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

Alan S. Wayne,[1] Van Huynh,[2] Nobuko Hijiya,[3] Rayne H. Rouce,[4] Patrick A. Brown,[5] Joerg Krueger,[6] Carrie L. Kitko,[7] Edward Dela Ziga,[8] Michelle L. Hermiston,[9] Michael K. Richards,[10] Andre Baruchel,[11] Petra C. Schuberth,[12] John Rossi,[12] Lang Zhou,[12] Lovely Goyal,[12] Rajul Jain,[12] Remus Vezan,[12] Behzad Kharabi Masouleh[12] and Daniel W. Lee[13]

[1]Children's Hospital Los Angeles, USC Norris Comprehensive Cancer Center and Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [2]CHOC Children's Hospital, Orange, CA, USA; [3]Columbia University Irving Medical Center, New York City, NY, USA; [4]Texas Children's Hospital, Houston, TX, USA; [5]Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; [6]The Hospital for Sick Children, University of Toronto, Ontario, Canada; [7]Vanderbilt University Medical Center, Nashville, TN, USA; [8]University of Miami Miller School of Medicine, Miami, FL, USA; [9]University of California San Francisco Benioff Children's Hospital, San Francisco, CA, USA; [10]Children's Minnesota, Minneapolis, MN, USA; [11]Hôpital Universitaire Robert Debré (APHP) and Université de Paris, Paris, France; [12]Kite, a Gilead Company, Santa Monica, CA, USA and [13]University of Virginia Children's Hospital, UVA Cancer Center, UVA School of Medicine, Charlottesville, VA, USA

Correspondence: A.S. Wayne
awayne@chla.usc.edu

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Abstract

Here we present the 3-year results of ZUMA-4, a phase I/II multicenter study evaluating the safety and efficacy of KTE-X19, an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in pediatric/adolescent patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Phase I explored two dose levels and formulations. The primary endpoint was the incidence of dose-limiting toxicities. Thirty-one patients were enrolled; KTE-X19 was administered to 24 patients (median age 13.5 years, range 3-20; median follow-up 36.1 months). No dose-limiting toxicities were observed. All treated patients had grade ≥3 adverse events, commonly hypotension (50%) and anemia (42%). Grade 3 cytokine release syndrome rates were 33% in all treated patients, 75% in patients given the dose of 2×10^6 CAR T cells/kg, 27% in patients given the dose of 1×10^6 cells/kg in the 68 mL formulation, and 22% in patients given the dose of 1×10^6 cells/kg in the 40 mL formulation; the percentages of patients experiencing grade ≥3 neurologic events were 21%, 25%, 27%, and 11% respectively. Overall complete remission rates (including complete remission with incomplete hematologic recovery) were 67% in all treated patients, 75% in patients given 2×10^6 CAR T cells/kg, 64% in patients given 1×10^6 cells/kg in the 68 mL formulation, and 67% in patients given 1×10^6 cells/kg in the 40 mL formulation. Overall minimal residual disease-negativity rates were 100% among responders; 88% of responders underwent subsequent allogeneic stem-cell transplantation. In the 1×10^6 (40 mL) group (recommended phase II dose), the median duration of remission censored at allogeneic stem-cell transplantation and median overall survival were not reached. Pediatric/adolescent patients with relapsed/refractory B-cell acute lymphoblastic leukemia achieved high minimal residual disease-negative remission rates with a manageable safety profile after a single dose of KTE-X19. Phase II of the study is ongoing at the dose of 1×10^6 CAR T cells/kg in the 40 mL formulation. ClinicalTrials.gov: NCT02625480.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, representing approximately 75% of childhood leukemias and 25% of all childhood cancers; 85% of these cases are B-cell precursor ALL (B-ALL).[1-3] Although most children with B-ALL achieve durable complete remissions (CR) after initial treatment, approximately 10-20% develop relapsed/refractory (R/R) B-ALL with reported 2-year event-free survival rates of 35-46% after a second salvage attempt.[2,3] While allogeneic stem-cell transplant (alloSCT) is a standard treatment option for many patients who relapse after first-line chemotherapy, some do not qualify for or are not indicated for alloSCT because of an inability to achieve CR, lack of a suitable donor, comorbidities, or late bone marrow relapse.[4-8] Rates of relapse fol-

lowing alloSCT remain high despite treatment advances and survival rates are low[2,9-11] especially for those with residual disease,[12,13] highlighting the need for more effective therapies in pediatric R/R B-ALL.

The CD19-targeting immunotherapeutic agent blinatumomab, approved for the treatment of R/R B-ALL in adults and children, has shown efficacy in pediatric R/R B-ALL with CR rates of 39-63%, though the median overall survival (OS) was 7.5-14.6 months with more favorable survival in patients who proceeded to alloSCT.[14-18] Tisagenlecleucel, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of R/R B-ALL in patients ≤25 years of age,[19,20] led to more favorable remission rates in a phase II study than those previously reported with blinatumomab, although patients who had received prior anti-CD19 therapies were excluded from that study.[21,22]

An anti-CD19 CAR T-cell therapy containing a CD3ζ and CD28 co-stimulatory domain, developed at the National Cancer Institute,[23,24] resulted in a 70% complete remission rate (CR+CR with incomplete hematologic recovery [CRi]) in children and adults ≤30 years of age with R/R B-ALL.[25] KTE-X19, an autologous anti-CD19 CAR T-cell therapy with a CD3ζ and CD28 co-stimulatory domain,[26,27] is approved by the Food and Drug Administration for the treatment of adults with R/R B-ALL.[26,28] The manufacturing process for KTE-X19 removes leukemic blasts, as the presence of blasts may result in manufacturing failures and exhaustion of anti-CD19 CAR T cells during *ex vivo* manufacturing.[29,30] KTE-X19 is manufactured at a centralized facility with worldwide shipment allowing for a fast turnaround time, which is critical for patients with rapidly proliferating disease and high tumor burden.[28,30,31]

Here we report the long-term results of phase I of the multicenter, single-arm, open-label, ZUMA-4 study evaluating the safety and efficacy of KTE-X19 in children and adolescents with R/R B-ALL.

Methods

Patients

In phase I of ZUMA-4, eligible patients were ≤21 years of age with a body weight of ≥6 kg and had R/R B-ALL, defined as refractory to first-line therapy, R/R after two or more lines of systemic therapy, or R/R after alloSCT if the patient was ≥100 days from alloSCT at the time of enrollment and off immunosuppressive medications for ≥4 weeks prior to enrollment. Prior treatment with blinatumomab was allowed (see *Online Supplementary Methods* for detailed eligibility criteria).

Study design and treatment

The phase I portion of ZUMA-4 was conducted at ten sites in the USA and one in Canada (*Online Supplementary Table S1*). The Institutional Review Board of each study site approved the study protocol. All patients or legally acceptable representatives (e.g., parent, legal guardian) provided written, informed assent/consent to participation in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. This trial is registered at *www.ClinicalTrials.gov* (NCT02625480).

The objective of phase I was to evaluate the safety of KTE-X19 and determine the recommended phase 2 dose (RP2D) of KTE-X19 based on the incidence of dose-limiting toxicities (DLT; defined in the *Online Supplementary Methods* and *Online Supplementary Table S2*) and the overall safety profile. DLT were evaluated in the first three patients treated at the starting dose of 2×10^6 CAR T cells/kg. One additional patient was enrolled to receive 2×10^6 CAR T cells/kg. A Safety Review Team analyzed safety data after these patients had been followed for 28 days post-infusion, and subsequent patients received 1×10^6 CAR T cells/kg to further evaluate the potential to mitigate the risk of cytokine release syndrome (CRS) and neurologic events and thereby improve the risk:benefit ratio. The 1×10^6 CAR T cells/kg dosing formulation was modified from 68 mL to 40 mL for patients in a second cohort to achieve a higher final product cell density as part of product optimization to increase cell viability during cryopreservation and thawing.

Patients underwent leukapheresis to obtain cells for CAR T-cell manufacturing, followed by subsequent conditioning chemotherapy with fludarabine 25 mg/m^2/day on days -4, -3, and -2, and cyclophosphamide 900 mg/m^2 on day -2. Fresh leukapheresis material was used for CAR T-cell manufacturing; the manufactured CAR T cells were cryopreserved for shipment to the sites and thawed prior to infusion. Specified bridging chemotherapy was permitted between leukapheresis and conditioning chemotherapy (*Online Supplementary Methods; Online Supplementary Table S3*). KTE-X19 was administered on day 0 at the target dose of 2×10^6 or 1×10^6 CAR T cells/kg (68 mL or 40 mL formulation). Hospitalization was required for a minimum of 7 days after the infusion, followed by response assessments at prespecified time-points (*Online Supplementary Methods*).

Patients receiving 1×10^6 CAR T cells/kg (68 mL) were treated under original toxicity management guidelines, which included administration of tocilizumab for neurologic events only in the context of concurrent CRS and initiation of steroids for grade 2 neurologic events; patients receiving 1×10^6 CAR T cells/kg (40 mL) were treated under revised toxicity management guidelines according to which steroids were initiated for grade 1 neurologic events (*Online Supplementary Table S4*).

Outcomes and assessments

The primary endpoint of the phase I part of the study was

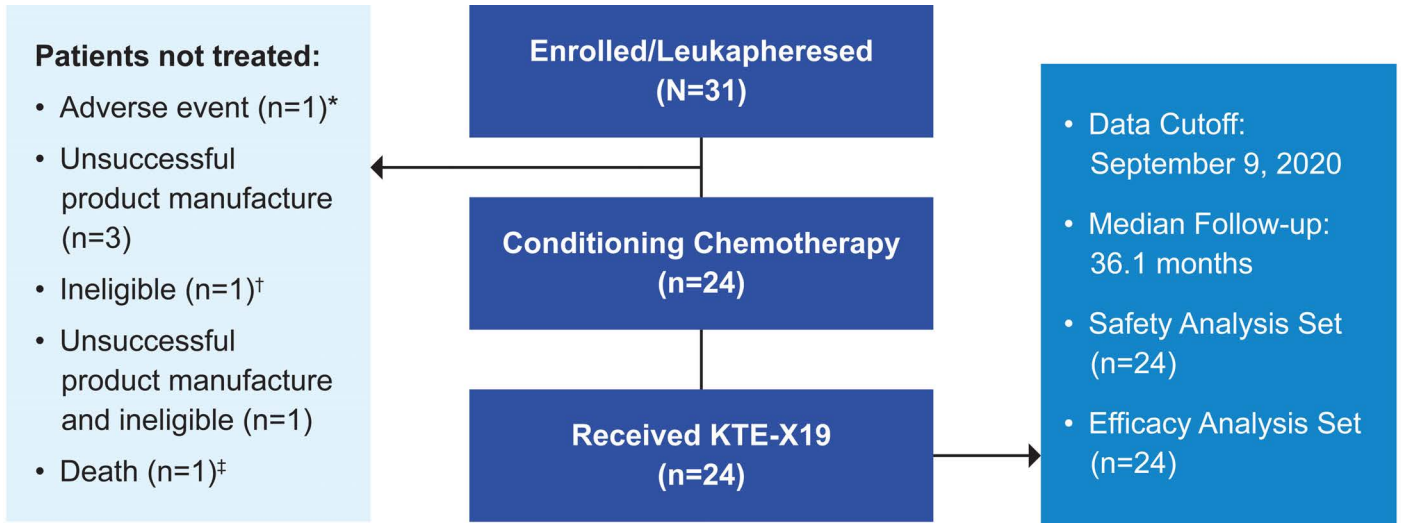

Figure 1. Flow diagram of patients in the ZUMA-4 study. *Central nervous system lesion (lesion right middle cranial fossa). †Ineligible due to an adverse event (pericardial effusion). ‡Death due to transverse myelitis.

the incidence of DLT in the set of patients evaluable for DLT, which included the first three patients treated with KTE-X19 at the 2×10^6 CAR T cells/kg dose. Secondary endpoints included safety, overall CR rate (CR+CRi), duration of remission (DOR), minimal residual disease (MRD)-negativity rate, alloSCT rate, OS, and relapse-free survival (RFS). CRS was graded according to the 2014 modified criteria of Lee *et al.*[32] Bone marrow evaluations and response assessments were conducted at day 28 and months 2 and 3 during the post-treatment period, and months 6, 9, 12, 15, 18, and 24 during the long-term follow-up period. MRD was tested in bone marrow using flow cytometry (Neogenomics, Fort Myers, FL, USA; sensitivity 0.01%). Additional endpoint and disease assessments are detailed in the *Online Supplementary Methods*.

Statistical analysis

The safety and efficacy analyses included all patients who received any dose of KTE-X19. Data are reported as of September 9, 2020. Additional statistical methods are described in the *Online Supplementary Methods*.

Results

Patients

Between February 17, 2016 and August 1, 2018, 31 patients were enrolled and underwent leukapheresis. The median time from leukapheresis to KTE-X19 product release was 14.0 days (range, 9.0-20.0) for all treated patients, 16.5 days (range, 12.0-23.0) from leukapheresis to delivery to study site, and 27.0 days (range, 18.0-41.0) from leukapheresis to infusion. Of the 31 enrolled patients, 24 (77%) received conditioning chemotherapy and were subsequently given KTE-X19. Seven patients were not given KTE-X19 for the following reasons: adverse event (n=1), unsuccessful product manufacture (n=3), ineligible due to adverse event (n=1), unsuccessful product manufacture and ineligible (n=1), and death (n=1) (Figure 1). Twenty-four patients received conditioning chemotherapy followed by KTE-X19; four patients received the 2×10^6 CAR T cells/kg dose, 11 received the 1×10^6 CAR T cells/kg (68 mL) dose formulation, and nine received the 1×10^6 CAR T cells/kg (40 mL) dose formulation. The median follow-up for all treated patients was 36.1 months (range, 24.0-53.9). The median age of treated patients was 13.5 years. Forty-two percent of patients had received three or more prior lines of therapy, including six patients (25%) who had previously undergone alloSCT, eight (33%) who had previously received blinatumomab, and one (4%) who had been treated with prior inotuzumab ozogamicin (Table 1). One patient (4%) had non-central nervous system extramedullary disease (*Online Supplementary Results*). Some patients had high-risk cytogenetics, including the Philadelphia chromosome t(9;22) mutation (n=4 [17%]), *MLL* translocation t(4;11) t(8;14) (n=1 [4%]), complex karyotype (≥5 abnormalities, n=4 [17%]), low hypodiploidy (30-39 chromosomes, n=1 [4%]), and near triploidy (60-78 chromosomes, n=2 [8%]). Of the 31 enrolled patients, 30 (97%) received bridging therapy per protocol with new baseline disease assessments performed just prior to conditioning chemotherapy.

Safety

Among the three DLT-evaluable patients receiving 2×10^6 CAR T cells/kg, no DLT were observed. All treated patients (n=24) experienced at least one grade ≥3 adverse event, most commonly hypotension (50%) and anemia (42%) (Table 2; *Online Supplementary Table S5*). Serious adverse events of any grade occurred in 71% of patients (*Online Supplementary Table S6*). Grade ≥3 infections occurred in 42% of patients (*Online Supplementary Table S7*).

CRS was reported in 21 of the 24 treated patients (88%), with eight (33%) experiencing grade ≥3 CRS (Table 3) according to modified Lee grading criteria.[32] No grade 4 or grade 5 CRS events occurred. The most common grade ≥3 CRS symptoms were hypotension (50%) and pyrexia (25%).

Table 1. Patients' characteristics.

Characteristic	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)
Age in years, median (range)	11.5 (8-18)	12 (4-17)	14 (3-20)	13.5 (3-20)
Sex, N (%)				
Male	2 (50)	8 (73)	5 (56)	15 (63)
Female	2 (50)	3 (27)	4 (44)	9 (38)
Lansky score, N (%)				
80	0	1 (9)	0	1 (4)
90	1 (25)	6 (55)	4 (44)	11 (46)
100	2 (50)	2 (18)	2 (22)	6 (25)
Karnofsky score, N (%)				
80	0	2 (18)	1 (11)	3 (13)
90	0	0	2 (22)	2 (8)
100	1 (25)	0	0	1 (4)
Number of prior lines of therapy, N (%)				
≤2	2 (50)	5 (45)	7 (78)	14 (58)
≥3	2 (50)	6 (55)	2 (22)	10 (42)
Prior blinatumomab, N (%)*	0	5 (45)	3 (33)	8 (33)
Prior inotuzumab ozogamicin, N (%)	0	1 (9)	0	1 (4)
Prior stem cell transplant, N (%)	1 (25)	4 (36)	1 (11)	6 (25)
Refractory subgroup pre-enrollment, N (%)				
Relapsed or refractory to ≥2nd-line therapy	2 (50)	3 (27)	6 (67)	11 (46)
Relapsed or refractory after alloSCT	1 (25)	4 (36)	1 (11)	6 (25)
Primary refractory	1 (25)	4 (36)	2 (22)	7 (29)
Percentage BM blasts at screening, median (range)	57 (41-99)	28 (7-98)	58 (6-97)	44 (6-99)
Percentage BM blasts before conditioning, median (range)	85 (49-100)	6 (0-89)	44 (1-82)	37 (0-100)

*Three patients (13%) received blinatumomab as the last prior therapy. alloSCT: allogeneic stem cell transplant; BM: bone marrow.

Any-grade and grade ≥3 hypoxia was observed in 13% and 8% of patients, respectively. The median time to the onset of CRS and duration after KTE-X19 infusion was 5 days (range, 1-14) and 7 days, respectively, with all events resolved.

Among all treated patients, any-grade neurologic events were reported in 16 patients (67%), and grade ≥3 events occurred in five patients (21%), with encephalopathy (13%) being the most common grade ≥3 event (Table 3). One grade 4, fully reversible neurologic event (brain edema) occurred in a patient who received 1×10^6 CAR T cells/kg (68 mL); for the management of this event, the patient was treated with dexamethasone, mannitol, sodium chloride, and tocilizumab. There were no grade 5 neurologic events. Overall, the median time to onset of neurologic events was 9.5 days (range, 3-60) after infusion, the median time from resolution of the first CRS to onset of the first neurologic event was 4 days (range, -3 to 52 [the first CRS resolved after the onset of the first neurologic event in 4 patients]), and the median duration of neurologic events was 8 days. Neurologic events resolved in 14 of 16 patients (88%). The neurologic events of the remaining two patients were ongoing at the time of death, which was due to an adverse event (n=1) or progressive disease (n=1). Ten of 16 patients (63%) who experienced neurologic events had concurrent CRS.

Among all treated patients, 42% received steroids, 63% received tocilizumab, and 46% received vasopressors (Table 3). Improved overall safety was observed in the nine patients treated with the 1×10^6 CAR T cells/kg (40 mL) dose under revised toxicity management, relative to the four patients treated with 2×10^6 CAR T cells/kg and the 11 patients treated with 1×10^6 CAR T cells/kg (68 mL) under the original guidelines. Of the patients receiving 2×10^6 CAR T cells/kg, 75% experienced grade ≥3 CRS, compared with 27% and 22% of patients receiving 1×10^6 CAR T cells/kg (68 mL and 40 mL, respectively). Grade ≥3 neurologic events were observed in 25% of patients who received 2×10^6 CAR T cells/kg and 27% of patients who received 1×10^6 CAR T cells/kg (68 mL) but were lowest (11%) in patients who received 1×10^6 CAR T cells/kg (40 mL). In addition, the median time to onset of neurologic events, as well as CRS, appeared to be delayed in the 1×10^6 CAR T cells/kg dose cohorts compared with the 2×10^6 CAR T cells/kg dose cohort (Table 3).

Among the eight patients (33%) who died on study, six

died from progressive disease (median, 190.5 days after KTE-X19 infusion), and two patients died from adverse events considered unrelated to KTE-X19, including disseminated mucormycosis (n=1, day 15 after KTE-X19 infusion) and *Escherichia* sepsis (n=1, day 409 after KTE-X19 infusion). Of those who died, three patients had received 2×10^6 CAR T cells/kg, four had received 1×10^6 CAR T cells/kg (68 mL), and one had received 1×10^6 CAR T cells/kg (40 mL). No patient tested positive for replication-competent retrovirus or antibodies to anti-CD19 CAR at any time.

Efficacy

With a median follow-up of 36.1 months (range, 24.0-53.9), all treated patients (n=24) were evaluable for efficacy. The overall remission rate by investigator assessment was 67%, with 29% of patients (n=7) achieving CR and 38%

Table 2. Adverse events.

Adverse events, 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
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

*Table includes adverse events of any grade occurring in ≥20% of all patients.

achieving CRi (n=9) (Table 4). In the 2×10^6, 1×10^6 (68 mL), and 1×10^6 (40 mL) CAR T cells/kg dose groups, the CR+CRi rate was 75%, 64%, and 67%, respectively. Prespecified subgroup analyses of CR+CRi are reported in *Online Supplementary Figure S1*. Of eight patients who had received prior blinatumomab therapy, three (38%) achieved CR+CRi (*Online Supplementary Figure S1, Online Supplementary Results*). The median time from infusion to first CR+CRi across dose levels was 30 days (range, 26-113 days). The overall MRD-negativity rate was 100% among the 16 patients with CR+CRi. Sixteen patients overall (67%) underwent alloSCT as subsequent consolidative therapy, including two, eight and six patients in the 2×10^6, 1×10^6 (68 mL), and 1×10^6 (40 mL) CAR T cells/kg dose groups, respectively. These included 14 of the 16 patients (88%) who achieved CR+CRi, the patient who achieved CR with partial hematologic recovery, and the patient with blast-free hypoplastic/aplastic bone marrow; the latter two subsequently achieved CR. Of all 16 transplanted patients, the median time to subsequent alloSCT was 2.3 months (range, 1.4-24.9) after KTE-X19; five of the 16 patients had received a prior transplant. Of the two patients who achieved CR+CRi but did not undergo a subsequent alloSCT, one died due to progressive disease, and one was lost to follow-up.

The median DOR for the 16 patients who achieved CR+CRi after KTE-X19 was 7.2 months (95% confidence interval [95% CI]: 4.1 months-not estimable) after censoring for subsequent alloSCT, and was 4.1 months, 10.7 months, and not reached in the 2×10^6, 1×10^6 (68 mL), and 1×10^6 (40 mL) CAR T cells/kg dose groups, respectively (Figure 2A). The median DOR was 14.2 months (95% CI: 3.9 months-not estimable) without censoring for subsequent alloSCT (*Online Supplementary Figure S2A*). The median DOR among the 14 patients with CR+CRi who underwent a subsequent alloSCT after KTE-X19 was 10.7 months (95% CI: 7.2

Table 3. Cytokine release syndrome and neurologic events.

Toxicity management, 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)	
Steroids	1 (25)		4 (36)		5 (56)		10 (42)	
Tocilizumab	3 (75)		6 (55)		6 (67)		15 (63)	
Vasopressors for treatment of CRS	3 (75)		4 (36)		2 (22)		9 (38)	
Adverse events, N (%)*	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
CRS†,‡	4 (100)	3 (75)	9 (82)	3 (27)	8 (89)	2 (22)	21 (88)	8 (33)
Pyrexia	3 (75)	3 (75)	9 (82)	2 (18)	5 (56)	1 (11)	17 (71)	6 (25)
Hypotension	4 (100)	4 (100)	8 (73)	6 (55)	4 (44)	2 (22)	16 (67)	12 (50)
Headache	1 (25)	0	3 (27)	0	3 (33)	0	7 (29)	0
Tachycardia	0	0	2 (18)	1 (9)	4 (44)	0	6 (25)	1 (4)
Chills	0	0	0	0	3 (33)	0	3 (13)	0
Febrile neutropenia	0	0	0	0	3 (33)	3 (33)	3 (13)	3 (13)
Hypoxia	1 (25)	1 (25)	1 (9)	0	1 (11)	1 (11)	3 (13)	2 (8)
Sinus tachycardia	0	0	3 (27)	0	0	0	3 (13)	0
Neurologic events‡,§	1 (25)	1 (25)	9 (82)	3 (27)	6 (67)	1 (11)	16 (67)	5 (21)
Confusional state	0	0	4 (36)	0	2 (22)	0	6 (25)	0
Encephalopathy	1 (25)	1 (25)	1 (9)	1 (9)	2 (22)	1 (11)	4 (17)	3 (13)
Aphasia	1 (25)	1 (25)	1 (9)	0	1 (11)	0	3 (13)	1 (4)
Lethargy	0	0	2 (18)	1 (9)	1 (11)	0	3 (13)	1 (4)
Tremor	0	0	2 (18)	0	1 (11)	0	3 (13)	0
Onset and duration of toxicity in days, median (range)								
CRS								
Time to onset	2 (1-4)		6 (3-14)		7 (1-9)		5 (1-14)	
Duration	10.5		7		8		7	
Neurologic events								
Time to onset	7 (7-7)		9 (4-14)		10 (3-60)		9.5 (3-60)	
Duration	NA‖		8		11		8	

*Includes symptoms of cytokine release syndrome and neurologic events occurring in ≥10% of all patients. †Cytokine release syndrome was categorized according to the 2014 modified grading system proposed by Lee *et al.*[32] ‡Individual symptoms of the cytokine release syndrome and neurologic events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. §One patient treated with 2×10^6 cells/kg had grade 2 seizure, and one patient treated with 1×10^6 cells/kg (68 mL) had grade 2 generalized tonic-clonic seizure. ‖The neurologic event was ongoing at the time of death. CRS: cytokine release syndrome; NA: not applicable.

months-not estimable). The median RFS for all treated patients (n=24) after censoring for subsequent alloSCT was 5.2 months (95% CI: 0.03 months-not estimable). The median RFS for the group that received 1×10^6 CAR T cells/kg (40 mL) was not reached and was 5.2 months (95% CI: 0.03 months-not estimable) and 9.1 months (95% CI: 0.03 months-not estimable) in the 2×10^6 and 1×10^6 (68 mL) cells/kg cohorts, respectively (Figure 2B). The median RFS was 7.4 months (95% CI: 0.03 months-not estimable) without censoring for subsequent alloSCT (*Online Supplementary Figure S2B*). For the 16 patients who proceeded to subsequent alloSCT, the median RFS was 9.1 months (95% CI: 9.1 months-not estimable). The median RFS of patients in the intention-to-treat group (i.e., all those enrolled) with and without censoring for subsequent alloSCT (*Online Supplementary Figure S3A, B*) was 6.1 months (95% CI: 0.03 months-not estimable) and 6.2 months (95% CI: 0.03 months-not estimable), respectively. The median OS was not reached among all treated patients and in both 1×10^6 CAR T cells/kg dose groups and was 8.0 months for the 2×10^6 CAR T cells/kg dose group (Figure 2C). The 24-month OS rate was 87.5% (95% CI: 38.7-98.1%) for the 1×10^6 cells/kg (40 mL) dose and 72.7% (95% CI; 37.1-90.3%) for the 1×10^6 cells/kg (68 mL) dose. In the intention-to-treat group, the median OS was not reached (*Online Supplementary Figure S3C*). Overall, as of the data cutoff, eight of 24 treated patients (33%) had died, one had discontinued the study due to withdrawal of consent, and one was lost to follow-up. The remaining 14 patients (58%) were still alive and in continued follow-up as of the data cutoff; all of these patients underwent subsequent alloSCT after the administration of KTE-X19.

Based on the safety and efficacy data analysis, the RP2D was 1×10^6 KTE-X19 cells/kg (40 mL formulation) with revised toxicity management.

Translational analysis

CAR T-cell expansion in peripheral blood measured by droplet digital polymerase chain reaction and expressed as the number of CAR gene copies/μg DNA in blood was observed across dose groups with peak CAR T-cell levels reached by day 14 followed by a subsequent CAR T-cell contraction to baseline (Figure 3A; *Online Supplementary Table S8*). Median CAR T-cell levels were undetectable in blood by droplet digital polymerase chain reaction across all dose groups at 3 months after KTE-X19 infusion (*Online Supplementary Table S8*). Median peak CAR gene copies/μg DNA in blood were similar between the 1×10^6 CAR T cells/kg dose cohorts but were higher in the 2×10^6 CAR T cells/kg cohort (Figure 3B; *Online Supplementary Figure S4A*). Patients achieving CR+CRi trended toward higher peak blood CAR gene copies/μg DNA in blood than non-responders, as did patients who were MRD negative compared to those who were MRD positive (Figure 3C, D; *Online Supplementary Figure S4B, C*). CAR gene copies/μg DNA in blood trended higher in patients who had grade ≥3 neurologic events compared with those who had grade ≤2 neurologic events (Figure 3E; *Online Supplementary Figure S4D*), while there was no apparent difference in CAR gene copies/μg DNA in blood for the small numbers of patients with either high- or low-grade CRS (Figure 3F; *Online Supplementary Figure S4E*). The median peak CAR gene copies/μg DNA in blood was 5.16×10^4 (range, 0-2.40×10^5) in the 16 patients who had not received prior blinatumomab therapy, and was 6.15×10^3 (range, 0-2.49×10^5) in the eight patients who had received prior blinatumomab.

Peak levels of multiple key serum cytokines, chemokines, and pro-inflammatory biomarkers occurred by day 7. Commensurate with peak CAR expansion, some serum analytes trended higher in patients dosed with 2×10^6 compared with 1×10^6 CAR T cells/kg (interleukin [IL]-2, IL-5, IL-

Table 4. Remission rates and minimal residual disease status.

Response category, 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)
Overall complete remission rate	3 (75)	7 (64)	6 (67)	16 (67)
Complete remission	0	3 (27)	4 (44)	7 (29)
Complete remission with incomplete hematologic recovery	3 (75)	4 (36)	2 (22)	9 (38)
Complete remission with partial hematologic recovery	0	1 (9)	0	1 (4)
Blast-free hypoplastic/aplastic bone marrow	0	0	1 (11)	1 (4)
No response	0	1 (9)	1 (11)	2 (8)
Unknown or not evaluable*	1 (25)	2 (18)	1 (11)	4 (17)
Overall MRD-negativity rate†	3 (75)	8 (73)	7 (78)	18 (75)

*Of the four patients whose response was unknown or not evaluable, two died and one had refractory disease before the first disease assessment. The remaining patient had refractory disease detected in the day 28 bone marrow assessment. †Minimal residual disease (MRD) negativity was assessed by flow cytometry with a sensitivity of 0.01% at day 28 and months 2 and 3. MRD results after allogeneic stem cell transplant or new anticancer therapies are excluded. MRD: minimal residual disease.

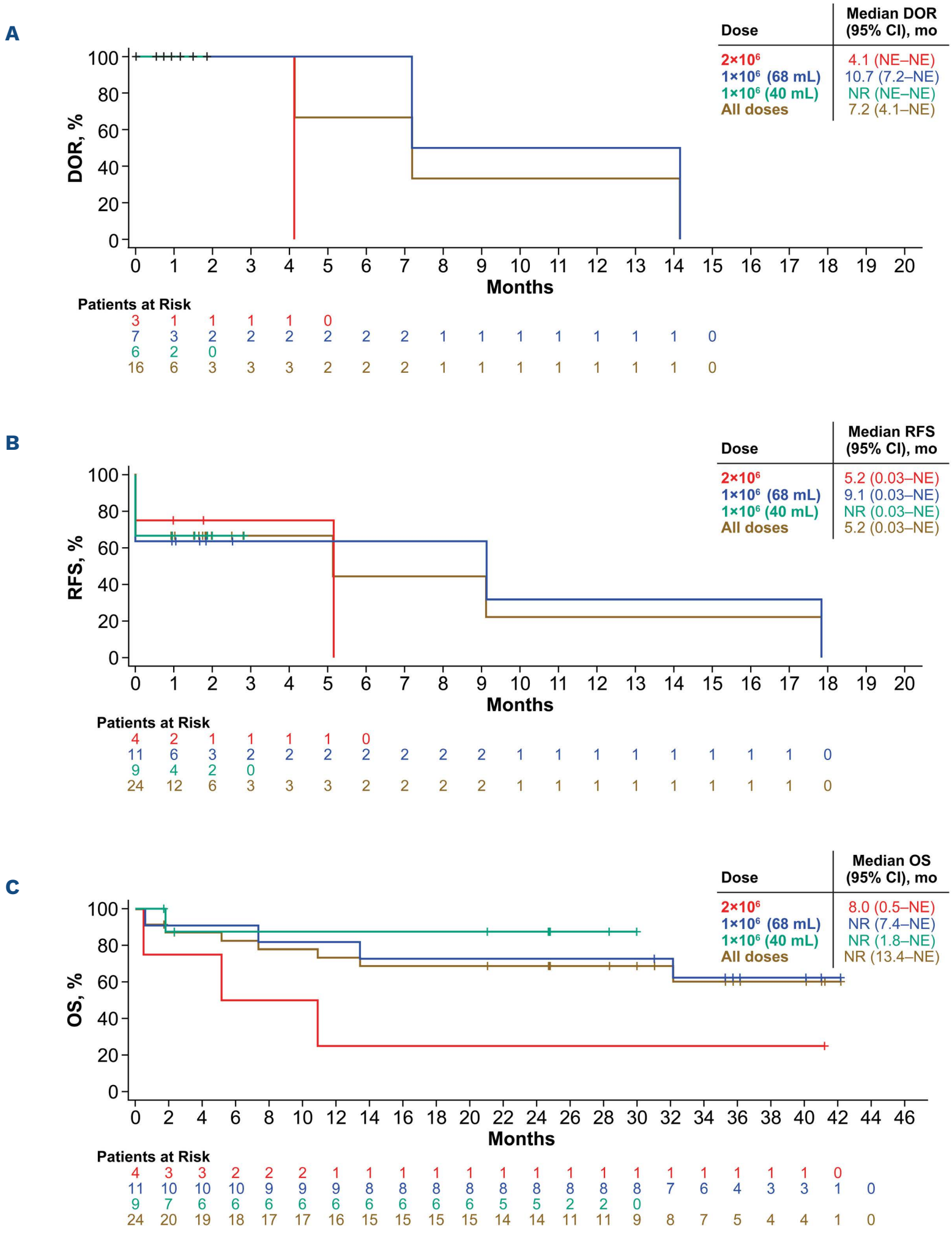

Figure 2. Duration of remission, relapse-free survival, and overall survival by dose level. (A) Kaplan-Meier curve of duration of remission. Patients who did not meet the criteria for relapse or who received subsequent anticancer therapy (including allogeneic stem-cell transplantation) and who remained alive were censored at the last evaluable disease assessment. (B) Kaplan-Meier curve of relapse-free survival. Patients who did not meet the criteria for relapse or who received subsequent anticancer therapy (including allogeneic stem-cell transplantation) and who remained alive were censored at the last evaluable assessment. (C) Kaplan-Meier curve of overall survival. Patients who had not died by the analysis data cutoff date were censored at their last contact date. DOR: duration of remission; mo: months; NE: not estimable; NR: not reached; OS: overall survival; RFS: relapse-free survival; 95% CI: 95% confidence interval.

6, IL-8, IL-10, IL-15, IL-16, ferritin, granzyme B, intercellular adhesion molecule 1, interferon-γ, and tumor necrosis factor-α) (Figure 4; *Online Supplementary Figure S5; Online Supplementary Table S9*).

Peak serum levels of vascular cell adhesion molecule-1 and IL-16 were associated with grade ≥3 CRS. Such associations were not observed in patients with grade ≥3 neurologic events, which may have been due to the small number of patients with such events (*Online Supplementary Table S10*). Product characteristics were similar

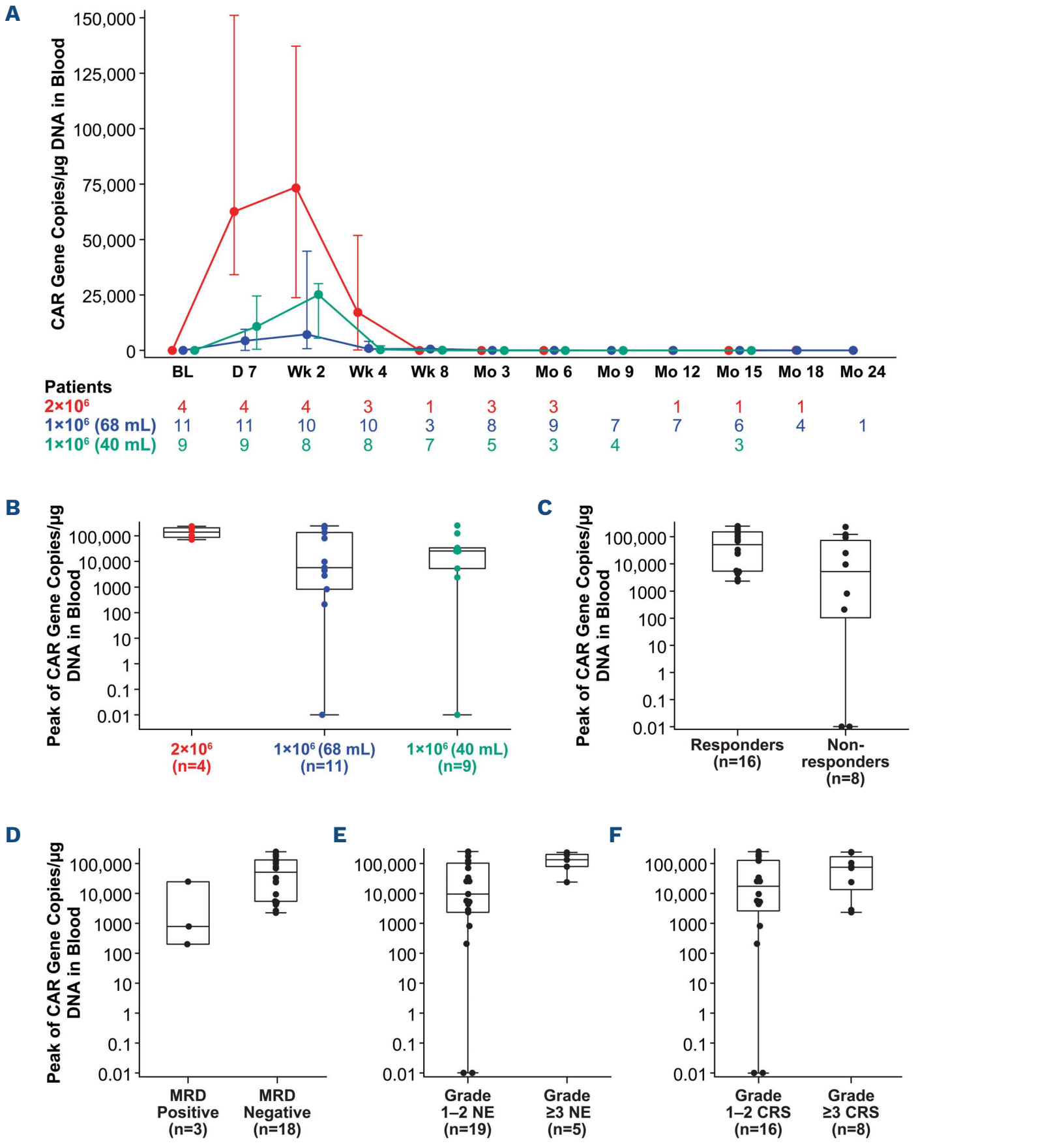

Figure 3. Peak chimeric antigen receptor gene copies/µg DNA and associations with response, minimal residual disease, and toxicity. (A) Expansion and persistence of chimeric antigen receptor (CAR) gene copies/µg DNA depicted as medians and interquartile ranges. (B) Peak CAR gene copies/µg DNA by dose level, including the two product formulations for the 1×10⁶ cells/kg dose level. (C-F) Association between peak CAR gene copies/µg DNA and overall remission rate (C), minimal residual disease (D), grade ≥3 neurologic events (E), and grade ≥3 cytokine release syndrome (F). Peak was defined as maximum CAR gene copies/µg of DNA in blood measured after infusion. Patients who were negative for minimal residual disease (MRD) included 16 responders (complete remission [CR] + CR with incomplete hematologic recovery [CRi]) and two non-CR+CRi patients, one with CR with partial hematologic recovery and one with blast-free hypoplastic/aplastic bone marrow. MRD assessment was not available for three patients. BL: baseline; CAR: chimeric antigen receptor; CRS: cytokine release syndrome; D: day; Mo: month; MRD: minimal residual disease; NE: neurologic events; Wk: week.

across dose levels (*Online Supplementary Table S11*). Proportions of less differentiated CCR7+ T cells in products trended higher in patients with CR+CRi and MRD negativity (*Online Supplementary Table S12*). This product profile also appeared to trend with higher levels of neurotoxicity but was not associated with CRS. The ratio of CD4 to CD8 T cells was not associated with response or toxicity.

Discussion

In phase I of ZUMA-4, no DLT were observed with KTE-X19 among the DLT-evaluable pediatric patients with R/R B-ALL. Although no DLT were observed at the initial dose of 2×10^6 CAR T cells/kg, a lower dose of 1×10^6 CAR T cells/kg with a 68 mL formulation was explored in a second cohort of patients in an effort to further improve the risk:benefit ratio, and dosing and toxicity management were further optimized in a third cohort at 1×10^6 CAR T cells/kg with a 40 mL formulation and revised toxicity management. This led to a more optimal risk:benefit ratio for the 1×10^6 CAR T cells/kg (40 mL) dose level with improvements for CRS and neurologic events. In addition, while MRD-negativity rates were ≥73% for all formulations, rates of MRD nega-

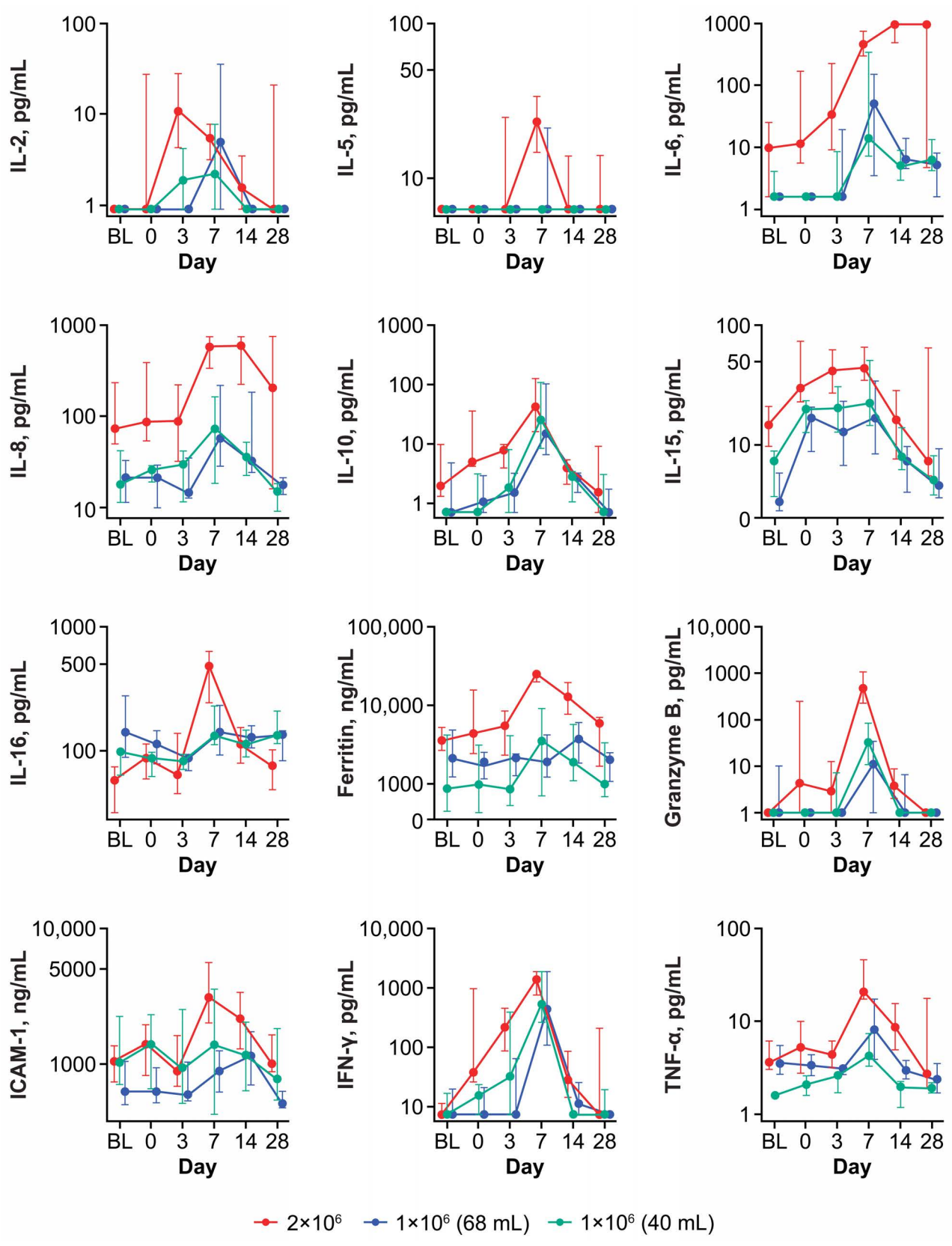

Figure 4. Levels of cytokines and inflammatory markers over time. Levels of key serum biomarkers depicted as medians and interquartile ranges by dose cohort over the first 4 weeks following KTE-X19 infusion. BL: baseline; ICAM: intercellular adhesion molecule 1; IFN-γ: interferon gamma; IL: interleukin; TNF-α: tumor necrosis factor alpha.

tivity and CR alone were highest in patients who received 1×10^6 CAR T cells/kg (40 mL). Importantly, the medians for DOR, RFS, and OS were not reached among the nine patients in the 1×10^6 CAR T cells/kg (40 mL) cohort, with most responders (5/6 [83%]) proceeding to subsequent alloSCT. Recognizing the limitations of a small cohort, nevertheless the 24-month OS rate in this group was 87.5%. These results suggest a meaningful durability of response with optimized dosing/formulation of KTE-X19 followed by subsequent alloSCT in pediatric/adolescent patients with R/R B-ALL.

The role of alloSCT following anti-CD19 CAR T-cell therapy in pediatric/adolescent patients with R/R B-ALL is still not well defined; studies in adult populations have provided somewhat conflicting results.[33,34] In the present study, the medians for DOR censored at subsequent alloSCT and OS were not reached in patients treated at the RP2D of 1×10^6 CAR T cells/kg (40 mL). Fourteen of the 16 patients (88%) who achieved CR+CRi, including five treated at the RP2D, underwent alloSCT as subsequent therapy. AlloSCT was not required per protocol but was allowed at the investigators' discretion. ZUMA-4 was not designed to assess outcomes after subsequent therapies; however, most responding patients proceeded to alloSCT after KTE-X19 as per investigators' decision.

An evaluation of DOR in ZUMA-4 without censoring for subsequent alloSCT revealed a favorable median of 14.2 months. Additionally, the median RFS with censoring for subsequent alloSCT was 5.2 months, but was 7.4 months without censoring. It has recently been reported that pediatric and young adults with R/R $CD19^+$ ALL who had no history of alloSCT, but who received consolidative alloSCT following anti-CD19 CAR T-cell therapy, trended toward improved leukemia-free survival with ≥1 year follow-up.[35] In a recently published phase I study of anti-CD19 CAR T-cell therapy in children and young adults with R/R B-ALL with 75% of MRD-negative responding patients proceeding to alloSCT, the median OS at 4.8 years follow-up was 70.2 months following alloSCT, the 5-year event-free survival following alloSCT was 61.9%, and the cumulative incidence of relapse following alloSCT was only 9.5% at 24 months.[36] Interestingly, a retrospective review of pediatric and young adult patients found that CD34-selected T-cell depleted alloSCT following CAR T-cell therapy may result in improved transplant-related mortality and OS *versus* that with unmodified alloSCT.[37]

It is difficult to draw conclusions from ZUMA-4 about the association between CAR T-cell persistence and durability of response given the low number of patients and the high rate of subsequent alloSCT. The median CAR T-cell levels in the blood of ZUMA-4 patients were undetectable across all doses at 3 months after the infusion, with the median time to alloSCT being 2.3 months and alloSCT likely eliminating remaining CAR T cells. Similarly, subsequent alloSCT precludes the assessment of B-cell aplasia in ZUMA-4. In studies with tisagenlecleucel, and in contrast to our study, subsequent alloSCT was performed in a minority of responding patients (12% to 16%).[38,39] With a short median follow-up of only 13.1 months approximately 40% of patients with a complete response to tisagenlecleucel relapsed, mostly with $CD19^-$ leukemia despite persistent CAR T cells.[21] After a median 24-month follow-up in that study, the 18-month OS rate was 70%,[38] whereas the 24-month OS rate in ZUMA-4 for patients treated at the RP2D was 87.5%. Data presented herein support the promising potential role for KTE-X19 in extending response durability and survival in pediatric/adolescent patients with R/R B-ALL, particularly if followed by alloSCT.

While differences in trial designs and patient populations preclude direct trial-to-trial comparisons, recent studies with blinatumomab, which also targets CD19, indicate a median OS of just 7.5 months in pediatric R/R B-ALL,[14] similar to results in adult ALL.[40] Also for blinatumomab, consolidation with subsequent alloSCT has shown improved outcomes (87% *vs*. 29% 1-year OS probability for patients with *vs*. without subsequent alloSCT, respectively).[17] Additionally, remission rates with blinatumomab were higher among pediatric patients with lower baseline tumor burden (<50% blasts; 56% CR) than in those with higher tumor burden (≥50% blasts; 33% CR).[14]

Data from ZUMA-4 suggest that KTE-X19 has the potential to offer more favorable efficacy in patients with high disease burden compared to results reported with blinatumomab. In ZUMA-4, a clear association between remission rates and bone marrow blasts prior to conditioning chemotherapy was not apparent, as CR rates were 83%, 50%, 80%, 50%, and 60% in patients with ≤5%, >5 to ≤25%, >25 to ≤50%, >50 to ≤75%, and >75 to 100% blasts at baseline, respectively. However, the small number of patients in each quartile, as well as the relatively high median tumor burden at baseline, limits interpretation (*Online Supplementary Figure S1*). This is in line with the findings of another pediatric and young adult study using CD19-directed CAR T-cell therapy in which no difference was observed in response rates based on disease burden.[41] Notably, however, a large retrospective study of pediatric and young adult patients with ALL found that pre-treatment disease burden was independently associated with poorer survival after CD19 CAR T-cell therapy.[42]

While CR+CRi rates appeared lower in patients who had received prior blinatumomab therapy in ZUMA-4, conclusions are limited due to the small number of patients. There are conflicting reports on the impact of prior anti-CD19 therapies, such as blinatumomab, in patients who later receive anti-CD19 CAR T-cell therapy. In a single institution study it was observed that prior blinatumomab

therapy was associated with a significantly higher rate of failure to achieve MRD-negative remission and also subsequent loss of remission with antigen escape after tisagenlecleucel in pediatric and adult R/R ALL.[43] In contrast, a large, multicenter retrospective study of CD19 CAR T-cell therapy in pediatric and young adult patients with R/R ALL found no difference in outcomes in regard to prior blinatumomab exposure, with the exception that non-response to blinatumomab was independently associated with lower CR, RFS, and event-free survival rates.[42] In ZUMA-4, one of three patients who had had a prior non-response to blinatumomab achieved a CR; however, the small numbers limit interpretation of these data.

The adverse event profile in ZUMA-4 was consistent with that in prior studies of anti-CD19 CAR T-cell therapies. For the patients who received KTE-X19, the median time from leukapheresis to product delivery to the study site was 16.5 days. In comparison, for the first 37 commercially manufactured tisagenlecleucel products for patients with B-ALL, the reported median throughput time was 23 days from receipt of the leukapheresed product to delivery to the clinical site.[44] The rapid turnaround time for treated patients in ZUMA-4 supports the feasibility in the setting of rapidly proliferating ALL. With the RP2D established, ZUMA-4 has transitioned into the phase II portion of the study.

We observed higher proportions of less differentiated CCR7$^+$ T cells in products in patients with CR+CRi and a trend in MRD-negative patients, as well as a trend toward higher peak CAR T-cell expansion in patients achieving CR/CRi and MRD negativity. These findings are consistent with a report that the frequency of CCR7$^+$ T cells in anti-CD19 CAR T-cell products correlates with CAR T-cell expansion.[45]

ZUMA-4 was limited by the small number of patients treated at each dose level; as such, the study was not powered to assess the contribution of various patients' characteristics to the outcomes observed. The durable outcomes reported herein are encouraging, although it is challenging to assess the long-term efficacy of KTE-X19 alone given that most responding patients proceeded to subsequent alloSCT. Future studies are warranted to determine which patients might benefit the most from KTE-X19 followed by alloSCT.

The unmet medical need in R/R pediatric ALL is greatest for patients who relapse early or have primary refractory disease with a 5-year OS rate of 21-28%.[2,4,8,46-48] In addition, the risk of treatment-related morbidity and mortality is 3-5 times greater in patients who have MRD-positive disease at the end of initial and later lines of therapy than in patients who have undetectable MRD.[3] To address this evolving unmet medical need, ZUMA-4 was further amended to broaden the eligibility criteria to include patients with MRD-positive disease and patients with early first relapse (≤18 months). Additionally, a second cohort was opened for pediatric patients with R/R non-Hodgkin lymphoma (diffuse large B-cell lymphoma, Burkitt lymphoma, and primary mediastinal B-cell lymphoma).

Disclosures

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Contributions

ASW, RV, RJ, and DWL designed the study. ASW, VH, NH, RHR, PAB, JK, MR, CLK, EDZ, MLH, MKR, AB, and DWL enrolled and treated patients and gathered data. PCS, JR, LZ, LG, BKM, RJ, and RV contributed to the verification, analysis, and interpretation of the data. All authors participated in writing the manuscript, had full access to the data, and approved the final submitted version.

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Data-sharing statement

Kite is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health, and access can be requested by contacting medinfo@kitepharma.com.

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