Three-year results from phase I of ZUMA-4: KTE-X19 in pediatric relapsed/refractory acute lymphoblastic leukemia

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Supplementary Data

Supplementary Methods

Patients

This phase 1 portion of ZUMA-4 enrolled patients with relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (B-ALL). In phase 2, eligibility criteria were expanded to include pediatric patients with R/R non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma, Burkitt's lymphoma, and primary mediastinal B-cell lymphoma. Phase 2 remains ongoing, and as such, patients with R/R B-NHL are not included in the present report.

Additional phase 1 inclusion criteria

- Morphological disease with >5% bone marrow blasts
- Lansky or Karnofsky performance status ≥80% at screening
- Patients with Philadelphia chromosome-positive disease were also eligible if they were intolerant to tyrosine kinase inhibitor therapy or if they had R/R disease despite treatment with at least two different tyrosine kinase inhibitors (TKI)
- In patients previously treated with blinatumomab, leukemic blasts with CD19 expression ≥90% was required
- Absolute neutrophil count (ANC) ≥500/μL unless in the opinion of the primary 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 principal 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 or Schwartz) ≥60 cc/min
    - Serum alanine aminotransferase and aspartate aminotransferase ≤5×upper limit of normal (ULN)

    - Total bilirubin ≤1.5×ULN, except in patients with Gilbert's syndrome
    - Left ventricular shortening fraction ≥30% or left ventricular ejection fraction ≥50%, no evidence of pericardial effusion as determined by an echocardiogram, and no clinically significant arrhythmias
    - No clinically significant pleural effusion
    - Baseline oxygen saturation >92% on room air
- Females of childbearing potential (defined as having first menses) must have a negative serum or urine pregnancy test

Additional phase 1 exclusion criteria

- Burkitt leukemia/lymphoma according to World Health Organization classification or chronic myelogenous leukemia lymphoid blast crisis
- History of malignancy other than nonmelanoma skin cancer or carcinoma in situ unless disease-free for ≥3 years
- History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study
- History or presence of any central nervous system (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
    - Detectable cerebrospinal blast cells in a sample of cerebrospinal fluid with <5 white blood cells per mm^3 with neurological changes (CNS-2), or detectable cerebrospinal blast cells in a sample of cerebrospinal fluid with ≥5 white blood cells per mm^3 with or without neurological changes (CNS-3) were also excluded
- History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, or Shwachman-Diamond syndrome
- History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other 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 (PCR) and/or nucleic acid testing
- Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infections and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite Medical Monitor
- Prior medication
    - Salvage systemic therapy (including chemotherapy, TKIs for Ph+ ALL, and blinatumomab) within 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 CRS (per Lee et al 2014) with prior CD19-directed therapy
    - 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, mycophenolate, 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)

- Corticosteroid therapy at a pharmacologic dose (≥0.7 mg/kg/day of hydrocortisone or equivalent doses of corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to enrollment

- 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
- Acute 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
- Live vaccine ≤4 weeks prior to enrollment
- Females 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
- In the investigator's judgment, the patient is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation
- 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

Dose formulations of the 1×10^6 chimeric antigen receptor T cells/kg dose level

Two formulations were explored for patients receiving the lower dose of 1×10^6 chimeric antigen receptor (CAR) T cells/kg, one with a total volume of 40 mL and the other with a volume of 68 mL. The 40 mL formulation was intended to maintain cell density and cell

viability during the freezing/thawing process. For patients weighing >100 kg, a maximum flat dose of 2×10^8 or 1×10^8 anti-CD19 CAR T cells was administered.

Study design and treatment

Dose-limiting toxicities (DLTs) were defined as follows: 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 >7 days; and all KTE-X19–related grade 4 non-hematologic toxicities regardless of duration with the exceptions noted in **Supplemental Table 2**. Specified bridging chemotherapy was permitted after leukapheresis and completed at least 7 days or 5 half-lives, whichever was shorter, prior to initiating conditioning chemotherapy consisting of intravenous (IV) fludarabine 25 mg/m^2/day on days -4, -3, and -2, and a single dose of IV cyclophosphamide 900 mg/m^2 on day -2. A single IV infusion of KTE-X19 was administered on day 0 at a target dose of 2×10^6 or 1×10^6 CAR T cells/kg. Hospitalization post-infusion was required for a minimum of 7 days. All patients completing the month 3 visit were followed in the long-term follow-up period for survival and disease status every 3 months through month 18, every 6 months from months 24 to 60, then once annually for up to 15 years. Patients could be removed from the study if they withdrew consent for further follow-up, were lost to follow-up, or died. Allogeneic stem cell transplant (alloSCT) was not required per the protocol but was allowed per investigator discretion.

Outcomes and assessments

Adverse events, including individual symptoms of cytokine release syndrome (CRS) and neurologic events (NEs), were graded according to the NCI Common Terminology Criteria for adverse events (AEs) version 4.03. Overall response was determined by investigator after bone marrow and peripheral blood assessments, as detailed in the table below. During the post-treatment follow-up period, bone marrow evaluations and response assessments were conducted at day 28 and months 2 and 3. While the timing of each visit was calculated from day 0, the day 28 visit had a scheduling window of ±3

days, the month 2 visit had a window of ±1 week, and the month 3 visit had a window of ±2 weeks, as also defined in the protocol. In patients who received bridging chemotherapy, an additional bone marrow aspirate was required between the end of bridging chemotherapy and day -4 (±2 days). For patients with extramedullary disease, response was assessed per the response criteria for extramedullary and CNS disease in the revised International Working Group criteria for malignant lymphoma as detailed in the table below.[1] A portion of the bone marrow aspirate taken at day 28 and months 2 and 3 was analyzed for minimal residual disease (MRD), which was tested by flow cytometry (Neogenomics) with a sensitivity of 0.01% using the following markers: CD3, CD9, CD10, CD13/CD33, CD19, CD20, CD34, CD38, CD45, CD58, and CD71.[2-4] MRD-negative is defined as MRD $<10^{-4}$ per the standard assessment. Translational analyses were performed on product, blood, and tumor samples to evaluate the pharmacokinetic and pharmacodynamic profile of KTE-X19 in pediatric R/R B-ALL as exploratory endpoints. Pharmacokinetic and pharmacodynamic assessments and associations with clinical outcomes were previously described.[5]

Overall disease response classification

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 “Extramedullary disease response” table below.

§In patients 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.

‡Blasts by morphology in BM.

#At day 28 or at the time of first presumed response, whichever is earlier, for patients who achieve a CR.

¶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 “Extramedullary disease response” 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.

Extramedullary disease response

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: ○ Nodal masses >1.5 cm in 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 >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 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	*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 2 lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node • ≥50% increase in the longest diameter of any single previously identified node >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.[1]

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

Statistical analysis

Incidence of AEs in all treated patients and changes in laboratory values were tabulated and summarized with descriptive statistics. Kaplan-Meier estimates and 2-sided 95% confidence intervals were generated for time-to-event endpoints. DOR was defined as the time between the first CR or CRi per investigator assessment to relapse or any death in the absence of documented relapse. Patients who did not meet the criteria for relapse or who received subsequent anticancer therapy (including alloSCT) and who remained alive were censored at the last evaluable disease assessment. Disease assessments obtained after new anticancer therapies (including alloSCT) will not contribute to the derivation of DOR. RFS was defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause. Patients who did not meet the criteria for relapse or who received subsequent anticancer therapy (including alloSCT) and who remained alive were censored at the last evaluable disease assessment. Patients who did not achieve a complete remission (CR or CRi) at

the analysis data cutoff were evaluated as having an RFS event at the KTE-X19 infusion date. OS is defined as the time from the KTE-X19 infusion date to the date of death from any cause. Patients who have not died by the analysis data cutoff date will be censored at the last date known to be alive. All statistical analyses were done in SAS version 9.4 (STAT 15.1).

Supplementary Results

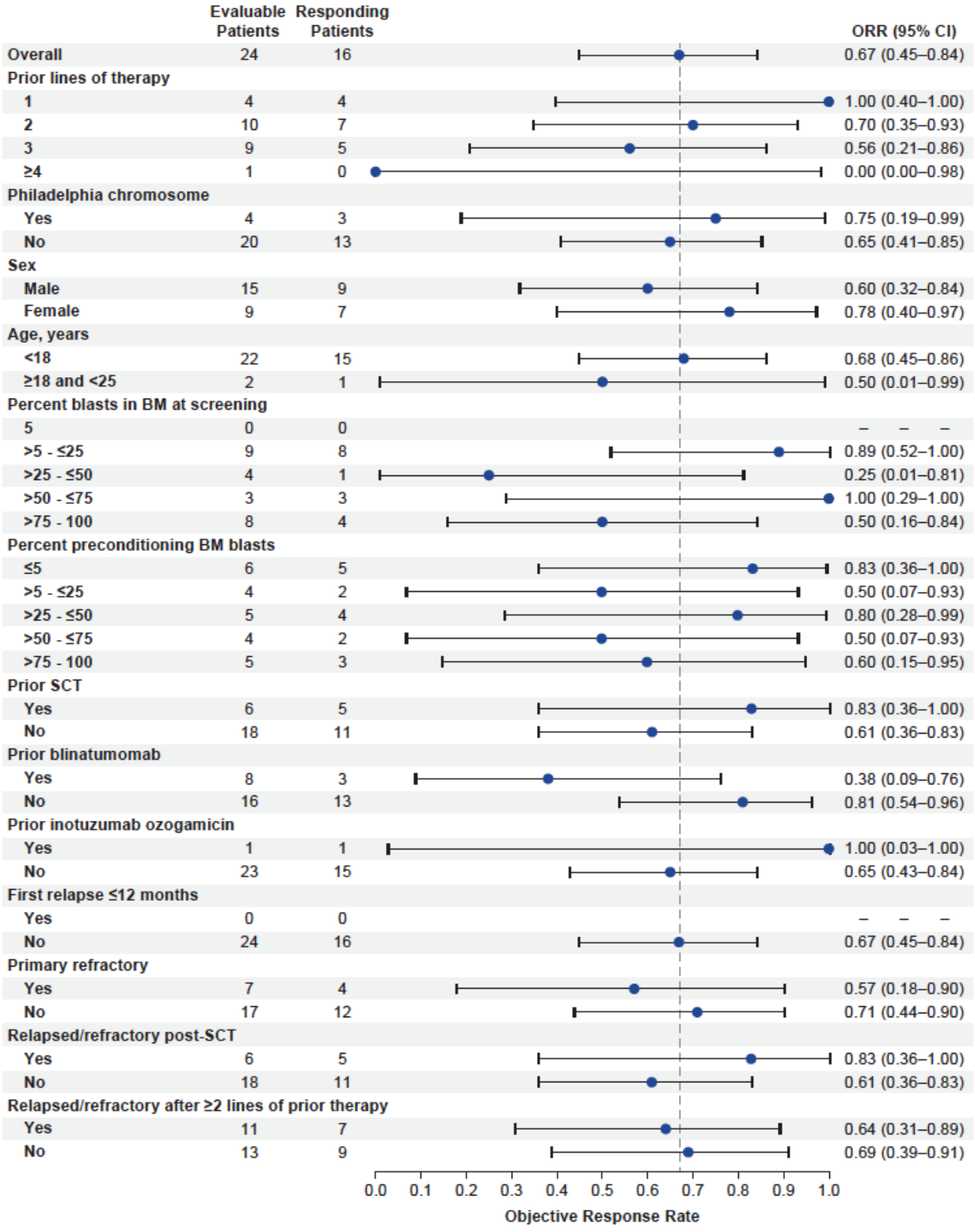
Patient with extramedullary disease

One patient had non-central nervous system extramedullary disease with non-target lesions in the left and right lobulated breasts and left axillary lymph nodes. These lesions were all absent on computed tomography scan at month 3, and the patient was considered to have a disease response of CR.

Patients with prior blinatumomab

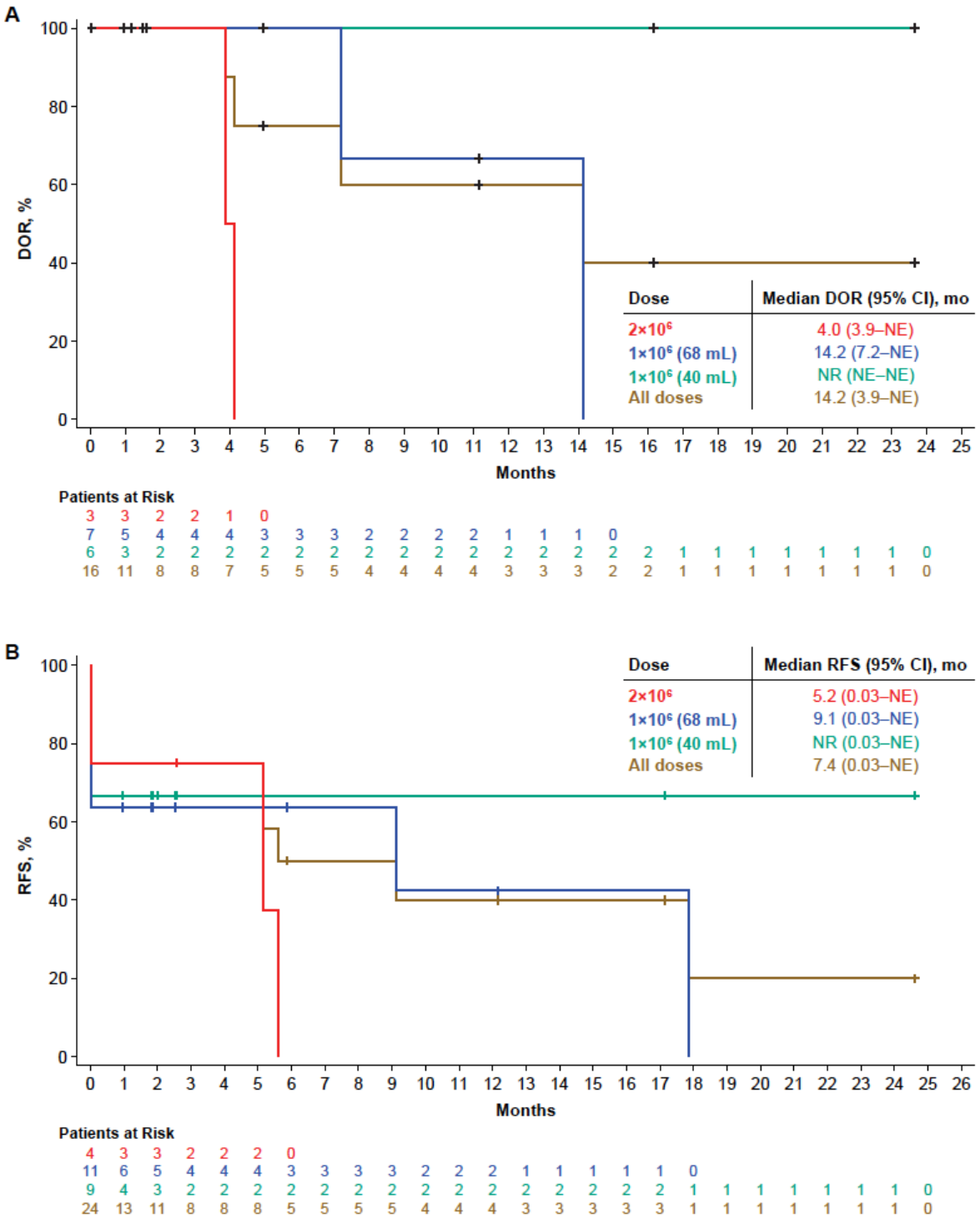
Eight patients were previously treated with blinatumomab and achieved a best response of CR (n=2), CRh (n=1), PD (n=2), and non-response (n=3) with blinatumomab. When these patients were treated with KTE-X19, 3 (38%) achieved a CR/CRi, 1 (13%) a CRh, 2 (25%) a non-response, and 2 (25%) did not have available response assessments with KTE-X19. Two of the 3 patients who had prior non-response to blinatumomab had available response assessments in ZUMA-4: one patient achieved a non-response and one achieved a CR with KTE-X19.

Supplementary Figure S1. Subgroup analysis of overall remission rate



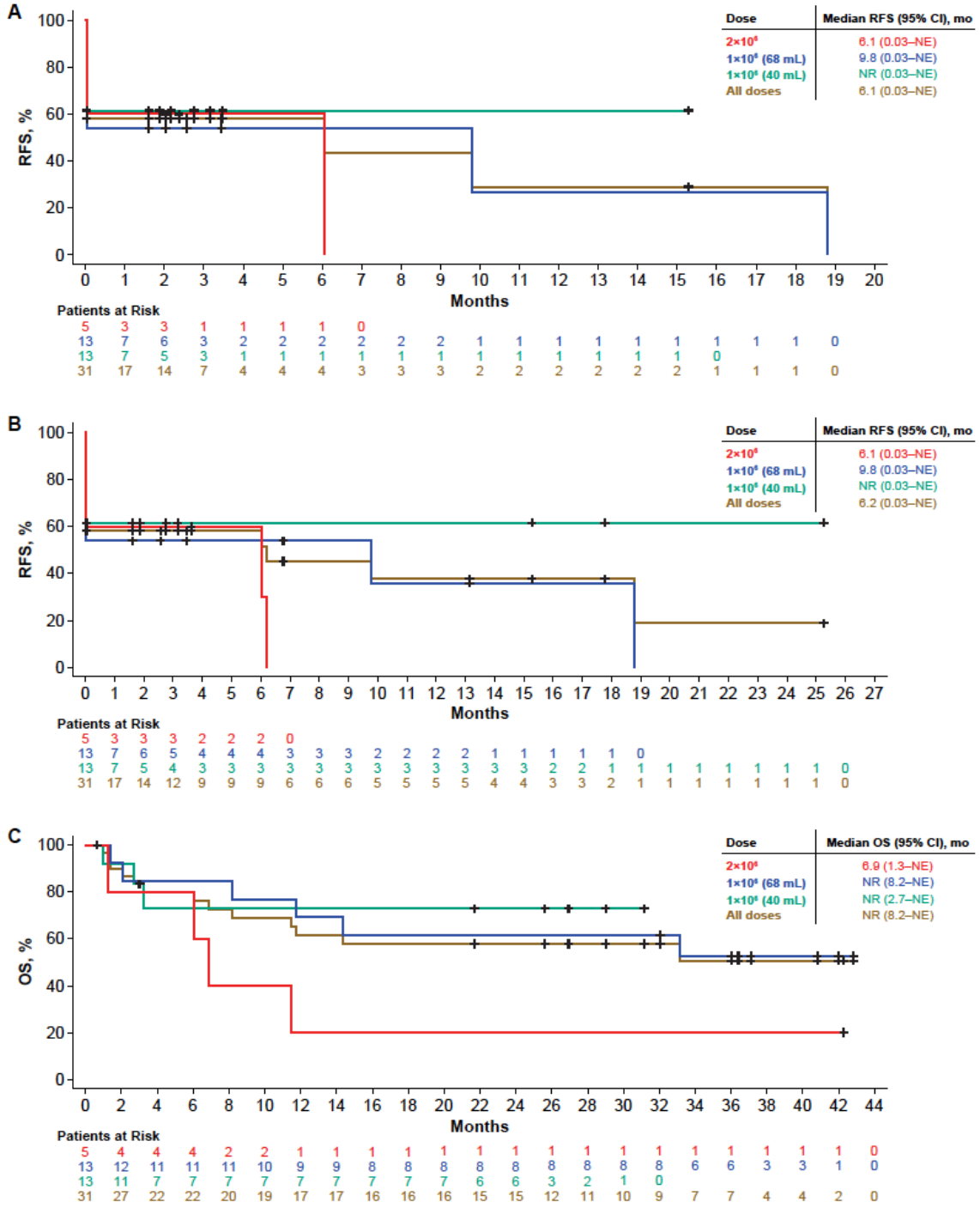
BM, bone marrow; ORR, overall remission rate; SCT, stem cell transplant.

Supplementary Figure S2. Duration of remission (A) and relapse-free survival (B) by dose level in all treated patients without censoring for subsequent alloSCT



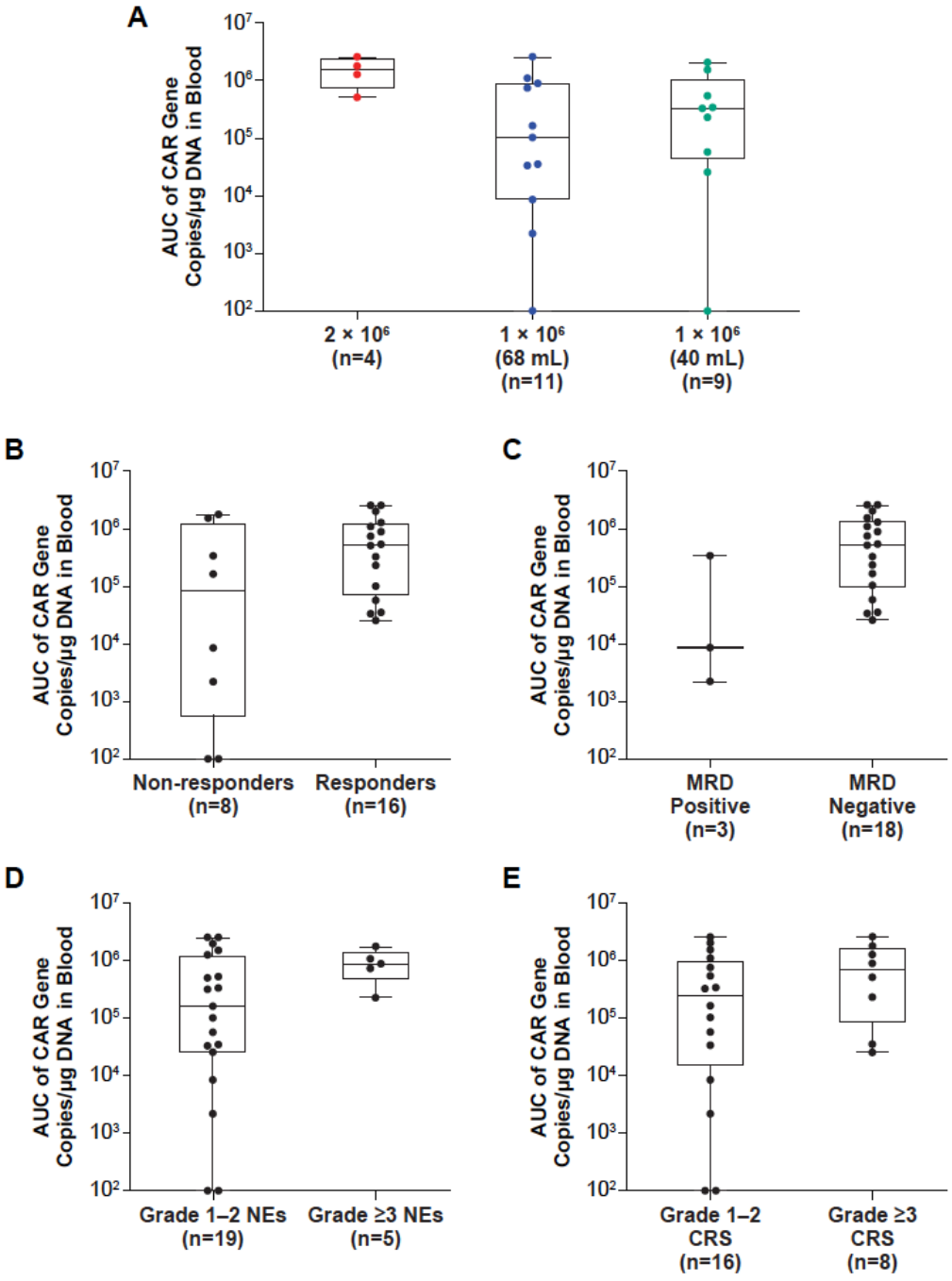
alloSCT, allogeneic stem cell transplant; DOR, duration of remission; NE, not estimable; NR, not reached; RFS, relapse-free survival.

Supplementary Figure S3. Relapse-free survival in the ITT population by dose level with (A) and without (B) censoring for subsequent alloSCT and overall survival in the ITT population (C)



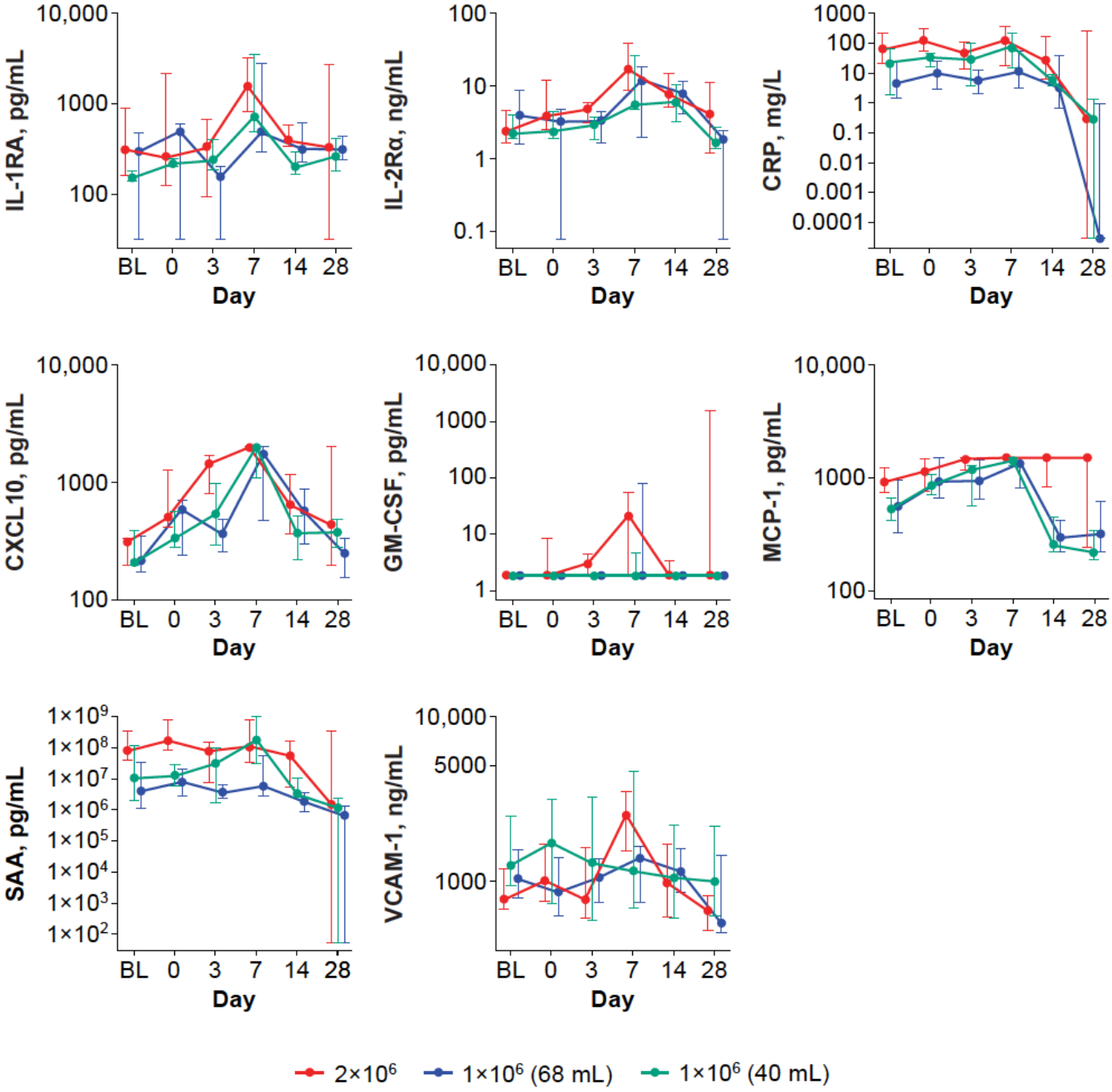
alloSCT, allogeneic stem cell transplant; ITT, intention-to-treat; NE, not estimable; NR, not reached; OS, overall survival; RFS, relapse-free survival.

Supplementary Figure S4. Associations between AUC of CAR gene copies/μg DNA and response, MRD rate, and toxicities



AUC is defined as the AUC in a plot of number of CAR gene copies/μg DNA in blood against scheduled visit from day 0 to day 28. AUC, area under the curve; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; MRD, minimal residual disease; NE, neurological event.

Supplementary Figure S5. Additional cytokine and inflammatory marker levels over time



BL, baseline; CRP, C-reactive protein; CXCL10, C-X-C motif chemokine ligand 10; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; MCP, monocyte attractant protein; Rα, receptor alpha; RA, receptor antagonist; SAA, serum amyloid A; VCAM, vascular cell adhesion molecule.

Supplementary Table S1. Full listing of study sites

Center	Lead Investigator
Johns Hopkins University, Baltimore	**Patrick Brown**
USCF Benioff Children's Hospital, San Francisco	**Michelle Hermiston**
Ann & Robert H Lurie Children's Hospital, Chicago*	**Nobuko Hijiya**
Children's Hospital of Orange County, Orange	**Van Huynh**
Monroe-Carell Jr Children's Hospital at Vanderbilt, Nashville	**Carrie Kitko**
The Hospital for Sick Children, Toronto	**Joerg Krueger**
University of Virginia Health System Children's Hospital, Pediatric Hematology/Oncology Clinic, Charlottesville	**Daniel Lee**
Children's Hospitals and Clinics of Minnesota, Minneapolis*	**Michael Richards**
Texas Children's Hospital, Houston	**Rayne Rouce**
Children's Hospital Los Angeles, Los Angeles	**Alan Wayne**
University of Miami Hospital and Clinics, Miami	**Edward Dela Ziga**

*ZUMA-4 was conducted at the institution indicated, but the primary affiliation of this investigator has since changed.

Supplementary Table S2. Criteria for dose-limiting toxicities

DLTs were 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: ○ Aphasia/dysphasia or confusion/cognitive disturbance which resolves to at least grade 1 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 ○ 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
• Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT ○ 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

CRS, cytokine release syndrome; DLT, dose-limiting toxicity; TLS, tumor lysis syndrome.

Supplementary Table S3. Bridging chemotherapy

Predefined Bridging Chemotherapy Regimens*,†	
Vincristine‡	1.5 mg/m^2 (maximum dose 2 mg) IV weekly × 4 doses with dexamethasone 6 mg/m^2 daily × 5 days
Attenuated VAD	Vincristine 1.5 mg/m^2 (maximum dose 2 mg) IV weekly × 4 doses with dexamethasone 6 mg/m^2 daily × 5 days, and doxorubicin 50 mg/m^2 IV × 1 dose (first week only)
Mercaptopurine (6-MP)	50 mg/m^2/dose PO once daily (administer at bedtime on an empty stomach to improve absorption)
Attenuated FLAG§	Fludarabine 25 mg/m^2 IV daily followed by cytarabine 2 g/m^2 IV daily for a total of 2 to 5 days per investigator discretion; G-CSF 5 µg/kg SC or IV starts on the day after completion of chemotherapy and continuing until ANC recovery to >1000/µL×2 consecutive days, or until the day before the start of conditioning chemotherapy, whichever comes first
Hydroxyurea	Doses titrated between 15 and 50 mg/kg/day (rounded to the nearest 500 mg capsule and given as a single daily oral dose on a continuous basis)
Cyclophosphamide and etoposide	Cyclophosphamide 440 mg/m^2 IV daily on Days 1-5 and etoposide 100 mg/m^2 daily on Days 1-5

*Doses listed were recommendations and could be adjusted at the investigator's discretion for age, comorbidities, or per local or institutional guidelines.

†Use of a TKI in combination with any of the above regimens is allowed for patients with Ph+ ALL and Ph-like ALL.

‡For patients who cannot tolerate vincristine, another alkaloid may be used.

§Concurrent treatment with intrathecal methotrexate should be avoided during the administration of FLAG chemotherapy.

ALL, acute lymphoblastic leukemia; ANC, absolute neutrophile count; FLAG, fludarabine, high-dose cytarabine, and G-CSF; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; Ph, Philadelphia chromosome; PO, oral; SC, subcutaneous; TKI, tyrosine kinase inhibitor; VAD, vincristine, doxorubicin, and dexamethasone.

Supplementary Table S4. Original and revised neurotoxicity management guidelines

NE Grade	Original Management Guidelines	Revised Management Guidelines
Grade 1	*Supportive Care and Evaluation* • Supportive care • Closely monitor neurologic status • Consider prophylactic levetiracetam	*Supportive Care and Evaluation* • Supportive care • Closely monitor neurologic status • Consider prophylactic levetiracetam*
	Tocilizumab • N/A	*Tocilizumab* • N/A
	Corticosteroids • N/A	*Corticosteroids* • Dexamethasone 0.2 mg/kg/dose (maximum dose 10 mg) IV × 1 or equivalent methylprednisolone dose (1 mg/kg/dose) × 1 • If not improving after 2 days, repeat dexamethasone or methylprednisolone and continue supportive care
Grade 2	*Supportive Care and Evaluation* • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Levetiracetam/antiepileptics if patient has seizures	*Supportive Care and Evaluation* • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications
	Tocilizumab • **For patients with concurrent CRS,** administer tocilizumab	*Tocilizumab* • **For patients with concurrent CRS**, administer tocilizumab

	12 mg/kg (if <30 kg) or 8 mg/kg (if ≥30 kg) IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if CRS not responsive, for a maximum of 3 doses • If improving, discontinue tocilizumab	12 mg/kg (if <30 kg) or 8 mg/kg (if >30 kg) IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen, for a maximum of 3 doses in 24 hours; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS
	Corticosteroids • **For patients with concurrent CRS**, if no improvement within 24 hours after starting tocilizumab, give dexamethasone 0.2 mg/kg/dose (maximum dose 10 mg) IV every 6 hours or equivalent methylprednisolone dose (1 mg/kg/dose) • **For patients without concurrent CRS**, dexamethasone 0.2 mg/kg/dose (maximum dose 10 mg) IV every 6 hours • If improving, taper corticosteroids • If not improving, manage as grade 3	*Corticosteroids* • Dexamethasone 0.2 mg/kg/dose (maximum dose 10 mg) IV or equivalent methylprednisolone dose (1 mg/kg/dose) every 6 hours • If improving, continue corticosteroids until the event is grade 1 or less, then quickly taper as clinically appropriate • If not improving, manage as appropriate grade below; consider contacting Medical Monitor
Grade 3	*Supportive Care and Evaluation* • Manage in monitored care or ICU	*Supportive Care and Evaluation* • Manage in monitored care or ICU
	Tocilizumab • Per grade 2	*Tocilizumab* • Per grade 2
	Corticosteroids • Dexamethasone 0.2 mg/kg/dose (maximum dose 10 mg) IV every 6 hours or equivalent methylprednisolone dose (1 mg/kg/dose)	*Corticosteroids* • Methylprednisolone 10 mg/kg/dose (maximum dose 500 mg) IV once daily • If improving, continue corticosteroids until the event is

	• If improving, taper corticosteroids • If not improving, manage as grade 4	grade 1 or less, then taper as clinically appropriate • If not improving, manage as appropriate grade below; contact Medical Monitor
Grade 4	*Supportive Care and Evaluation* • Per grade 3 • Mechanical ventilation may be required	*Supportive Care and Evaluation* • Per grade 3 • Mechanical ventilation may be required
	Tocilizumab • Per grade 2	*Tocilizumab* • Per grade 2
	Corticosteroids • Methylprednisolone 10 mg/kg/dose (maximum dose 500 mg) BID IV × 3 days • If improving, taper corticosteroids • If not improving, consider alternate immunosuppressants	*Corticosteroids* • Methylprednisolone 10 mg/kg/dose (maximum dose 500 mg) BID IV • If improving, continue corticosteroids until the event is grade 1 or less, then taper as clinically appropriate • If not improving, consider alternative therapy†; contact Medical Monitor

*Prophylactic levetiracetam applies to all grades.

†Initiation of alternative therapy should be discussed with the Medical Monitor and includes (but is not limited to) anakinra, siltuximab, ruxolitinib, cyclophosphamide, intravenous immunoglobulin, and antithymocyte globulin.

BID, twice daily; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; EEG, electroencephalogram; ICU, intensive care unit; IV, intravenous; MRI, magnetic resonance imaging; NE, neurologic event.

Supplementary Table S5. Adverse events occurring in ≥5% of all patients

n (%)*	2×10^6 cells/kg (n=4)		1×10^6 cells/kg, 68 mL (n=11)		1×10^6 cells/kg, 40 mL (n=9)		All patients (N=24)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	4 (100)	4 (100)	11 (100)	11 (100)	9 (100)	9 (100)	24 (100)	24 (100)
Pyrexia	4 (100)	3 (75)	11 (100)	3 (27)	8 (89)	2 (22)	23 (96)	8 (33)
Hypotension	4 (100)	4 (100)	8 (73)	6 (55)	6 (67)	2 (22)	18 (75)	12 (50)
Headache	2 (50)	0	8 (73)	2 (18)	7 (78)	0	17 (71)	2 (8)
Anemia	1 (25)	1 (25)	3 (27)	3 (27)	7 (78)	6 (67)	11 (46)	10 (42)
Nausea	2 (50)	2 (50)	5 (45)	1 (9)	4 (44)	0	11 (46)	3 (13)
Hypokalemia	3 (75)	2 (50)	3 (27)	1 (9)	4 (44)	3 (33)	10 (42)	6 (25)
Vomiting	0	0	4 (36)	0	6 (67)	0	10 (42)	0
Neutrophil count decreased	0	0	3 (27)	3 (27)	6 (67)	6 (67)	9 (38)	9 (38)
Tachycardia	0	0	4 (36)	1 (9)	5 (56)	0	9 (38)	1 (4)
Hypertension	3 (75)	2 (50)	4 (36)	0	1 (11)	0	8 (33)	2 (8)
Febrile neutropenia	1 (25)	1 (25)	3 (27)	3 (27)	3 (33)	3 (33)	7 (29)	7 (29)
Abdominal pain	1 (25)	0	3 (27)	0	2 (22)	0	6 (25)	0
Confusional state	0	0	4 (36)	0	2 (22)	0	6 (25)	0
Constipation	0	0	4 (36)	0	2 (22)	0	6 (25)	0
Decreased appetite	1 (25)	1 (25)	2 (18)	0	3 (33)	2 (22)	6 (25)	3 (13)
Fatigue	0	0	3 (27)	0	3 (33)	0	6 (25)	0
Hypogammaglobulinemia	0	0	2 (18)	0	4 (44)	0	6 (25)	0
Hypomagnesemia	2 (50)	0	1 (9)	0	3 (33)	0	6 (25)	0
Platelet count decreased	2 (50)	2 (50)	2 (18)	2 (18)	2 (22)	2 (22)	6 (25)	6 (25)
White blood cell count decreased	1 (25)	1 (25)	2 (18)	2 (18)	3 (33)	2 (22)	6 (25)	5 (21)
Cough	0	0	3 (27)	0	2 (22)	0	5 (21)	0
Hypophosphatemia	1 (25)	0	2 (18)	1 (9)	2 (22)	1 (11)	5 (21)	2 (8)
Hypoxia	1 (25)	1 (25)	3 (27)	1 (9)	1 (11)	1 (11)	5 (21)	3 (13)
Pain	2 (50)	0	1 (9)	0	2 (22)	0	5 (21)	0
Diarrhea	0	0	1 (9)	0	3 (33)	1 (11)	4 (17)	1 (4)

Dizziness	0	0	2 (18)	0	2 (22)	0	4 (17)	0
Encephalopathy	1 (25)	1 (25)	1 (9)	1 (9)	2 (22)	1 (11)	4 (17)	3 (13)
Face edema	0	0	1 (9)	0	3 (33)	0	4 (17)	0
Neutropenia	0	0	2 (18)	2 (18)	2 (22)	2 (22)	4 (17)	4 (17)
Prothrombin time prolonged	3 (75)	0	1 (9)	0	0	0	4 (17)	0
Pulmonary edema	1 (25)	1 (25)	2 (18)	0	1 (11)	0	4 (17)	1 (4)
aPTT prolonged	2 (50)	0	0	0	1 (11)	0	3 (13)	0
Aphasia	1 (25)	1 (25)	1 (9)	0	1 (11)	0	3 (13)	1 (4)
Arthralgia	0	0	1 (9)	0	2 (22)	0	3 (13)	0
Chills	0	0	0	0	3 (33)	0	3 (13)	0
Epistaxis	0	0	2 (18)	1 (9)	1 (11)	0	3 (13)	1 (4)
Hyperglycemia	0	0	0	0	3 (33)	2 (22)	3 (13)	2 (8)
Infusion-related reaction	1 (25)	0	1 (9)	0	1 (11)	0	3 (13)	0
INR increased	0	0	0	0	3 (33)	0	3 (13)	0
Lethargy	0	0	2 (18)	1 (9)	1 (11)	0	3 (13)	1 (4)
Lymphocyte count decreased	0	0	3 (27)	3 (27)	0	0	3 (13)	3 (13)
Sinus tachycardia	0	0	3 (27)	0	0	0	3 (13)	0
Tremor	0	0	2 (18)	0	1 (11)	0	3 (13)	0
ALL	0	0	1 (9)	1 (9)	1 (11)	1 (11)	2 (8)	2 (8)
Back pain	0	0	1 (9)	0	1 (11)	0	2 (8)	0
Blood bilirubin increased	0	0	1 (9)	0	1 (11)	1 (11)	2 (8)	1 (4)
Bradycardia	0	0	2 (18)	1 (9)	0	0	2 (8)	1 (4)
Hyperbilirubinemia	1 (25)	1 (25)	0	0	1 (11)	1 (11)	2 (8)	2 (8)
Hyperhidrosis	0	0	1 (9)	0	1 (11)	0	2 (8)	0
Hypoesthesia	0	0	0	0	2 (22)	0	2 (8)	0
Hypoalbuminemia	0	0	1 (9)	0	1 (11)	0	2 (8)	0
Hypocalcemia	0	0	2 (18)	1 (9)	0	0	2 (8)	1 (4)
Myalgia	1 (25)	0	1 (9)	0	0	0	2 (8)	0
Oropharyngeal pain	1 (25)	0	0	0	1 (11)	0	2 (8)	0
Pain in extremity	0	0	1 (9)	0	1 (11)	0	2 (8)	0
Paresthesia	0	0	1 (9)	0	1 (11)	0	2 (8)	0
Pleural effusion	1 (25)	0	0	0	1 (11)	0	2 (8)	0

Proctalgia	0	0	0	0	2 (22)	0	2 (8)	0
Pruritus	1 (25)	0	1 (9)	0	0	0	2 (8)	0
Rash	0	0	0	0	2 (22)	0	2 (8)	0
Rash maculopapular	0	0	1 (9)	1 (9)	1 (11)	0	2 (8)	1 (4)
Sepsis	0	0	2 (18)	2 (18)	0	0	2 (8)	2 (8)
Somnolence	0	0	2 (18)	0	0	0	2 (8)	0
Stomatitis	0	0	1 (9)	0	1 (11)	0	2 (8)	0
Transfusion reaction	0	0	1 (9)	0	1 (11)	0	2 (8)	0

ALL, acute lymphoblastic leukemia; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

Supplementary Table S6. Serious adverse events occurring in ≥5% of all patients

n (%)	N=24			
	Any	Grade 3	Grade 4	Grade 5
Patients with at least 1 event	17 (71)	5 (21)	6 (25)	4 (17)
Hypotension	10 (42)	7 (29)	2 (8)	0
Pyrexia	9 (38)	0	0	0
Tachycardia	5 (21)	1 (4)	0	0
Encephalopathy	4 (17)	3 (13)	0	0
Confusional state	3 (13)	0	0	0
Headache	3 (13)	0	0	0
Acute lymphocytic leukemia	2 (8)	0	0	2 (8)
Sepsis	2 (8)	0	2 (8)	0
Sinus tachycardia	2 (8)	0	0	0

Supplementary Table S7. Grade ≥3 infections

n (%)	N=24			
	Any	Grade 3	Grade 4	Grade 5
Patients with at least 1 event	10 (42)	4 (17)	4 (17)	2 (8)
Sepsis	2 (8)	0	2 (8)	0
Appendiceal abscess	1 (4)	1 (4)	0	0
Arthritis bacterial	1 (4)	1 (4)	0	0
Bacterial infection	1 (4)	0	1 (4)	0
Cellulitis	1 (4)	1 (4)	0	0
Chorioretinitis	1 (4)	1 (4)	0	0
Clostridium bacteremia	1 (4)	0	1 (4)	0
Device related infection	1 (4)	1 (4)	0	0
Disseminated mucormycosis	1 (4)	0	0	1 (4)
Enterobacter bacteremia	1 (4)	1 (4)	0	0
Escherichia infection	1 (4)	1 (4)	0	0
Escherichia sepsis	1 (4)	0	0	1 (4)
Eye infection toxoplasmal	1 (4)	1 (4)	0	0
Fungal retinitis	1 (4)	1 (4)	0	0
Osteomyelitis	1 (4)	1 (4)	0	0
Paronychia	1 (4)	1 (4)	0	0
Pseudomonal bacteremia	1 (4)	1 (4)	0	0
Pseudomonas infection	1 (4)	1 (4)	0	0
Septic shock	1 (4)	0	1 (4)	0
Staphylococcal bacteremia	1 (4)	1 (4)	0	0
Systemic candida	1 (4)	1 (4)	0	0
Urinary tract infection	1 (4)	1 (4)	0	0
Varicella	1 (4)	1 (4)	0	0

Supplementary Table S8. CAR gene copies in blood over time

CAR Gene Copies per µg DNA in Blood	2×10^6	1×10^6 68 mL	1×10^6 40 mL
Baseline	(n=4)	(n=11)	(n=9)
Median	0	0	0
Range	0–0	0–0	0–0
Day 7	(n=4)	(n=11)	(n=9)
Median	62,600	4374	10,800
Range	13,000–232,000	0–133,000	0–249,000
Week 2	(n=4)	(n=10)	(n=8)
Median	73,600	7249.5	25,200
Range	2414–173,000	0–240,000	2325–40,100
Week 4	(n=3)	(n=10)	(n=8)
Median	17,200	680	453.6
Range	243–51,800	0–4617	0–37,800
Week 8	(n=1)	(n=3)	(n=7)
Median	0	607.5	0
Range	0–0	105–972	0–13,200
Month 3	(n=3)	(n=8)	(n=5)
Median	0	0	0
Range	0–0	0–162	0–113
Month 6	(n=3)	(n=9)	(n=3)
Median	0	0	0
Range	0–0	0–510	0–0
Month 9	(n = 0)	(n = 7)	(n = 4)
Median	-	0	0
Range	-	0–0	0–0
Month 12	(n=1)	(n=7)	(n=0)
Median	0	0	-
Range	0–0	0–0	-
Month 15	(n=1)	(n=6)	(n=3)
Median	0	0	0
Range	0–0	0–0	0–0

Month 18	(n=1)	(n=4)	(n=0)
Median	0	0	-
Range	0–0	0–0	-

CAR, chimeric antigen receptor.

Supplementary Table S9. Select serum biomarkers at baseline and at post-infusion peak

		2×10^6 cells/kg (n=4)		1×10^6 cells/kg, 68 mL (n=11)		1×10^6 cells/kg, 40 mL (n=9)	
Function		**Baseline**	**Peak**	**Baseline**	**Peak**	**Baseline**	**Peak**
Homeostatic/ proliferative	**IL-15, pg/mL**						
	Median	14.9	72.0	3.3	23.2	7.3	38.2
	Range	7.5–24.2	53.5–116.9	1.4*–14.5	6.6–91.1	1.4*–26.6	13.6–65.7
	IL-2, pg/mL						
	Median	0.9*	47.8	0.9*	16.6	0.9*	8.3
	Range	0.9*–0.9*	20.8–163.3	0.9*–2.1	0.9*–690.4	0.9*–0.9*	0.9*–101.1
Pro-inflammatory	**IL-6, pg/mL**						
	Median	9.8	976.0†	1.6*	90.8	1.6*	23.3
	Range	1.6*–32.6	976.0†–976.0†	1.6*–13.5	1.6*–976.0†	1.6*–13.9	6.7–976.0†
	CRP, mg/L						
	Median	62.2	261.7	4.5	39.7	23.2	115.8
	Range	2.8–379.1	149.7–496.0†	1.2–200.4	5.0–300.1	0.4–135.5	42.3–496.0†
	SAA, mg/L						
	Median	7.5×10^7	2.7×10^8	3.9×10^6	4.9×10^7	1.0×10^7	5.8×10^8
	Range	1.1×10^7–6.3×10^8	1.6×10^8–$1.4\times10^{9\dagger}$	7.4×10^5–1.1×10^8	3.5×10^6–1.2×10^9	8.9×10^5–9.9×10^8	9.9×10^6–$1.4\times10^{9\dagger}$
	IL-5, pg/mL						
	Median	6.3*	23.6	6.3*	6.3*	6.3*	6.3*
	Range	6.3*–6.3*	23.1–43.8	6.3*–56.8	6.3*–73.7	6.3*–6.3*	6.3*–6.3*

	Ferritin, ng/mL						
	Median	3528.4	$2.5\times10^{4\dagger}$	2104.0	5915.8	876.1	5745.9
	Range	2169.1–6570.4	1.4×10^{4}–2.5×10^{4}	595.0–2.5×10^{4}	1084.8–2.5×10^{4}	83.3–4567.7	1116.1–$3.2\times10^{4\dagger}$
	IL-1RA, pg/mL						
	Median	307.8	3366.7	292.3	2223.8	148.7	1677.4
	Range	132.9–1368.5	847.3–4000.0	31.2–695.4	300.1–4000.0	77.6–684.0	91.9–9000.0†
	IL-2Rα, ng/mL						
	Median	2.3	29.9	3.9	11.9	2.2	16.5
	Range	1.2–6.6	11.2–56.3	0.1–71.6	3.1–60.8	1.6–100.0†	2.4–100.0†
	TNF-α, pg/mL						
	Median	3.6	30.7	3.6	11.1	1.6	5.2
	Range	2.6–8.7	14.0–70.2	1.6–9.2	2.9–34.0	0.7*–4.9	1.7–31.3
	ICAM-1, ng/mL						
	Median	1046.1	4868.8	622.5	1398.2	1018.0	1875.9
	Range	674.1–1440.2	1626.2–7723.4	290.3–1991.8	591.9–7204.9	264.4–2656.5	749.2–5906.3
	VCAM-1, ng/mL						
	Median	778.0	3417.8	1040.7	1615.3	1254.0	2565.3
	Range	643.6–1553.8	823.6–4125.8	450.9–2406.4	859.1–2778.1	514.2–3460.0	807.5– 5594.2
Immuno-modulating	**GM-CSF, pg/mL**						
	Median	1.9*	130.6	1.9*	1.9*	1.9*	1.9*
	Range	1.9*–1.9*	42.1–1500.0†	1.9*–1.9*	1.9*–468.9	1.9*–1.9*	1.9*–97.9
	IFN-γ, pg/mL						
	Median	7.5*	1876.0†	7.5*	725.7	7.5*	1876.0†

	Range	7.5*–15.2	633.5–1876.0†	7.5*–291.9	42.4–1876.0†	7.5*–61.6	7.5*–1876.0†
	IL-16, pg/mL						
	Median	57.9	521.7	141.40	212.5	97.80	242.0
	Range	19.1*–78.1	112.7–2502.0	69.5–375.8	117.9–629.5	44.9–112.4	104.2–3414.2
Chemokines	**IL-10, pg/mL**						
	Median	1.90	124.9	0.70*	42.3	0.70*	47.0
	Range	0.70*–17.6	16.7–466.0†	0.70*–58.4	3.2–466.0†	0.70*–6.20	1.8–466.0†
	IL-8, pg/mL						
	Median	72.5	750.0†	21.1	108.0	17.8	105.4
	Range	45.9–371.6	428.2–750.0†	4.6–108.7	14.2–750.0†	10.5–106.2	45.6–750.0†
	CXCL10, pg/mL						
	Median	307.7	2000.0†	217.2	2000.0†	205.7‡	2000.0†,‡
	Range	107.7–331.6	2000.0†–2000.0†	78.0–1034.5	487.4–2000.0†	72.9–475.1	277.6–2000.0†
	MCP-1, pg/mL						
	Median	913.3	1500.0†	554.5	1500.0†	525.6‡	1500.0†,‡
	Range	623.5–1500.0†	1500.0†–1500.0†	289.7–1366.7	671.2–1500.0†	318.7– 942.1	1197.8–1500.0†
Effector	**Granzyme B, pg/mL**						
	Median	1.0*	599.1	1.0*	19.4	1.0*	49.2
	Range	1.0*–1.0*	31.4–1.0×10^{4}†	1.0*–33.4	1.0*–166.1	1.0*–65.9	1.0*–5477.4

*Value represents lower limit of quantification in assay used.

†Value represents upper limit of quantification in assay used.

‡Based on available data: baseline, n=6; peak, n=7.

CRP, C-reactive protein; CXCL, C-X-C motif chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; ICAM, intercellular adhesion molecule; IL, interleukin; IP, interferon γ-induced protein; MCP, monocyte chemoattractant protein; Rα, receptor alpha; RA, receptor antagonist; SAA, serum amyloid A; TNF-α, tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule.

Supplementary Table S10. Association of serum biomarkers with cytokine release syndrome and neurologic events

		Cytokine Release Syndrome			Neurologic Events		
Function	**Peak Value - Median (range)**	**Grade ≥3 (n=8)**	**Grade 0–2 (n=16)**	***P* Value**	**Grade ≥3 (n=5)**	**Grade 0–2 (n=19)**	***P* Value**
Homeostatic/ proliferative	IL-15, pg/mL	52.4 (13.6–116.9)	36.4 (6.6–91.1)	0.3123	57.4 (13.6–116.9)	34.9 (6.6–78.5)	0.1355
	IL-2, pg/mL	47.8 (2.1–163.3)	8.7 (2.1–163.3)	0.1112	35.3 (2.1–124.0)	9.0 (0.9*–690.4)	0.3741
Pro-inflammatory	IL-6, pg/mL	817.1 (6.7–976.0†)	71.1 (1.6*–976.0†)	0.4026	976.0† (6.7–976.0†)	90.8 (1.6*–976.0†)	0.3137
	CRP, mg/L	139.4 (5.0–496.0†)	81.8 (9.2–300.1)	0.2838	129.2 (18.1–496.0†)	99.5 (5.0–300.1)	0.6187
	SAA, pg/mL	5.10×10^8 (3.85×10^6–1.38×10^{9}†)	1.01×10^8 (3.48×10^6–1.38×10^{9}†)	0.1679	1.22×10^9 (1.49×10^7–1.38×10^{9}†)	1.61×10^8 (3.48×10^6–1.38×10^{9}†)	0.2859
	IL-5, pg/mL	14.7 (6.3*–26.2)	6.3* (6.3*–73.7)	0.4014	6.3* (6.3*–42.0)	6.3* (6.3*–73.7)	0.7031
	Ferritin, ng/mL	16,800 (1084.8–2.5×10^4)	5921.0 (1116.1–3.2×10^{4}†)	0.3902	10,800 (3046.8–2.5×10^4)	6096.1 (1084.8–3.2×10^{4}†)	0.6952
	IL-1RA, pg/mL	1906.6 (395.0-9000.0†)	2298.7 (91.9-4000.0)	0.5193	2223.8 (395.0–4000.0)	2373.6 (91.9–9000.0†)	0.9716
	IL-2Rα, ng/mL	19.6 (3.5–56.3)	12.7 (2.4–100.0†)	0.5005	18.6 (8.0–34.7)	13.4 (2.4–100.0†)	0.5456

	TNF-α, pg/mL	12.2 (2.8–40.8)	9.1 (1.7–70.2)	0.5607	12.5 (2.8–40.8)	9.8 (1.7–70.2)	0.7223
	ICAM-1, ng/mL	2758.8 (1398.2–7723.4)	1516.6 (591.9–7204.9)	0.0708	1611.1 (1347.7–6890.6)	1717.2 (591.9–7723.4)	0.8311
	VCAM-1, ng/mL	2813.8 (1836.7–5101.9)	1401.9 (807.4–5594.2)	0.0156	1836.7 (963.9–5101.9)	1883.6 (807.4–5594.2)	0.6697
Immuno-modulating	GM-CSF, pg/mL	52.7 (1.9*–198.0)	1.9* (1.9*–1500.0†)	0.2335	63.3 (1.9*–100.5)	1.9* (1.9*–1500.0†)	0.3312
	IFN-γ, pg/mL	1876.0† (42.4–1876.0†)	720.6 (7.5*–1876.0†)	0.4041	1876.0† (81.2–1876.0†)	725.7 (7.5*–1876.0†)	0.3525
	IL-16, pg/mL	500.6 (144.7–2502.0)	213.9 (104.2–3414.2)	0.0466	231.0 (152.6–2502.0)	265.8 (104.2–3414.2)	0.8870
Chemokines	IL-10, pg/mL	85.8 (6.6–466.0†)	41.3 (1.8–466.0†)	0.3421	143.4 (9.1–466.0†)	47.0 (1.8–466.0†)	0.2550
	IL-8, pg/mL	413.0 (14.2–750.0†)	106.4 (24.3–750.0†)	0.3709	750.0† (45.6–750.0†)	107.4 (14.2–750.0†)	0.1236
	CXCL10, pg/mL	2000.0† (705.0–2000.0†)	2000.0† (277.6–2000.0†)	0.7982	2000.0† (1080.4–2000.0†)	2000.0† (277.6–2000.0†)	0.5072
	MCP-1, pg/mL	1500.0† (823.3–1500.0†)	1500.0† (671.2–1500.0†)	1.0000	1500.0† (1197.8–1500.0†)	1500.0† (671.2–1500.0†)	0.6357
Effector	Granzyme B, pg/mL	164.7 (11.5–10,000.0†)	40.4 (1.0*–5477.4)	0.0803	35.9 (19.4–10,000.0†)	49.2 (1.0*– 5477.4)	0.6691

*Value represents lower limit of quantification in assay used.

†Value represents upper limit of quantification in assay used.

CRP, C-reactive protein; CXCL, C-X-C motif chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; ICAM, intercellular adhesion molecule; IL, interleukin; IP, interferon γ-induced protein; MCP, monocyte attractant protein; Rα, receptor alpha; RA, receptor antagonist; SAA, serum amyloid A; TNF-α, tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule.

Supplementary Table S11. Product characteristics by dose

Median characteristic (range)	2×10^6 (n=4)	1×10^6, 68 mL (n=11)	1×10^6, 40 mL (n=9)
T-cell subsets, %			
Naïve	32.6 (12.7-67.2)	53.0 (1.7-93.1)	38.6 (3.8-75.3)
Central memory	15.4 (10.4-23.2)	9.1 (3.3-54.2)	11.9 (1.6-56.7)
Effector	15.7 (4.9-20.1)	8.6 (1.1-72.0)	10.4 (1.9-66.1)
Effector memory	36.1 (4.6-57.8)	10.8 (2.1-74.7)	14.6 (3.1-61.5)
CD4, %	36.2 (12.4-63.9)	38.3 (8.3-80.4)	40.1 (16.5-56.9)
CD8, %	63.9 (35.3-87.6)	61.7 (19.3-91.7)	56.6 (43.1-82.8)
CD4/CD8 ratio	0.6 (0.1-1.8)	0.6 (0.1-4.2)	0.7 (0.2-1.3)
CCR7+, %	48.0 (23.1–90.4)	73.8 (17.3–96.6)	80.2 (6.8–89.4)
IFN-γ production in co-culture (pg/mL)*	4325.0 (2145.0-8299.0)	5234.0 (42.0-19,500.0)	7341.0 (2824.0-13,500.0)
Transduction, %	49.9 (31.1-66.5)	67.7 (33.6-87.8)	49.0 (32.0-72.0)
Viability, %	90.3 (83.6–95.0)	91.0 (76.0–97.0)	91.0 (87.0–94.0)

*Co-culture experiments were performed using Toledo cells mixed in a 1:1 ratio with KTE-X19 product cells. IFN-γ was measured in cell culture media 24 hours post-incubation using a qualified ELISA.

ELISA, enzyme-linked immunosorbent assay; IFN-γ, interferon gamma.

Supplementary Table S12. Product characteristics by response, MRD status, cytokine release syndrome, and neurologic events

Median characteristic (range)	Complete remission (CR+CRi) (n=16)	No response (n=8)
CCR7+, %	81.0 (9.7–96.6)	38.0 (6.8–87.4)
CD4/CD8 ratio	0.7 (0.1–1.8)	0.5 (0.1–4.2)
Median characteristic (range)	**MRD negative (n=18)**	**MRD positive (n=3)**
CCR7+, %	81.0 (9.7–96.6)	18.8 (6.8–82.3)
CD4/CD8 ratio	0.7 (0.1–1.8)	0.2 (0.1–0.5)
Median characteristic (range)	**Grade ≥3 CRS (n=8)**	**Grade ≤2 CRS (n=16)**
CCR7+, %	78.2 (38.7–92.0)	73.2 (6.8–96.6)
CD4/CD8 ratio	0.7 (0.4–1.8)	0.6 (0.1–4.2)
Median characteristic (range)	**Grade ≥3 NE (n=5)**	**Grade ≤2 NE (n=19)**
CCR7+, %	86.9 (57.2–92.0)	69.4 (6.8–96.6)
CD4/CD8 ratio	0.7 (0.5–1.6)	0.6 (0.1–4.2)

CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRS, cytokine release syndrome; MRD, minimal residual disease; NE, neurologic event.

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