response for subjects who had the best response of CRh. MRD− is defined as MRD < 10^{-4}.

MRD− remission rate for subjects with blast-free hypoplastic or aplastic bone marrow: The incidence of an MRD− response for subjects who had the best response of blast-free hypoplastic or aplastic response. MRD− is defined as MRD < 10^{-4}.

Mortality rate 100 days after allo-SCT: The rate of deaths within 100 days after allo-SCT for subjects who undergo allo-SCT.

PR rate: The incidence of PR.

Changes over time in the EQ-5D scale score and EQ-5D VAS score: The changes of the EQ-5D scale score and EQ-5D VAS score at each assessment time compared to baseline will be presented.

6. ANALYSIS SUBSETS

The following analysis sets are defined for each study phase separately.

6.1. mITT

The mITT analysis set will consist of all subjects enrolled and treated with KTE-X19 in Phase 2. This analysis set will be used for all efficacy analyses unless specified otherwise.

6.2. Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of KTE-X19.

6.3. FAS

The FAS will consist of all enrolled (leukapheresed) subjects and will be used for the summary of subject disposition, subject listings of deaths, and efficacy analyses, which is specified in Section 9.5.

6.4. mITT Retreatment Analysis Set

The mITT retreatment analysis set will consist of all subjects who undergo retreatment with KTE-X19 at any dose administered in Phase 2. This set will be used for all retreatment efficacy analyses.

6.5. Safety Retreatment Analysis Set

The safety retreatment analysis set will consist of all subjects who undergo retreatment with KTE-X19. This set will be used for all retreatment safety analyses.

6.6. Subgroup Analysis Sets

Subgroup analyses of selected efficacy and safety endpoints may be performed for the baseline covariates defined in Section 4.2.

6.7. DLT-evaluable Analysis Set

The DLT-evaluable analysis set includes the first 3-6 subjects in Phase 1 who are treated with the target KTE-X19 dose and followed for at least 28 days or received a dose of KTE-X19 lower than the target dose but experienced a DLT during the 28-day postinfusion period, up to the time at which a dose level has been evaluated for DLT and deemed safe. Additional subjects who are subsequently enrolled and treated in Phase 1 for the purpose of assessment of the overall safety in the same dose level or a lower dose level will not be considered as part of the DLT-evaluable analysis set, and DLT will not be assessed for such subjects.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

The SRT will review the safety data during Phase 1 of the study and make a recommendation to progress the study from Phase 1 to Phase 2 based on the incidence of DLT and review of SAEs.

The DSMB will meet once during the Phase 2 portion of the study. The DSMB will review safety data and will be chartered to make trial conduct recommendations based on the risk versus benefit of treatment with KTE-X19. No early stopping for efficacy or futility is planned in the interim analysis.

7.1. Phase 1 – Safety Interim Analyses

The SRT will evaluate the incidence of DLTs and SAEs after 3 subjects have been treated in a dose cohort and have met the criteria for the DLT-evaluable analysis set. The SRT may recommend progression to the Phase 2 portion of the trial.

Study enrollment may be paused in Phase 1 (DLT Evaluation Period) following any Grade 5 AE that occurs within 30 days of KTE-X19 dosing, regardless of attributions.

7.2. Phase 2 – Interim Safety Analyses

An independent DSMB will be chartered to make recommendations on study conduct. The DSMB will meet once during the study. Details may be found in the Data Safety Monitoring Board Charter.

The interim analysis will be conducted after 20 subjects in the mITT analysis set in Phase 2 have had the opportunity to be followed for 30 days after the KTE-X19 infusion. This interim analysis will be for safety only.

As part of its oversight of the study, the DSMB also will assess whether to pause enrollment in Phase 2 after 10, 20, and 35 subjects enrolled in Phase 2 have been treated with KTE-X19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following is met:

- Subject incidence of the following Grade 4 KTE-X19-related AEs lasting more than 7 days is > 33%:
  - Neurotoxicity
  - CRS (per Lee 2014 criteria)
  - Other nonhematological SAE
  - Treatment-related infection

7.3. Access to Aggregate and Subject-level Data and Individual Subject Treatment Assignments

This study is open label. Subjects, the study sponsor, and investigators will be aware that each subject is planned to be treated with KTE-X19. Data handling procedures, designed to maintain the trial credibility and validity in this open-label single-arm study, are described in the Trial Integrity Document (TID).

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The database will be subject to the edit checks outlined in the Data Management Plan (DMP) and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analysis and the final database lock. For interim analyses, snapshots may include data that has not passed all data cleaning procedures at the time the data are extracted for snapshot.

8.2. Electronic Transfer and Archival of Data

The Medidata Rave system will be used to collect the data in this study. Datasets (raw data, study data tabulation model [SDTM] data, and/or analysis data model [ADAM] data) for planned analyses will be archived. Any additional unplanned analyses that occur after the primary analysis and prior to the final analysis will also be archived. Key data external to the clinical study database (see below) will be included in the relevant SDTM and ADAM modules when the external data are available.

Data from the central pathology laboratory, the product manufacture (total T cells, CAR T cells (transduction ratio), duration of manufacturing time), central laboratory assessment of subject serum samples (CAR T cell levels in the peripheral blood, cytokine levels, antibody assays, RCR testing), MRD, and central radiology and clinical review will be generated from contract laboratories, Kite Pharma, and central imaging vendor. These data will be transferred to Kite study team and held in a peripheral directory and not built into the clinical trial database. At the time when analyses require these data, they may be merged with the SDTM and ADAM datasets.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy

The method for handling missing data is described in the definition for each efficacy endpoint. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date and the corresponding censoring date for survival, the algorithm in Appendix 1 will be used.

8.3.2. Safety

Partial AE start dates will be imputed. If dates are missing or incomplete for AE start dates, the algorithm defined in Appendix 1 will be used. Completely missing death dates or death dates with only a year reported will not be imputed.

8.4. Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include violations of eligibility criteria and violations that may have an impact on the efficacy evaluation. Lack of protocol compliance will be evaluated by summarizing the subject incidence of important protocol deviations. High rates of important protocol deviations may indicate bias.

Endpoints derived from investigator assessment of radiologic scans and clinical disease assessments may be subject to bias; the concordance between investigator and central review of radiologic scans and clinical disease assessments will be summarized.

8.5. Outliers

Descriptive statistics will be used to identify potential outliers in any key variables analyzed. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6. Distributional Characteristics

The primary analysis of the primary endpoint is an exact binomial test used to compare the observed OCR rate (CR + CRi) in the mITT analysis set to an OCR rate of 40%. This test assumes the independence of the individual subject responses.

An exact 95% confidence interval (CI) will be generated about the response rate. The Clopper-Pearson method will be used to generate this interval.

8.7. Validation and Configuration Management

Programs for the development of the SDTM and ADAM datasets and the generation of the tables, figures, and listings (TFL) will be developed and maintained according to Kite Standard Operating Procedures (SOP). The software and version used to generate analyses will be indicated in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

The goal of the primary statistical analysis is to compare the observed OCR (CR + CRi) rate in the mITT analysis set to a historical control rate of 40% using an exact binomial test. Hypothesis testing will be 1 sided, and all 95% CIs will be 2 sided. At the time of the test of the overall study population, 95% CIs for the OCR rate in Phase 2 will be presented.

The timing of the interim and primary analyses will be based on subject accrual and disease assessment milestones. The primary analysis clinical study report (CSR) will be written at the primary analysis.

Analyses of the Phase 1 and Phase 2 portions of the study will be presented separately.

9.2. Subject Accountability

The number of subjects screened, enrolled/leukapheresed, treated with bridging chemotherapy, treated with intrathecal chemotherapy for CSF prophylaxis, treated with conditioning chemotherapy, treated with KTE-X19, and retreated with KTE-X19 will be summarized. The reasons for discontinuing treatment and survival follow-up periods will be summarized. Summaries of actual and potential follow-up time will be provided.

The number of subjects enrolled by country and site will be summarized.

The number of subjects in each analysis set along with reasons for exclusion will be provided.

9.3. Important Protocol Deviations

The clinical study team will define important protocol deviation (IPD) categories and review, at a minimum, all IPDs prior to the database snapshot for the primary efficacy analysis. IPDs will be categorized by deviation type (eg, entry/eligibility, use of excluded medication). The subject incidence of IPDs will be summarized overall and by deviation category.

9.4. Demographic and Baseline Characteristics

Summary statistics and frequencies for the demographic and baseline characteristics will be tabulated.

9.5. Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set.

The key efficacy analyses will also be presented in the following populations:

- Phase 2 FAS
- Phase 1 by cohort in the safety analysis set

- Combined Phase 1 and Phase 2 at 1.0 x 10^6 anti-CD19 CAR T cells/kg dose levels, both on

  — Subjects who have been treated with KTE-X19

  — FAS.

For subjects retreated with KTE-X19, disease assessments obtained prior to retreatment but not disease assessment obtained after retreatment will be included in the primary summaries of OCR rate, rate of MRD− remission, DOR, and RFS. Disease assessments obtained after retreatment may be included in the summaries of OCR rate, rate of MRD− remission, DOR, and RFS after retreatment with KTE-X19. The subject's OS time will be derived from the last date known to be alive regardless of retreatment time.

9.5.1. OCR (CR + CRi) Rate

9.5.1.1. Primary Analysis of OCR (CR + CRi) Rate

The subject incidence of OCR (CR + CRi) will be calculated. An exact binomial test will be used to compare the observed OCR rate per independent review in the mITT analysis set to the hypothesized historical control rate of 40%. The subject incidence of best response of CR and CRi will be tabulated. CIs will be provided about the OCR (CR + CRi) rate, as well as the CR rate and CRi rate separately, calculated with the Clopper-Pearson method.

The primary analysis of OCR rate will include subjects from the mITT analysis set in Phase 2. A sensitivity analysis of the OCR rate will be conducted in the FAS.

The CR rate will be calculated for the mITT analysis set and FAS. A 95% CI will be provided about the CR rate using the Clopper-Pearson method.

9.5.1.2. Subgroup Analyses of OCR (CR + CRi) Rate

The OCR (CR + CRi) rate with 95% CIs will be generated for subgroups of the mITT analysis set defined by the selected covariates as listed in Section 4.2.

A forest plot of the proportion (and 95% CI) of subjects achieving CR or CRi for each of these subgroups will be generated.

9.5.1.3. Analyses of OCR Rate – Phase 1

Analyses of OCR rate in Phase 1 based on investigator assessment may occur at any time during Phase 1. The purpose of these analyses may include publications, preliminary evaluation of benefit-risk, and to inform decisions on dose.

At a minimum, CR + CRi rates, CR rates and 95% CIs will be generated for each dose cohort (if applicable) in Phase 1.

9.5.2. DOR

The primary analysis of DOR will use the Kaplan-Meier method and consider all relapses and deaths as events for DOR. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR. Kaplan-Meier plots, and estimate of the median DOR, and 2-sided 95% CIs will be generated. Estimates of the proportion of subjects who remained in response at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. DOR will be analyzed in both mITT and FAS.

A sensitivity analysis will be conducted in which disease assessments obtained after allo-SCT are included in the derivation of DOR.

A sensitivity analysis of DOR will be conducted in which the DOR for subjects undergoing TKI is censored at the last disease assessment prior to the resumption of TKI therapy.

A sensitivity analysis of DOR will be conducted in which receiving allo-SCT or subsequent anti-cancer therapy are considered events.

A sensitivity analysis of DOR may be conducted with non-disease mortality considered a competing risk.

In the cases where subjects missed at least two consecutive visits and deemed relapse in the next following up visit, a sensitivity analysis of DOR may be conducted in which such cases will be censored at the last disease assessment before the consecutively missed disease assessment visits.

9.5.3. Rate of MRD− Remission

The MRD− remission rate and 95% CIs will be estimated for all treated subjects, subjects with a CR, subjects with a CRi, and subjects with either a CR or CRi combined.

9.5.4. Allo-SCT Rate

The subject incidence rate of on-study allo-SCT will be summarized overall, by subjects achieving a CR + CRi, by subjects achieving a CR, and by subjects achieving a CRi. Corresponding 95% CIs may be generated.

9.5.5. Relapse-free Survival

Kaplan-Meier (KM) plots, estimate of the median RFS, and 2-sided 95% CIs will be generated. Estimates of the RFS rates at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Median RFS may be estimated for MRD− responders and MRD+ responders.

A sensitivity analysis of RFS will be conducted in the FAS. RFS for enrolled subjects is defined as the time from enrollment until relapse or death from any cause.

A sensitivity analysis will be conducted in which disease assessments obtained after allo-SCT are included in the derivation of RFS.

A sensitivity analysis of RFS will be conducted in which the RFS for subjects undergoing TKI is censored at the last disease assessment prior to the resumption of TKI therapy.

In the cases where subjects missed at least two consecutive visits and deemed relapse in the next following up visit, a sensitivity analysis of RFS may be conducted in which such cases will be censored at the last disease assessment before the consecutively missed disease assessment visits.

9.5.6. Overall Survival

KM plots, estimate of the median OS, and 2-sided 95% CIs will be generated. Estimates of OS rates at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Median OS may be estimated for MRD− responders and MRD+ responders.

Graphical summaries of the time to CR or CRi, DOR, retreatment, relapse, and death times from the time of KTE-X19 infusion depicted on a horizontal time axis for each subject ("swim lane plot") may be provided.

The OS will also be analyzed in the FAS. OS for enrolled subjects is defined as the time from enrollment until death from any cause.

9.5.7. OCR (CR + CRi) Rate Among Subjects Retreated with KTE-X19

The subject incidence of subjects retreated with KTE-X19 will be tabulated. The subject incidence of CR, CRi, and CR and CRi combined after retreatment among subjects retreated with KTE-X19 will be tabulated. Corresponding CIs will be provided.

9.5.8. DOR Among Subjects Retreated with KTE-X19

The analysis of DOR to retreatment among subjects responding to retreatment with KTE-X19 will use the same methods as the analysis of DOR.

9.6. Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize all AEs and laboratory values with an onset on or after the KTE-X19 infusion date and prior to the retreatment period (if applicable). Additional summary tables may be provided to present the AEs that occurred within certain study periods. For subjects who undergo retreatment with KTE-X19, AEs occurring in the KTE-X19 retreatment period may be summarized separately.

AEs will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of AEs will be graded using the CTCAE version 4.03.

CRS will be graded using a revised CRS grading scale (see details in protocol) developed by Lee and colleagues {Lee 2014}. Individual symptoms associated with CRS will be graded per CTCAE version 4.03.

Fatal AEs that are attributed to disease progression may be included in the death summary with a primary death reason of "disease progression" regardless of the coded CTCAE version 4.03 preferred term.

Subjects enrolled but not dosed with KTE-X19 will be followed for AEs for 30 days after the last study-specific procedure. AEs reported in these subjects will be archived in the study database and available in SDTM and ADAM datasets but will not be tabulated in AE summaries.

9.6.1. AEs

The subject incidence of the following TEAEs will be tabulated:

- All AEs
- All SAEs
- All KTE-X19-related AEs
- All KTE-X19-related SAEs
- All Grade 3 or higher AEs
- All Grade 3 or higher KTE-X19-related AEs
- Fatal AEs
- AEs of interest, including identified risks and potential risks

By-subject listings of deaths through 30 days after KTE-X19 infusion and SAEs will be provided overall and by treatment period.

Subgroup analyses of AEs may be generated for selected covariates from the list in Section 4.2.

The time to onset and resolution and the duration of CRS will be summarized. Cardiac arrhythmias and cardiac failure in the context of CRS may be summarized.

The time to onset and resolution and the duration of neurologic events will be summarized.

Cytopenias will be summarized by categories of neutropenia, anemia, and thrombocytopenia; cytopenias present on or after 30 days from KTE-X19 infusion will also be summarized.

Infections will be summarized by categories (bacterial infections, viral infections, opportunistic infections, and other infections).

Potential secondary malignancies will be identified within the system organ class of neoplasms benign, malignant, and unspecified (including cysts and polyps). Potential secondary malignancies will be listed.

9.6.2. Procedures and Concomitant Medications

The incidences of procedure and concomitant medications used to manage AEs will be tabulated (see Section 9.6.7).

9.6.3. Laboratory Test Results

Laboratory results will be graded according to CTCAE version 4.03. The incidence of post-infusion worst-grade laboratory toxicities for all analytes will be provided. Additional summaries for the shift from baseline to the worst toxicity grade after KTE-X19 infusion may also be generated.

9.6.4. Anti-CD19 CAR Antibodies

The subject incidence of any anti-KTE-X19 antibodies will be tabulated. For subjects testing positive for antibodies, the persistence of the antibodies over time will be summarized.

9.6.5. RCR

The subject incidence of RCR detected in blood samples will be tabulated overall and by assessment time. The persistence of RCR over time will be summarized.

9.6.6. Exposure to Study Treatment

Summary statistics and subject listings will be provided for the following:

- Total body surface area-adjusted dose of cyclophosphamide
- Total body surface area-adjusted dose of fludarabine
- Weight-adjusted dose of KTE-X19
- Total CAR T cells of the KTE-X19 infusion
- Total T cells of the KTE-X19 infusion

Separate summaries will be presented for retreatment with conditioning chemotherapy and KTE-X19 among subjects in the safety retreatment analysis set.

9.6.7. Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be provided and summarized by medication category and WHO drug coded term. The subject incidence of procedures will be tabulated. The duration and indication of concomitant medications of interest (eg, steroids and tocilizumab) may be summarized.

9.6.8. EQ-5D for Subjects in Phase 2

EQ-5D and VAS scores will be summarized at baseline and after study treatment visits. Changes in the EQ-5D and VAS scores from baseline at each post-study treatment visit will also be summarized with descriptive statistics.

Further analyses of these quality-of-life data may be described in a supplemental statistical analysis plan.

9.7. Subsequent Anticancer Therapy

The incidence and type (by WHO drug coded term) of subsequent anticancer therapy will be summarized.

9.8. Schedule of Study Treatment

Summary statistics will be provided for the following durations:

- Days from leukapheresis to product release
- Days from leukapheresis to receipt of KTE-X19 at the study site
- Days from leukapheresis to administration of KTE-X19
- Duration of hospitalization following the KTE-X19 infusion

9.9. Lymphocyte Subsets

Summary statistics for the levels of lymphocytes and the subject incidence of lymphopenia, B-cell aplasia, recovery after lymphopenia, and recovery after B-cell aplasia will be provided for each subject based on lymphocyte subsets measured prior to conditioning chemotherapy, on the day of the KTE-X19 infusion, and at Week 4, Month 3, Month 6, Month 12, Month 15, and Month 24. Graphical summaries of the median value and interquartile range over time may be provided. Among subjects who experience lymphopenia or B-cell aplasia, summary statistics for the time to the onset of these conditions will be provided. The duration of lymphopenia and B-cell aplasia will be summarized; the duration of these events for subjects with persistent lymphopenia or B-cell aplasia at the last lymphocyte measurement will be censored at that time. The use of IVIG treatment in the presence of B-cell aplasia may be summarized.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

11. REFERENCES

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124 (2):188-95.

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17 (4):343-6.

Topp MS, Gokbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16 (1):57-66.

12. HISTORY OF REVISIONS

Version	Date	Protocol	Description of Changes
Original (1.0)	16 May 2018	Original to Amendment 5	N/A
2.0	30 May 2020	Amendment 6	• Remove reference and definitions of study administrative periods that are irrelevant to the analysis from the SAP in Section 3.1; • Patients with prior Blinatumomab will be more than 5 patients, so the primary endpoints and selected secondary endpoints will be evaluated in subgroup analysis by subjects with or without prior Blinatumomab; • Definition of 'on-study' is updated to include death event; • Definition of 'actual follow-up time' is updated to include last date known alive; • Added "Time to onset, and duration of important identified risks CRS and neurologic events will be summarized." • Methods of confidence interval calculation – only keep the main method: clopper-pearson and remove the sensitivity methods; • Added the definition of secondary malignancy. • Added the analysis of "Days from leukapheresis to receipt of KTE-X19 at the study site" • Minor format changes. • Re-treatment period definition updated in Section 5.2 • RFS and OS for all enrolled subjects are added. • A sensitivity analysis of DOR in which allo-SCT and subsequent anti-cancer therapy are considered as events is added.

13. APPENDICES

Appendix 1. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates

The following data will be imputed using the following algorithm:

- AE start dates
- Deaths (please see exceptions below)
- Concomitant medication start dates
- Subsequent anticancer therapy start dates

Table 1. Imputation Rules for Partial or Missing Start Dates

		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		
Start Date		**< Day 0**	**≥ Day 0**	**< Day 0 *yyyymm***	**≥ Day 0 *yyyymm***	**< Day 0 *yyyy***	**≥ Day 0 *yyyy***	**Missing**
Partial *yyyymm*	= Day 0 *yyyymm*	2	1	2	1	n/a	1	1
	≠ Day 0 *yyyymm*		2		2	2	2	2
Partial *yyyy*	= Day 0 *yyyy*	3	1	3	1	n/a	1	1
	≠ Day 0 *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = impute the date of Day 0
2 = impute the first of the month
3 = impute January 1 of the year
4 = impute January 1 of the stop year
Note: if the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing death dates:

1) If death year and month are available but day is missing:

- If mmyyyy for the last date known to be alive = mmyyyy for death date, set death date to the day after the last date known to be alive.
- If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.

2) If both month and day are missing for death date or a death date is completely missing, do not impute and censor the subject survival time at the analysis data cutoff date or the last date known to be alive, whichever is later.

Appendix 2. Derivation of Time-to-event Endpoints and Last Date Known to Be Alive

Additional details on the derivations of duration of remission (DOR), relapse-free survival (RFS), and overall survival (OS) are provided below.

1) **DOR**: DOR is defined only for subjects who experience a CR or CRi and is the time from the first OCR (CR or CRi) to relapse or death due to any cause.

- **Primary analysis of DOR:**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT
Remain in remission without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date prior to data cutoff

- **Sensitivity analysis of DOR (not censoring at SCT):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (excluding allo-SCT)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (excluding allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy excluding allo-SCT
Withdrawal of consent or lost to follow-up prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to data cutoff

- **Sensitivity analysis of DOR (censoring for TKI):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT and resumption of TKI
Withdrawal of consent or lost to follow-up prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to data cutoff

- **Sensitivity analysis of DOR (both allo-SCT and subsequent therapy as events):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Event	Start date of new therapy including allo-SCT
Remain in remission without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date prior to data cutoff

2) **RFS:** RFS for all dosed subjects on the mITT set is defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause.

- **Primary analysis of RFS:**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (including allogenic SCT but excluding resumption of TKI) before any disease assessment	Event	KTE-X19 infusion date
Remain in remission and alive without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT.
Remained in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled and treated with KTE-X19 but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	KTE-X19 infusion date

- **Sensitivity analysis of RFS (not censoring at SCT):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (excluding allo-SCT)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (excluding allogenic SCT and resumption of TKI) before any disease assessment	Event	KTE-X19 infusion date

Circumstance	Event/Censored	Date of Event/Censoring
Remain in remission and alive without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (excluding allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy excluding allo-SCT.
Remained in remission without new anti-cancer therapy (excluding allo-SCT and resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled and treated with KTE-X19 but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	KTE-X19 infusion date

- **Sensitivity analysis of RFS (censoring at TKI):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (including allo-SCT and resumption of TKI) before any disease assessment	Event	KTE-X19 infusion date
Remain in remission and alive without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (including allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy (including allo-SCT and resumption of TKI)
Remained in remission without new anti-cancer therapy (including allo-SCT and resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled and treated with KTE-X19 but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	KTE-X19 infusion date

3) RFS for all enrolled subjects is defined as the time from the enrollment date to the date of disease relapse or death from any cause.

- **Analysis of RFS for all enrolled subjects:**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (including allogenic SCT but excluding resumption of TKI) before any disease assessment	Event	Enrollment date
Remain in remission and alive without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT.
Remained in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	Enrollment date

4) **OS:** OS is defined as the time from the KTE-X19 infusion to the date of death from any cause.

Circumstance	Event/Censored	Date of Event/Censoring
Death before data cutoff date for analysis	Event	Date of death
Death after data cutoff date for analysis	Censored	Data cutoff date
Known to be alive after data cutoff date for analysis	Censored	Data cutoff date
Alive up through data cutoff date and no further information available after data cutoff date	Censored	Last date known to be alive
Full withdrawal of consent or lost to follow-up prior to data cutoff date	Censored	Last date known to be alive prior to full consent withdrawal or lost to follow-up

5) OS for all enrolled subjects, which is defined as the time from the enrollment date to the date of death from any cause, will use the same censoring strategy as described above.

6) Last date known to be alive

The last date known to be alive with be derived by obtaining the maximum complete date among the following data modules:

- Start date of AE (including targeted AE)
- Leukapheresis dates
- Conditioning chemotherapy administration dates
- KTE-X19 infusion dates
- Bone marrow assessment dates
- Cerebrospinal fluid analysis dates
- Hematology specimen collection dates
- Minimal residual disease analysis dates
- Extramedullary disease assessment dates (including positron emissions tomography assessment, target lesion assessment, non-target lesion assessment, new lesion assessment, and disease response assessment dates)
- Long-term follow-up subject status date where status = ‘alive’
- End-of-treatment disposition where status is not equal to death or lost to follow-up
- End of post-treatment assessment period where status is not equal to death or lost to follow-up
- End-of-study data where end-of-study reason is not equal to death or lost to follow up