KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study

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Summary

Background Despite treatment with novel therapies and allogeneic stem-cell transplant (allo-SCT) consolidation, outcomes in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia remain poor, underlining the need for more effective therapies.

Methods We report the pivotal phase 2 results of ZUMA-3, an international, multicentre, single-arm, open-label study evaluating the efficacy and safety of the autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy KTE-X19 in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia. Patients were enrolled at 25 sites in the USA, Canada, and Europe. Eligible patients were aged 18 years or older, with Eastern Cooperative Oncology Group performance status of 0–1, and morphological disease in the bone marrow (>5% blasts). After leukapheresis and conditioning chemotherapy, patients received a single KTE-X19 infusion (1×10^6 CAR T cells per kg bodyweight). The primary endpoint was the rate of overall complete remission or complete remission with incomplete haematological recovery by central assessment. Duration of remission and relapse-free survival, overall survival, minimal residual disease (MRD) negativity rate, and allo-SCT rate were assessed as secondary endpoints. Efficacy and safety analyses were done in the treated population (all patients who received a dose of KTE-X19). This study is registered with ClinicalTrials.gov, NCT02614066.

Findings Between Oct 1, 2018, and Oct 9, 2019, 71 patients were enrolled and underwent leukapheresis. KTE-X19 was successfully manufactured for 65 (92%) patients and administered to 55 (77%). The median age of treated patients was 40 years (IQR 28–52). At the median follow-up of 16·4 months (13·8–19·6), 39 patients (71%; 95% CI 57–82, p<0·0001) had complete remission or complete remission with incomplete haematological recovery, with 31 (56%) patients reaching complete remission. Median duration of remission was 12·8 months (95% CI 8·7–not estimable), median relapse-free survival was 11·6 months (2·7–15·5), and median overall survival was 18·2 months (15·9–not estimable). Among responders, the median overall survival was not reached, and 38 (97%) patients had MRD negativity. Ten (18%) patients received allo-SCT consolidation after KTE-X19 infusion. The most common adverse events of grade 3 or higher were anaemia (27 [49%] patients) and pyrexia (20 [36%] patients). 14 (25%) patients had infections of grade 3 or higher. Two grade 5 KTE-X19-related events occurred (brain herniation and septic shock). Cytokine release syndrome of grade 3 or higher occurred in 13 (24%) patients and neurological events of grade 3 or higher occurred in 14 (25%) patients.

Interpretation KTE-X19 showed a high rate of complete remission or complete remission with incomplete haematological recovery in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia, with the median overall survival not reached in responding patients, and a manageable safety profile. These findings indicate that KTE-X19 has the potential to confer long-term clinical benefit to these patients.

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Introduction

Although adults with B-precursor acute lymphoblastic leukaemia respond to initial treatment, 40–50% of patients relapse, with an overall poor prognosis.[1] The 1-year overall survival rate is 26% after first salvage therapy and decreases with subsequent relapses.[1,2] Although the novel agents blinatumomab and inotuzumab ozogamicin lead to a proportion of patients with complete remission or complete remission with incomplete haematological recovery of 35·1% (blinatumomab) and 80·7% (inotuzumab ozogamicin), median overall survival remains at less than 8 months and is largely contingent on allogeneic stem-cell transplant (allo-SCT) consolidation.[3–7] Although allo-SCT

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See Comment page 466

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Research in context

Evidence before this study

We searched the PubMed database to identify clinical trials in humans published from database inception to April 26, 2021, using the terms "chimeric antigen receptor" AND "adult" AND ("B-cell acute lymphoblastic leukemia" OR "B-precursor acute lymphoblastic leukemia") AND "clinical trial" NOT "review". Clinical data on the use of chimeric antigen receptor (CAR) T-cell therapy in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia were scarce. Among the 20 articles retrieved, most reported data from small, single-centre clinical studies. Three articles reported findings from multicentre clinical trials of young adult populations (≤25 years), including two reports on the anti-CD19 CAR T-cell therapy tisagenlecleucel (the primary analysis and a subanalysis of Japanese patients) and one report on an anti-CD19 CAR T-cell therapy evaluated at the Memorial Sloan Kettering Cancer Center and the Dana-Farber Cancer Institute. No multicentre studies of CAR T-cell therapy in only adult patients were identified.

Added value of this study

Outcomes in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia are poor and worsen with each subsequent relapse. The benefit of novel agents in relapsed or refractory patients largely depends on consolidation with allogeneic stem-cell transplant (allo-SCT); however, most patients do not proceed to transplant, and post-transplant morbidity and mortality remain high, underlining a substantial unmet medical need. We did the pivotal ZUMA-3 trial of KTE-X19 CAR T-cell therapy in the largest population of adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia to date. KTE-X19 resulted in a high and durable rate of overall complete remission or complete remission with incomplete haematological recovery: 39 (71%) patients had complete remission or complete remission with incomplete haematological recovery, of whom 31 (56%) had complete remission. Among responders, 38 (97%) patients had minimal residual disease negativity. Despite most patients having high disease burden and heavy pretreatment, including novel agents, allo-SCT, or both, the rate of overall complete remission or complete remission with incomplete haematological recovery was largely consistent across these patient subgroups. After a median follow-up of 16·4 months, median overall survival was 18·2 months across all treated patients. Among responders, median overall survival was not yet reached. The safety profile of KTE-X19 was manageable, with most instances of cytokine release syndrome and neurological events occurring early, and no deaths due to cytokine release syndrome. Additionally, in a long-term analysis of patients treated at the pivotal dose level in phase 1, median overall survival was not reached in those who achieved a response, and no new safety signals were observed after the median follow-up of 39·9 months. An exploratory analysis combined across patients in phases 1 and 2 treated at the pivotal dose level with a larger sample size also supported the phase 2 findings.

Implications of all the available evidence

Before ZUMA-3, CAR T-cell therapy had shown encouraging efficacy in children and young adults (≤25 years) with relapsed or refractory B-precursor acute lymphoblastic leukaemia, but it had not been studied extensively in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia. Our findings showing a rapid manufacturing time, durable responses, a median overall survival of more than 1·5 years, and manageable safety in a heavily pretreated adult patient population with high disease burden suggest that KTE-X19 could confer long-term and clinically meaningful benefit to adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia.

is the most established curative option for relapsed or refractory disease, most patients do not proceed to allo-SCT;[8,9] mortality, morbidity, and relapse rate post transplant remain high, suggesting a high unmet medical need for new treatment options for relapsed or refractory B-precursor acute lymphoblastic leukaemia.[2,8–11]

Chimeric antigen receptor (CAR) T-cell therapies targeting CD19 represent a promising approach for the treatment of relapsed or refractory B-precursor acute lymphoblastic leukaemia.[12] Encouraging results with an anti-CD19 CAR T-cell therapy were shown in a phase 1 study of adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia at the Memorial Sloan Kettering Cancer Center, including a complete remission rate of 83%;[13] in a phase 1 study of paediatric and young adult patients by the National Cancer Institute, 62% of patients had complete remission.[14] These findings indicate the potential of anti-CD19 CAR T-cell therapies in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia. Nevertheless, a clear benefit of CAR T-cell therapies targeting CD19 in these adult patients has yet to be shown, and there are no approved products for patients older than 25 years.[13,15–17]

The presence of leukaemic blasts in peripheral blood can potentially lead to manufacturing failure by limiting the number of T cells available for the manufacturing of CAR T-cell products.[18–20] KTE-X19 is an autologous anti-CD19 CAR T-cell therapy that is produced through a manufacturing process that removes malignant cells, reducing the potential for activation and exhaustion of anti-CD19 CAR T cells in the ex-vivo manufacturing process.[19,20] KTE-X19 is approved for the treatment of adults with relapsed or refractory mantle cell lymphoma in the USA (as brexucabtagene autoleucel) and in the EU (as autologous anti-CD19-transduced $CD3^+$ cells).[21,22]

ZUMA-3 is a phase 1–2, single-arm, open-label study evaluating KTE-X19 in adult relapsed or refractory B-precursor acute lymphoblastic leukaemia. Phase 1 of ZUMA-3 showed a manageable safety profile for KTE-X19 in adult relapsed or refractory B-precursor acute lymphoblastic leukaemia and established 1×10^6 cells per kg as the recommended phase 2 dose, with a rate of overall complete remission or complete remission with incomplete haematological recovery of 83%.[20] Here, we report the pivotal phase 2 results of ZUMA-3, an international, multicentre study of CAR T-cell therapy evaluated in the largest population of adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia to date.

Methods

Study design and patients

Patients were enrolled in phase 2 of the single-arm, open-label ZUMA-3 study at 25 sites in the USA, Canada, and Europe (appendix pp 2–3). Patients were aged 18 years or older, had Eastern Cooperative Oncology Group performance status of 0–1, and had relapsed or refractory B-precursor acute lymphoblastic leukaemia with morphological disease in the bone marrow (>5% blasts) at study entry. Relapsed or refractory disease was defined as primary refractory, first relapse with remission of 12 months or less, relapsed or refractory after at least two previous lines of systemic therapy, or relapsed or refractory after allo-SCT. Patients could have received previous blinatumomab. Additional eligibility criteria are listed in the appendix (pp 4–6). Patients provided written informed consent and the study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board or independent ethics committee at each study site approved the protocol.

Procedures

Patients underwent leukapheresis to obtain cells for KTE-X19 manufacturing before receiving conditioning chemotherapy (intravenous fludarabine 25 mg/m² on days –4, –3, and –2; and intravenous cyclophosphamide 900 mg/m² on day –2). KTE-X19 was manufactured by Kite, a Gilead Company (Santa Monica, CA, USA). A single KTE-X19 infusion was administered at a target dose of 1×10^6 CAR T cells per kg bodyweight on day 0. Patients with a bodyweight greater than 100 kg received a flat dose of 1×10^8 CAR T cells. Prespecified bridging chemotherapy to stabilise the patient's condition during KTE-X19 manufacturing was allowed at the physician's discretion. Hospitalisation after KTE-X19 infusion was required for at least 7 days. Bone marrow was evaluated for disease assessment via biopsy or aspirate. CNS disease status was assessed via evaluation of cerebrospinal fluid samples. CNS-1 disease was defined as the absence of leukaemia in cerebrospinal fluid. CNS-2 disease was defined as detectable cerebrospinal blasts with less than five white blood cells per mm³.

Outcomes

The primary endpoint was the rate of overall complete remission or complete remission with incomplete haematological recovery by central assessment in patients treated with KTE-X19. Secondary endpoints were the centralised minimal residual disease (MRD) negativity rate, assessed by a validated flow cytometry method (MRD negativity defined as MRD $<10^{-4}$ [ie, sensitivity of 0·01%]);[23] investigator-assessed rate of overall complete remission or complete remission with incomplete haematological recovery; duration of remission and relapse-free survival with patients undergoing new anticancer therapies (including allo-SCT) censored; overall survival; allo-SCT rate; safety; incidence of anti-KTE-X19 antibodies; and patient-reported outcomes measured by EQ-5D-5L and visual analogue scale (VAS) scores. Exploratory endpoints included levels of CAR T cells in blood and cytokines in

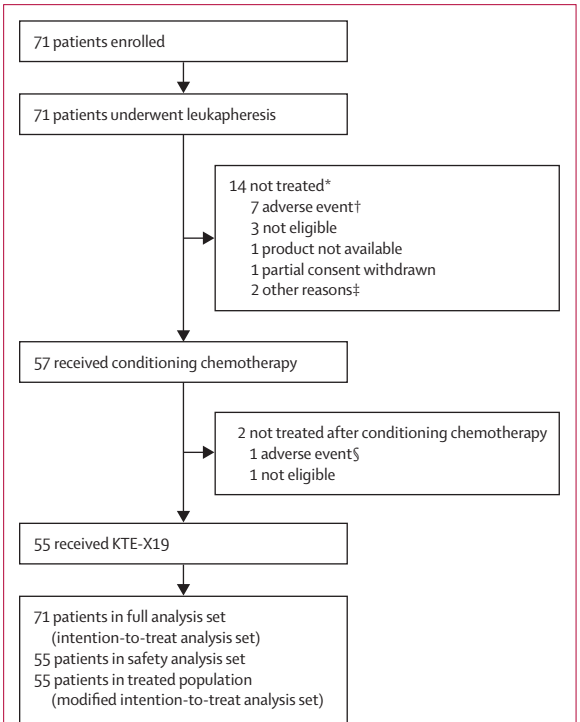

Figure 1: **Trial profile**
CAR=chimeric antigen receptor. *Products were not successfully manufactured for six patients; these patients were reported by the sites as not treated for the following reasons: adverse event (n=1), product not available (n=1), partial consent withdrawn (n=1), eligibility not met (n=1), and other (n=2). †Adverse events leading to treatment discontinuation before conditioning chemotherapy included sepsis (n=1), acute lymphoblastic leukaemia (n=1), fungal pneumonia and sepsis (in the same patient, n=1), deep vein thrombosis (n=1), encephalopathy and cardiac arrest (in the same patient, n=1), myositis (n=1), and hemiparesis due to air embolism (n=1). ‡One patient experienced clinical deterioration after the 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 the product was not successfully manufactured from the initial leukapheresis attempt. §After conditioning chemotherapy, one patient did not proceed to KTE-X19 infusion due to an adverse event of bacteraemia.

See Online for appendix

	Treated patients (n=55)	Enrolled patients (n=71)
Age, years	40 (28–52)	44 (30–59)
≥65 years	8 (15%)	11 (15%)
Sex		
Female	22 (40%)	30 (42%)
Male	33 (60%)	41 (58%)
Race		
White	37 (67%)	51 (72%)
Asian	3 (5%)	4 (6%)
Black or African American	1 (2%)	2 (3%)
American Indian or Alaska Native	1 (2%)	1 (1%)
Other	9 (16%)	9 (13%)
Missing	4 (7%)	4 (6%)
ECOG performance status of 1*	39 (71%)	53 (75%)
Philadelphia chromosome positive	15 (27%)	19 (27%)
Extramedullary disease at screening	6 (11%)	8 (11%)
CNS-1 disease at baseline†‡	55 (100%)	69 (97%)
Number of previous therapies§	2 (2–3)	2 (2–3)
Three or more	26 (47%)	35 (49%)
Previous blinatumomab	25 (45%)	33 (46%)
Previous inotuzumab ozogamicin	12 (22%)	16 (23%)
Previous allogeneic SCT	23 (42%)	28 (39%)
Relapsed or refractory subgroup		
Primary refractory	18 (33%)	21 (30%)
Relapsed or refractory to two or more previous systemic therapy lines	43 (78%)	54 (76%)
First relapse with remission ≤12 months	16 (29%)	20 (28%)
Relapsed or refractory post allogeneic SCT¶	24 (44%)	29 (41%)
(Continued from previous column)		
Bone marrow blasts at screening		
n	55	70
Median (IQR)	65% (24–87)	70% (25–89)
≤5%‖	0	1 (1%)
>5% to 25%‖	16 (29%)	17 (24%)
M3 bone marrow involvement (>25% blasts)‖	39 (71%)	52 (73%)
Bone marrow blasts at baseline‡		
n	55	70
Median (IQR)	60% (17–90)	67% (34–90)
≤5%‖	5 (9%)	6 (8%)
>5% to 25%‖	10 (18%)	10 (14%)
M3 bone marrow involvement (>25% blasts)‖	40 (73%)	54 (76%)
Bone marrow blasts at preconditioning after bridging chemotherapy		
n	46	48
Median (IQR)	59% (25–87)	63% (27–89)
≤5%‖	5 (9%)	5 (7%)
>5% to 25%‖	7 (13%)	7 (10%)
M3 bone marrow involvement (>25% blasts)‖	34 (62%)	36 (51%)

Data are median (IQR) or n (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. SCT=stem-cell transplant. *All other patients had ECOG performance status of 0. †Among treated patients, five had CNS-2 disease at screening and data were missing for three patients; per protocol, sites could administer intrathecal chemotherapy between screening and baseline, which could have resulted in a change of CNS status. ‡Baseline refers to the last value taken before conditioning chemotherapy. §Among treated patients, six had previous blinatumomab and previous inotuzumab ozogamicin, 11 patients had previous blinatumomab and previous SCT, five patients had previous inotuzumab ozogamicin and previous SCT, and two patients had previous blinatumomab, previous inotuzumab ozogamicin, and previous SCT. ¶Includes one patient who received autologous SCT. ‖The denominator for percentages is 55 for treated patients and 71 for enrolled patients.

Table 1: **Baseline characteristics**

serum. Additional assessment details are described in the appendix (pp 7–9).

The severity of all adverse events, including neurological events and symptoms of cytokine release syndrome, was graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Cytokine release syndrome was graded according to the grading system proposed by Lee and colleagues.[24]

Duration of remission was defined as the time from first complete remission or complete remission with incomplete haematological recovery (central assessment) to relapse or death without documented relapse. Disease assessments obtained after new anticancer therapies (including allo-SCT) did not contribute to the derivation of duration of remission. Patients who had complete remission could resume tyrosine kinase inhibitor therapy 2 months after KTE-X19 infusion, and these patients contributed to the derivation of duration of remission. Overall survival was defined as the time from KTE-X19 infusion to the date of death from any cause. Relapse-free survival was defined as the time from KTE-X19 infusion to the date of disease relapse or death from any cause. Patients who did not reach complete remission or complete remission with incomplete haematological recovery as of the data cutoff date were evaluated as having a relapse-free survival event at day 0. For duration of remission and relapse-free survival, sensitivity analyses were done in which disease assessments obtained after allo-SCT were included in the derivation of duration of remission and relapse-free survival. For cases of non-disease-related mortality, a sensitivity analysis of duration of remission was planned in which the non-disease-related mortality was considered as the competing risk; however, no such cases were identified. In the case of death without documented relapse, the duration of remission analysis would consider the death an event, not a censored or competing risk.

Statistical analysis

Treated patients were considered to include all patients who received a dose of KTE-X19; this analysis set was used for the hypothesis testing of the primary endpoint and other efficacy analyses, as well as safety analyses. The intention-to-treat population comprised all enrolled patients. The phase 1 long-term population consisted of all patients in phase 1 treated with any dose of KTE-X19. The phase 1 and phase 2 combined population consisted of all patients treated in phase 1 and phase 2 at the recommended phase 2 dose of KTE-X19 (1×10^6 CAR T cells per kg bodyweight; appendix p 10). Subgroup analyses based on baseline disease and treatment covariates were done for selected endpoints.

Per protocol, the primary efficacy analysis was done when all KTE-X19–treated patients had completed at least the 6-month disease assessment. The study had approximately 93% power to distinguish between an active therapy with a rate of complete remission or complete remission with incomplete haematological recovery of 65% and a prespecified, historical control rate of 40% or less,[4,25] with a one-sided α of 0·025. Based on this hypothesis, the planned sample size was 50 patients. If primary endpoint testing was significant, the MRD negativity rate was to be tested against a control rate of 30%.[25] An exact binomial test was used to compare the observed rate of complete remission or complete remission with incomplete haematological recovery to the historical control rate. Two-sided 95% CIs were calculated using the Clopper-Pearson method. To evaluate associations of CAR T-cell levels with clinical outcomes, nominal p values were determined by the Wilcoxon rank sum test for two-group comparisons and Kruskal-Wallis test with post-hoc Dunn test for three-group comparisons. Additional statistical analysis details are provided in the appendix (pp 10–11). SAS (version 9.4) was used for statistical analyses. This study is registered with ClinicalTrials.gov, NCT02614066.

Role of the funding source

In collaboration with the authors, the sponsor participated in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Oct 1, 2018, and Oct 9, 2019, 71 patients were enrolled and underwent leukapheresis. KTE-X19 was successfully manufactured for 65 (92%) patients and administered to 55 (77%; figure 1). The median time from leukapheresis to KTE-X19 manufacturing release was 13 days (IQR 11–14) for US patients and 14·5 days (13–19) for European patients. 16 patients discontinued for the following reasons: adverse events (n=8), ineligibility (n=4), partial consent withdrawn (n=1), product unavailable (n=1), and other reasons (n=2; figure 1). As of Sept 9, 2020, median follow-up was 16·4 months (IQR 13·8–19·6).

	Treated patients (n=55)
Overall complete remission or complete remission with incomplete haematological recovery	39 (71%)*
Complete remission	31 (56%)
Complete remission with incomplete haematological recovery	8 (15%)
Blast-free hypoplastic or aplastic bone marrow	4 (7%)
No response	9 (16%)
Unknown or not evaluable†	3 (5%)

Data are n (%). *95% CI 57–82, p<0·0001. †The three patients who were unknown or not evaluable died (at days 8, 15, and 18) before the first disease assessment.

Table 2: **Rate of overall complete remission or complete remission with incomplete haematological recovery based on central assessment**

Among KTE-X19-treated patients, the median age was 40 years (IQR 28–52), with eight (15%) patients aged 65 years or older. 26 (47%) patients had received three or more previous therapies; 25 (45%) previously received blinatumomab, 12 (22%) previously received inotuzumab ozogamicin, and 23 (42%) previously received allo-SCT (table 1). 18 (33%) patients had primary refractory disease, 24 (44%) had relapsed or refractory disease post allo-SCT, and 43 (78%) had relapsed or refractory disease to two or more lines of systemic therapy. 51 (93%) patients received bridging chemotherapy; 34 patients (62%) had confirmed M3 bone marrow involvement (>25% bone marrow blasts) after bridging chemotherapy (table 1).

The primary endpoint was met, with 39 patients (71%; 95% CI 57–82, p<0·0001) reaching complete remission or complete remission with incomplete haematological recovery by central assessment, of whom 31 (56%) had complete remission (table 2). 40 (73%) patients had complete remission or complete remission with incomplete haematological recovery based on investigator assessment, with 33 (60%) reaching complete remission (appendix p 18). Complete remission or complete remission with incomplete haematological recovery rates were largely consistent among most subgroups, including patients aged 65 years or older (eight [100%] of eight patients), those with one previous line of therapy (nine [90%] of ten patients), or those who previously received blinatumomab (15 [60%] of 25 patients), inotuzumab ozogamicin (eight [67%] of 12 patients), or allo-SCT (16 [70%] of 23 patients; figure 2). Among 39 patients with complete remission or complete remission with incomplete haematological recovery, median time to first complete remission or complete remission with incomplete haematological recovery was 1·1 months (IQR 1·0–1·9). Among all enrolled patients (n=71), 39 (55%) achieved complete remission or complete remission with incomplete haematological recovery by central assessment (appendix p 19).

The secondary efficacy endpoint of MRD negativity rate was met with 42 (76%) of all treated patients having MRD

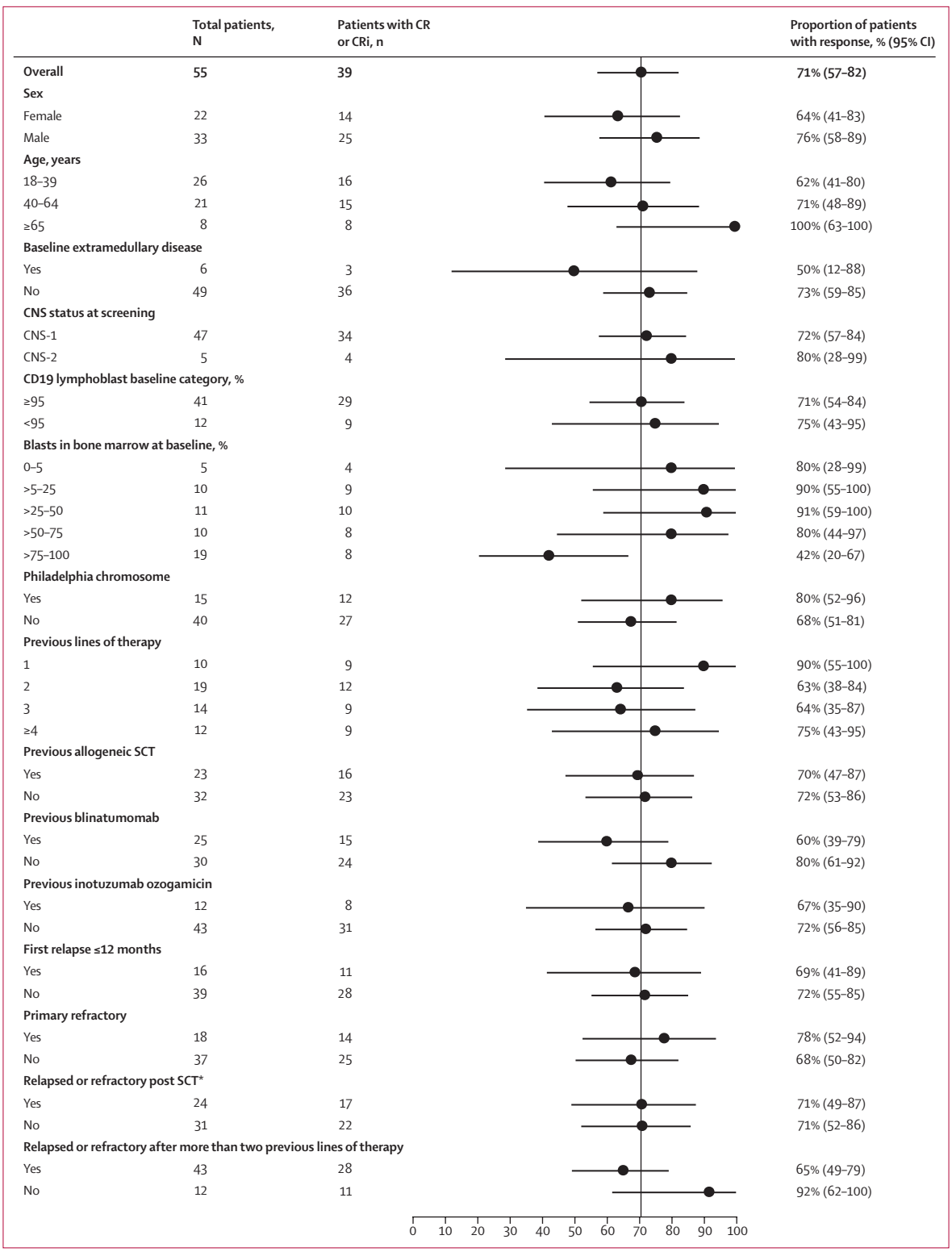

Figure 2: **Subgroup analyses of overall CR or CRi rate for baseline and clinical covariates based on central assessment**
The Clopper-Pearson method was used to calculate the 95% CIs. CR=complete remission. CRi=complete remission with incomplete haematological recovery. SCT=stem-cell transplant. *Includes one patient who received autologous SCT.

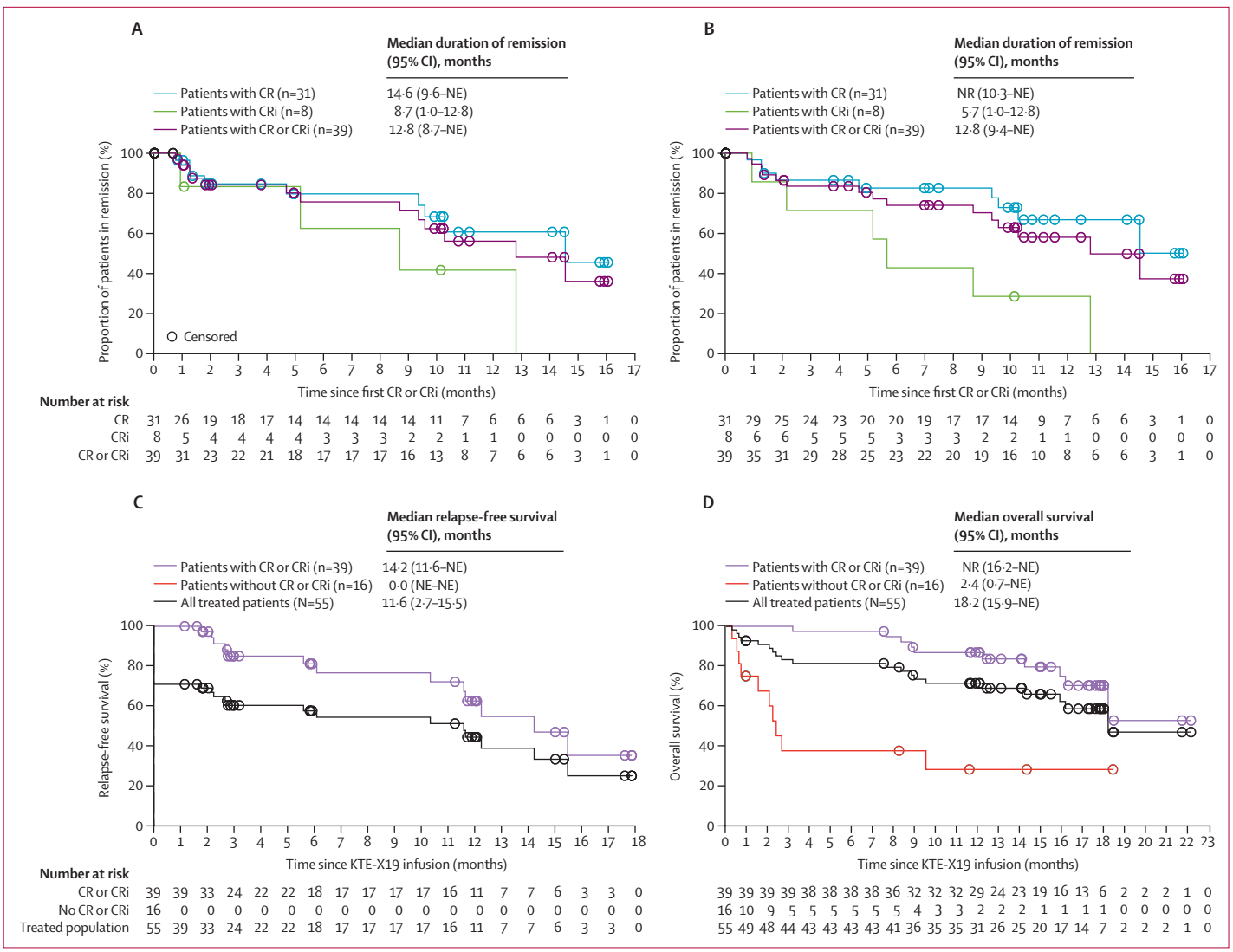

Figure 3: **Duration of remission, relapse-free survival, and overall survival**

(A, B) Kaplan-Meier estimates of the duration of remission by central assessment, with (A) and without (B) censoring of patients at subsequent allogeneic stem-cell transplant. Among the 55 treated patients, 29 had an event, including 12 who relapsed and one who died. (C) Kaplan-Meier estimate of relapse-free survival by central assessment, with censoring of patients at subsequent allogeneic stem-cell transplant. (D) Kaplan-Meier estimate of overall survival. CR=complete remission. CRi=complete remission with incomplete haematological recovery. NE=not estimable. NR=not reached.

negativity (p<0·0001); among responders, 38 (97%) of 39 had MRD negativity, with samples unavailable for one patient. Ten (18%) patients received allo-SCT after KTE-X19 infusion, at the discretion of the treating physician (appendix p 11). Median time to allo-SCT was 98 days (IQR 72–134) after KTE-X19 infusion.

The median duration of remission both with and without censoring patients at subsequent allo-SCT was 12·8 months (95% CI 8·7–not estimable with censoring, 9·4–not estimable without censoring; figure 3A, B). At data cutoff, 12 (31%) of the 39 patients with complete remission or complete remission with incomplete haematological recovery were in ongoing remission; nine (23%) proceeded to subsequent allo-SCT, five (13%) proceeded to other anticancer therapies, 12 (31%) relapsed, and one (3%) died. Median relapse-free survival both with and without censoring patients at subsequent allo-SCT was 11·6 months (2·7–15·5) in all treated patients and 14·2 months (11·6–not estimable) in responders (figure 3C, appendix p 13). The relapse-free survival rate at 6 months was 58% (95% CI 43–70) and the overall survival rate at 12 months was 71% (57–82). Rates of relapse-free survival at 6 months and of overall survival at 12 months were largely consistent among subgroups (appendix pp 14–15), including patients with at least 25% bone marrow blasts, Philadelphia chromosome-positive disease, previous allo-SCT, or previous blinatumomab. Median overall survival was 18·2 months (15·9–not estimable) in all treated patients and was not reached in responders (figure 3D).

	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any adverse event*	55 (100%)	0	3 (5%)	8 (15%)	34 (62%)	10 (18%)†
Pyrexia	52 (95%)	8 (15%)	24 (44%)	17 (31%)	3 (5%)	0
Hypotension	37 (67%)	2 (4%)	19 (35%)	13 (24%)	3 (5%)	0
Anaemia	29 (53%)	0	2 (4%)	25 (45%)	2 (4%)	0
Nausea	21 (38%)	12 (22%)	9 (16%)	0	0	0
Sinus tachycardia	21 (38%)	9 (16%)	9 (16%)	3 (5%)	0	0
Headache	20 (36%)	12 (22%)	8 (15%)	0	0	0
Chills	18 (33%)	13 (24%)	5 (9%)	0	0	0
Platelet count decreased	18 (33%)	1 (2%)	0	3 (5%)	14 (25%)	0
Hypoxia	16 (29%)	1 (2%)	4 (7%)	7 (13%)	4 (7%)	0
Fatigue	15 (27%)	12 (22%)	3 (5%)	0	0	0
Hypokalaemia	15 (27%)	5 (9%)	6 (11%)	3 (5%)	1 (2%)	0
Hypophosphataemia	15 (27%)	2 (4%)	2 (4%)	11 (20%)	0	0
Neutrophil count decreased	15 (27%)	0	0	1 (2%)	14 (25%)	0
Tremor	15 (27%)	14 (25%)	0	1 (2%)	0	0
Confusional state	14 (25%)	5 (9%)	7 (13%)	2 (4%)	0	0
Tachycardia	14 (25%)	3 (5%)	11 (20%)	0	0	0
White blood cell count decreased	14 (25%)	0	1 (2%)	4 (7%)	9 (16%)	0
Alanine aminotransferase increased	12 (22%)	4 (7%)	1 (2%)	6 (11%)	1 (2%)	0
Diarrhoea	12 (22%)	7 (13%)	3 (5%)	2 (4%)	0	0
Encephalopathy	12 (22%)	1 (2%)	7 (13%)	3 (5%)	1 (2%)	0
Hypomagnesaemia	12 (22%)	12 (22%)	0	0	0	0
Cytokine release syndrome‡						
Any	49 (89%)	11 (20%)	25 (45%)	7 (13%)	6 (11%)	0
Pyrexia	46 (94%)	7 (14%)	20 (41%)	16 (33%)	3 (6%)	0
Hypotension	33 (67%)	1 (2%)	16 (33%)	13 (27%)	3 (6%)	0
Sinus tachycardia	18 (37%)	7 (14%)	8 (16%)	3 (6%)	0	0
Chills	14 (29%)	10 (20%)	4 (8%)	0	0	0
Hypoxia	14 (29%)	1 (2%)	2 (4%)	7 (14%)	4 (8%)	0
Tachycardia	12 (24%)	3 (6%)	9 (18%)	0	0	0
Fatigue	10 (20%)	8 (16%)	2 (4%)	0	0	0
Headache	10 (20%)	6 (12%)	4 (8%)	0	0	0
Neurological events						
Any	33 (60%)	6 (11%)	13 (24%)	13 (24%)	0	1 (2%)
Tremor	15 (27%)	14 (25%)	0	1 (2%)	0	0
Confusional state	14 (25%)	5 (9%)	7 (13%)	2 (4%)	0	0
Encephalopathy	12 (22%)	1 (2%)	7 (13%)	3 (5%)	1 (2%)	0

Data are n (%). *In the first row, the worst grade of adverse event for each participant is shown. All other rows show adverse events, cytokine release syndrome symptoms, and neurological events of any grade occurring in at least 20% of patients. †Four patients had grade 5 acute lymphocytic leukaemia, and six patients had other grade 5 adverse events: brain herniation (day 8; related to KTE-X19), pneumonia (day 15), septic shock (day 18, related to conditioning chemotherapy and KTE-X19), fungal pneumonia (day 46), sepsis (day 72), and respiratory failure (day 491). ‡Percentages for individual cytokine release syndrome symptoms were calculated out of the 49 patients who experienced cytokine release syndrome.

Table 3: **Adverse events, cytokine release syndrome, and neurological events in the safety analysis set (n=55)**

All treated patients had at least one adverse event. The most common adverse events of grade 3 or higher were anaemia (27 [49%] of 55 patients) and pyrexia (20 [36%] patients; table 3). Grade 3 or higher cytopenia occurred in 42 (76%) patients (appendix p 20) and were present on or after day 30 post KTE-X19 infusion in 20 (36%) patients (appendix p 21). Serious adverse events occurred in 41 (75%) patients.

Cytokine release syndrome occurred in 49 (89%) patients, with grade 3 or 4 cytokine release syndrome occurring in 13 (24%); no grade 5 cytokine release syndrome events occurred (table 3). Median time to onset of cytokine release syndrome was 5 days (IQR 3–7) and median duration was 7·5 days (5–18). Neurological events occurred in 33 (60%) patients, with events of grade 3 or higher occurring in 14 patients (25%), including one grade 5 event (brain herniation; table 3). Median time to onset of neurological events was 9 days (7–11) and median duration was 7 days (4–19). Most cytokine release syndrome and neurological events resolved (appendix p 11). Tocilizumab was given to 44 (80) patients, steroids were given to 41 (75%), and vasopressors were given to 22 (40%).

14 (25%) patients had infections of grade 3 or higher. One patient had grade 3 tumour lysis syndrome and one patient who received previous allo-SCT had grade 2 graft-versus-host disease; both events were KTE-X19-related. All patients were confirmed to be negative for anti-KTE-X19 antibodies. No patient developed replication-competent retrovirus. No hypogammaglobulinaemia of grade 3 or higher occurred; six (11%) patients received immunoglobulin. By month 3, for patient-reported outcomes measured by EQ-5D-5L, the proportion of evaluable patients reporting no problems for each dimension was similar to or higher than at baseline. VAS scores were stable or improved after KTE-X19 infusion for the majority of evaluable patients across timepoints (31 [79%] of 39 at day 28, 24 [92%] of 26 at month 3, 20 [80%] of 25 at month 6, seven [70%] of ten at month 9, and 13 [93%] of 14 at month 12; appendix pp 11–12).

20 (36%) treated patients had died as of the data cutoff date, primarily from progressive disease (13 [24%] patients). Six (11%) patients died due to grade 5 adverse events other than acute lymphoblastic leukaemia: two related to KTE-X19 (brain herniation [day 8] and septic shock [day 18]) and four unrelated to KTE-X19 treatment. One patient died due to another reason (appendix p 11).

All patients with evaluable bone marrow samples (n=53) had confirmed baseline CD19 expression. Median time to peak CAR T-cell levels in blood after KTE-X19 infusion (n=50) was 15 days (IQR 11–16; appendix pp 22–23); CAR T cells were no longer detectable by PCR in 22 (79%) of 28 patients with evaluable samples at 6 months. An inverse relationship was observed between CAR T-cell expansion and bone marrow blasts at screening (appendix p 24); no other meaningful associations with CAR T-cell expansion were observed. The median peak CAR T-cell level in blood was 40·47 cells per µL (IQR 6·04–76·70) among 29 evaluable patients with complete remission. In ten of 12 ongoing responders with evaluable samples at month 12, all had recovered peripheral B cells; only one (10%) had detectable CAR T cells. In 11 of 16 patients with non-complete

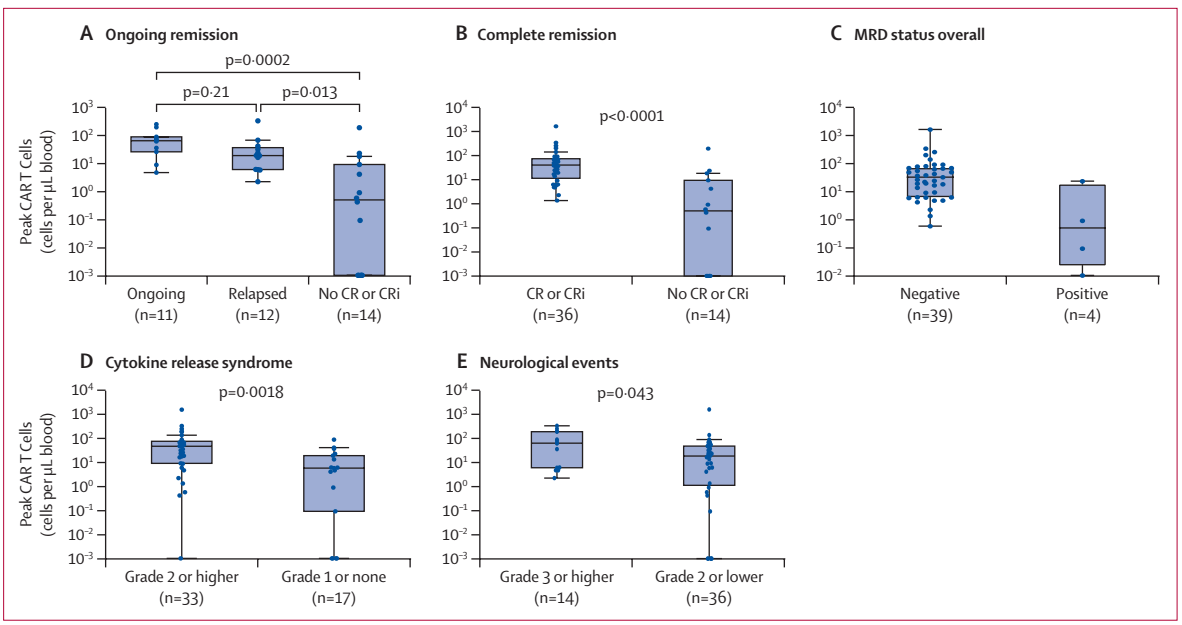

Figure 4: **Peak CAR T-cell levels and associations with response and adverse events**
CAR=chimeric antigen receptor. CR=complete remission. CRi=complete remission with incomplete haematological recovery. MRD=minimal residual disease.

remission or complete remission with incomplete haematological recovery (four with blast-free hypoplastic or aplastic bone marrow, nine with no response, and three unknown or not evaluable) with evaluable samples at baseline, all had detectable B cells at baseline, nine had measurable CAR T-cell expansion (one had no expansion and one had no post-infusion data), and one experienced B-cell aplasia. B-cell aplasia was more profound in patients with complete remission or complete remission with incomplete haematological recovery versus patients without complete remission or complete remission with incomplete haematological recovery (appendix pp 25–26). In eight of nine non-responders with available pharmacokinetic data, the median peak CAR T-cell level in blood was 0 cells per µL (0–0·49). Six of nine patients with available data at relapse had detectable CD19 expression.

CAR T-cell expansion was highest in patients with ongoing complete remission or complete remission with incomplete haematological recovery, followed by relapsed patients, and lowest in patients without complete remission or complete remission with incomplete haematological recovery (figure 4A, appendix p 16); expansion was higher in responders relative to non-responders (figure 4B). CAR T-cell expansion was also positively associated with MRD negativity (figure 4C, appendix pp 16, 27); median CAR T-cell levels were more than 60 times higher in patients with MRD-negative versus MRD-positive status after infusion. All MRD-positive patients had morphological disease. CAR T-cell expansion was also positively associated with cytokine release syndrome of grade 2 or higher and neurological events of grade 3 or higher (figure 4D, E, appendix p 16).

Most cytokines peaked at 8 days after infusion (appendix pp 17, 28). Elevated levels of serum IL-6 were associated with cytokine release syndrome and neurological events of grade 3 or higher (nominal p<0·05). Elevated levels of inflammatory cytokines and chemokines measured in serum (eg, IFN-γ, IL-8, IL-15, and IL-2Rα) were associated with cytokine release syndrome of grade 3 or higher (appendix pp 29–31). CAR T-cell product characteristics are shown in the appendix (p 32).

ZUMA-3 phase 1 results were previously published, with a median of 22·1 months of follow-up.[20] In a long-term analysis using a data cutoff date of Sept 9, 2020, the investigator-assessed rate of complete remission or complete remission with incomplete haematological recovery among patients treated at the 1×10^6 dose level in phase 1 (n=23; median follow-up 39·9 months) was 78% (18 patients; complete remission rate 70% [16 patients]). Median overall survival was 22·4 months; among responders, median overall survival was not reached (appendix p 12). In a combined phase 1 and 2 analysis at the pivotal 1×10^6 dose level (n=78), the investigator-assessed rate of complete remission or complete remission with incomplete haematological recovery was 74% (58 patients; complete remission rate, 63% [49 patients]; appendix p 33). Median duration of remission was 13·4 months, median relapse-free survival was 10·3 months, and median overall survival was 22·4 months. Median overall survival was not reached among responders.

Discussion

Outcomes in adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia remain poor and worsen with each subsequent relapse,[2]

representing a high unmet medical need. The use of novel agents, such as blinatumomab or inotuzumab, and consolidation with allo-SCT has shown overall survival of less than 8 months, coupled with high treatment-related morbidity and mortality.[4,5,26,27] Additionally, many patients are ineligible or relapse before receiving the transplant.[8,9,28] In ZUMA-3 phase 2, KTE-X19 resulted in a high and durable response rate by central assessment in the largest, adult-only, relapsed or refractory B-precursor acute lymphoblastic leukaemia patient population to date.

Despite most patients having high disease burden and heavy pretreatment, including novel agents, allo-SCT, or both, rates of overall complete remission or complete remission with incomplete haematological recovery were largely consistent across patient subgroups based on these covariates, although the study was not powered for these subgroup analyses. Among the highest response rates were those observed in patients with one previous line of therapy (nine [90%] of ten patients) and patients aged 65 years or older (eight [100%] of eight patients), indicating that KTE-X19 could also provide benefit to certain subsets of patients, such as older patients who are frequently excluded from allo-SCT and generally have poorer outcomes.[29,30]

Despite high disease burden, KTE-X19 was successfully manufactured for 65 of 71 enrolled patients and administered to 55, leading to high and durable response rates after a single infusion. Additionally, the rapid manufacturing time of KTE-X19 resulted in a median time from leukapheresis to manufacturing release of 13 days for US patients and 14·5 days for European patients. Tisagenlecleucel, an anti-CD19 CAR T-cell therapy approved in patients aged 25 years and younger with relapsed or refractory B-precursor acute lymphoblastic leukaemia, was reported to have a median throughput time in the USA of 23 days for the first 37 commercially manufactured products (inclusive of shipment time), including 11 days for core manufacturing and 9 days for testing and disposition.[31] Only ten (18%) patients subsequently received allo-SCT, and sensitivity analyses suggest that the median duration of remission was unchanged by allo-SCT consolidation. Among responders, median overall survival was not yet reached, and the MRD negativity rate was 97% (38 patients), with one patient not having samples evaluable for MRD assessment. The exploratory combined phase 1 and 2 analysis of the pivotal 1×10^6 dose level with a larger sample size (n=78) supported the phase 2 findings. Overall, these data suggest that KTE-X19 leads to a high complete remission or complete remission with incomplete haematological recovery rate, which translates into clinically meaningful improvements in survival for adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia.

The safety profile of KTE-X19 was generally manageable, with most symptoms of cytokine release syndrome and neurological events occurring early, and no reported deaths due to cytokine release syndrome. Two KTE-X19-related grade 5 events occurred (brain herniation and septic shock). Descriptive analysis of the EQ-5D-5L indicated that the majority of evaluable patients experienced improved or stable quality of life over time, and a more pronounced improvement was seen with the VAS score. Since the previous report,[20] there were no new safety signals among patients treated in phase 1, indicating favourable long-term safety in relapsed or refractory B-precursor acute lymphoblastic leukaemia.

Early and rapid expansion of CAR T cells in blood was consistent with that previously reported for KTE-X19,[19] with a decrease to baseline levels within 3–6 months in all patients. Higher CAR T-cell levels were associated with neurotoxicity of grade 3 or higher and cytokine release syndrome of grade 2 or higher, similar to findings in previous reports.[19,20] In contrast to non-responders, those in ongoing remission had robust CAR T-cell expansion with recovery of normal peripheral B cells by 12 months, indicating that durable responses might not require long-term functional CAR T-cell persistence in this patient population.

Differences in trial designs, patient populations, and methodology present challenges in comparing results across TOWER (blinatumomab),[4] INO-VATE (inotuzumab ozogamicin),[5] and ZUMA-3 (KTE-X19). The complete remission or complete remission with incomplete haematological recovery rate was 35·1% in TOWER and 80·7% in INO-VATE, with complete remission rates of 33·6% in TOWER and 35·8% in INO-VATE.[4,5] In ZUMA-3, a 71% complete remission or complete remission with incomplete haematological recovery rate (39 patients) and a 56% complete remission rate (31 patients) were seen in treated patients, nearly half of whom had previous blinatumomab, and a 55% complete remission or complete remission with incomplete haematological recovery rate (39 patients) and a 44% complete remission rate (31 patients) were seen in enrolled patients. Furthermore, median overall survival was not reached in responders and was more than 1·5 years among treated patients. These results compare favourably with previously reported median overall survival of less than 8 months for blinatumomab and inotuzumab ozogamicin.[3–7] Additionally, median duration of remission was 12·8 months in ZUMA-3 compared with 4·6 months in the INOVATE trial.[5] The median duration of remission of 7·3 months reported in the TOWER study included patients who achieved complete remission, complete remission with incomplete haematological recovery, and complete remission with partial haematological recovery.[4]

Anti-CD19 CAR T-cell therapy has shown encouraging efficacy in adult relapsed or refractory B-precursor acute lymphoblastic leukaemia. Tisagenlecleucel was reported to have an 81% complete remission or complete remission with incomplete haematological recovery rate in patients aged 3–23 years; however, only 17% of patients

were aged 18–23 years, limiting understanding of the tisagenlecleucel benefit in adults.[32,33] Single-centre studies in adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia have reported complete remission rates of 69% with tisagenlecleucel and 83% with an anti-CD19 CAR T-cell therapy from the Memorial Sloan Kettering Cancer Center, although both studies also included patients with less than 5% bone marrow blasts or even MRD-negative status at infusion.[13,17] Although these single-centre studies reported high complete remission or complete remission with incomplete haematological recovery rates among patients with generally high disease burden, they did not require disease burden of more than 5% at enrolment as in ZUMA-3.

A potential limitation of this study was its single-arm design. However, the study was done in multiple centres in North America and Europe, which facilitated the accrual of the largest adult-only population of patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia to date. Further analyses with longer follow-up are warranted to better understand the long-term safety and efficacy of KTE-X19 in this population.

In conclusion, ZUMA-3 phase 2 showed that a single infusion of KTE-X19 could induce durable remission with manageable safety in heavily pretreated adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia, addressing a substantial unmet need. The rapid manufacturing time supports the feasibility of providing this novel therapy to adult patients with rapidly progressive disease. As such, KTE-X19 has the potential for long-term clinical benefit in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia.

Contributors

The study was designed in a collaboration between Kite, a Gilead Company (study sponsor), and the authors. All authors contributed to the conduct, analysis, verification, and interpretation of data and writing of the manuscript, with medical writing support funded by the sponsor. BDS, CF, JD, TS, FM, JMR, RV, BKM, and RH designed the study. BDS, AG, OOO, ACL, NB, RDC, TL, MRBi, MST, DT, KMO, MLA, YL, MRBa, GJS, JHP, MS, MA, MCM, WGW, DJD, PS, DJ, and RH enrolled and treated patients, and gathered and interpreted data. CF, JD, TS, FM, JMR, RV, and BKM analysed, verified, and interpreted the data. All authors participated in writing the manuscript, provided feedback throughout the development process, and approved the final submitted version. All authors had full access to all of the study data. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

BDS reports honoraria from Kite, a Gilead Company, and BeiGene; a consultancy or advisory role for BeiGene, Pepromene Bio, Kite, a Gilead Company, Celgene, Bristol Myers Squibb (BMS), Juno, Novartis, Pfizer, Amgen, Precision Biosciences, Adaptive Biotechnologies, and Jazz Pharmaceuticals; research funding from Kite, a Gilead Company, Jazz Pharmaceuticals, Incyte, Chotiner Pediatric Research Foundation, Lymphoma Research Foundation, and the National Institutes of Health; travel support from Kite, a Gilead Company; a leadership or fiduciary role for the National Cancer Center Network, the International Working Group for Acute Leukemia and CAR T, and the Society of Hematologic Oncology; and payment for expert testimony from Bayer. AG reports consultancy or advisory role for Amgen, Kite, a Gilead Company, Atara, Wugen, and Celgene; and research funding from Amgen and Kite, a Gilead Company. 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Data sharing

Kite, a Gilead Company, is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health. As such, Gilead shares anonymised individual patient data (IPD) upon request or as required by law or regulation.

Qualified external researchers can request IPD for studies of Gilead compounds approved in the USA and the EU with a marketing authorisation date on or after Jan 1, 2014, and publicly listed on ClinicalTrials.gov or the EU Clinical Trials Register. For studies of newly approved compounds or indications, the IPD will be available for request 6 months after US Food and Drug Administration or European Medicines Agency approval. Such requests are at Gilead's discretion and are dependent on the nature of the request, the merit of the research proposed, availability of the data, and the intended use of the data. If Gilead agrees to the release of clinical data for research purposes, the requester will be required to sign a data sharing agreement to ensure protection of patient confidentiality before the release of any data.

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