ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

ABSTRACT

BACKGROUND

Patients with relapsed or refractory mantle-cell lymphoma who have disease progression during or after the receipt of Bruton's tyrosine kinase (BTK) inhibitor therapy have a poor prognosis. KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, may have benefit in patients with relapsed or refractory mantle-cell lymphoma.

METHODS

In a multicenter, phase 2 trial, we evaluated KTE-X19 in patients with relapsed or refractory mantle-cell lymphoma. Patients had disease that had relapsed or was refractory after the receipt of up to five previous therapies; all patients had to have received BTK inhibitor therapy previously. Patients underwent leukapheresis and optional bridging therapy, followed by conditioning chemotherapy and a single infusion of KTE-X19 at a dose of 2×10^6 CAR T cells per kilogram of body weight. The primary end point was the percentage of patients with an objective response (complete or partial response) as assessed by an independent radiologic review committee according to the Lugano classification. Per the protocol, the primary efficacy analysis was to be conducted after 60 patients had been treated and followed for 7 months.

RESULTS

A total of 74 patients were enrolled. KTE-X19 was manufactured for 71 patients and administered to 68. The primary efficacy analysis showed that 93% (95% confidence interval [CI], 84 to 98) of the 60 patients in the primary efficacy analysis had an objective response; 67% (95% CI, 53 to 78) had a complete response. In an intention-to-treat analysis involving all 74 patients, 85% had an objective response; 59% had a complete response. At a median follow-up of 12.3 months (range, 7.0 to 32.3), 57% of the 60 patients in the primary efficacy analysis were in remission. At 12 months, the estimated progression-free survival and overall survival were 61% and 83%, respectively. Common adverse events of grade 3 or higher were cytopenias (in 94% of the patients) and infections (in 32%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 15% and 31% of patients, respectively; none were fatal. Two grade 5 infectious adverse events occurred.

CONCLUSIONS

KTE-X19 induced durable remissions in a majority of patients with relapsed or refractory mantle-cell lymphoma. The therapy led to serious and life-threatening toxic effects that were consistent with those reported with other CAR T-cell therapies. (Funded by Kite, a Gilead company; ZUMA-2 ClinicalTrials.gov number, NCT02601313.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wang at the Department of Lymphoma–Myeloma, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at miwang@mdanderson.org.

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Mantle-cell lymphoma is a B-cell non-Hodgkin's lymphoma that generally has an aggressive clinical course.[1,2] Bruton's tyrosine kinase (BTK) inhibitors have greatly improved outcomes in patients with relapsed or refractory mantle-cell lymphoma,[3,4] yet patients who have disease progression after the receipt of BTK inhibitor therapy have a very poor prognosis, with an objective response occurring in 25 to 42% of patients and a median overall survival of 6 to 10 months with salvage therapies.[2,5-7] Although allogeneic stem-cell transplantation is an option for some patients with relapsed or refractory mantle-cell lymphoma, non–relapse-related mortality, even with reduced-intensity conditioning therapy, remains high at 10 to 24%.[8]

Recently, anti-CD19 chimeric antigen receptor (CAR) T-cell therapies have shown considerable efficacy in patients with relapsed or refractory aggressive B-cell lymphoma.[9-12] Among patients with refractory large B-cell lymphoma who were treated with axicabtagene ciloleucel, an autologous anti-CD19 CAR T-cell therapy containing a CD3ζ T-cell activation domain and a CD28 signaling domain, 47% were alive after 39 months of follow-up, and the median survival was 25.8 months.[13] An earlier study that used this CAR T-cell construct showed promising efficacy in a patient with mantle-cell lymphoma who had a complete response that had been ongoing for more than 17 months as of the data-cutoff date.[14]

Patients with a high content of leukemic blasts in the peripheral blood may have relatively few T cells in the starting material used for the manufacturing of CAR T-cell products, which can lead to manufacturing failure.[15] KTE-X19 is an anti-CD19 CAR T-cell therapy produced in a manufacturing process that removes circulating CD19-expressing malignant cells for use in patients with leukemia or mantle-cell lymphoma. The removal of these cells reduces the possible activation and exhaustion of anti-CD19 CAR T cells during the ex vivo manufacturing process. Considering the very poor prognosis with currently available therapies in patients with relapsed or refractory mantle-cell lymphoma after treatment with a BTK inhibitor, we initiated the single-group, multicenter, open-label, phase 2 ZUMA-2 trial to evaluate KTE-X19 in patients with relapsed or refractory mantle-cell lymphoma. Here, we report the efficacy and safety results from the ZUMA-2 trial.

Methods

Patients and Trial Design

We conducted this trial at 20 sites in the United States and Europe (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Eligible adults (≥18 years of age) had histologically confirmed mantle-cell lymphoma with either cyclin D1 overexpression or presence of the translocation t(11;14) and had disease that was either relapsed or refractory to up to five previous regimens for mantle-cell lymphoma (see the Supplementary Methods section in the Supplementary Appendix). Previous therapy must have included anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and BTK inhibitor therapy with ibrutinib or acalabrutinib. BTK inhibitor therapy was not required to be the last line of therapy before trial entry, and patients were not required to have disease that was refractory to BTK inhibitor therapy. Eligible patients had an absolute lymphocyte count of at least 100 cells per cubic millimeter.

All the patients provided written informed consent, and the trial was conducted in accordance with the principles of the Declaration of Helsinki. The trial protocol (available at NEJM.org) and statistical analysis plan were designed in a collaboration between the sponsor (Kite, a Gilead company) and the authors. The protocol was approved by the institutional review board at each site. The first draft of the manuscript was written by the first author. Medical writing assistance was funded by the sponsor. All the authors, including both academic authors and those who are employees of the sponsor, contributed to the analysis and interpretation of the data.

All the patients underwent leukapheresis to obtain cells for KTE-X19 manufacturing. Conditioning chemotherapy (fludarabine at a dose of 30 mg per square meter of body-surface area per day and cyclophosphamide at a dose of 500 mg per square meter per day) was administered on days −5, −4, and −3 before a single intravenous infusion of KTE-X19 was administered at a dose of 2×10^6 CAR T cells per kilogram of body weight on day 0.

There was no phase 1 study. The dose of KTE-

X19 was determined on the basis of studies of axicabtagene ciloleucel in patients with large B-cell lymphoma and of KTE-X19 in patients with acute lymphoblastic leukemia.[10,16-18] After leukapheresis and before conditioning therapy, patients who had a high disease burden could receive bridging therapy, at the investigator's discretion, with dexamethasone or equivalent glucocorticoid, ibrutinib, or acalabrutinib (or a combination of glucocorticoid plus ibrutinib or acalabrutinib), after which repeat baseline positron-emission tomography–computed tomography (PET-CT) was performed. Bridging therapy was not intended to be curative but to keep the patient's condition stable during the manufacturing period. Hospitalization after the infusion of KTE-X19 was required through day 7.

End Points and Assessments

The primary end point was the percentage of patients with an objective response (complete or partial response) as assessed by the independent radiology review committee according to the Lugano classification (see the Supplementary Methods section).[19] Bone marrow evaluation in addition to PET-CT was necessary to confirm a complete response.[19]

Secondary end points included the duration of response, progression-free survival, overall survival, the percentage of patients with an investigator-assessed objective response according to the criteria of Cheson et al.,[20] the incidence of adverse events, the levels of CAR T cells in blood and cytokines in serum, and changes in scores from baseline to month 6 in the five-level version of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire. Details regarding disease and biomarker assessments are provided in the Supplementary Methods section. Minimal residual disease (sensitivity, 1 in 100,000 cells) was assessed as an exploratory analysis. Minimal residual disease was assessed in cryopreserved peripheral-blood mononuclear cells obtained at baseline and at months 1, 3, and 6 and was analyzed by means of next-generation sequencing with the use of the clonoSEQ assay (Adaptive Biotechnologies). We assessed various subgroups that were based on prognostic features, such as morphologic characteristics, the presence or absence of *TP53* mutation, and the Ki-67 proliferation index (Ki-67 is a marker of cellular proliferation, as detected by immunohistochemical testing).

Statistical Analysis

The primary efficacy analysis was conducted after 60 patients had been enrolled, treated, and evaluated for response for 6 months after the week 4 disease assessment, as required by the protocol. This analysis had a power of at least 96% to distinguish between an active therapy with 50% of patients having an objective response and a therapy with which 25% or less of patients had a response, at a one-sided alpha level of 0.025. Per the protocol, all the efficacy end points were analyzed in the 60 treated patients in the primary efficacy analysis. Safety analyses included all the patients who had received treatment. Associations between outcomes and CAR T-cell and cytokine levels were measured with the use of the Wilcoxon rank-sum test for two independent samples and with the Kruskal–Wallis test for the comparison of two or more independent samples. The P values and confidence intervals were not adjusted for multiple testing.

Results

Patients

From October 24, 2016, to April 16, 2019, a total of 74 patients were enrolled in the trial and underwent leukapheresis. KTE-X19 was successfully manufactured for 71 patients (96%) and administered to 68 (92%) (Fig. S1 in the Supplementary Appendix). The median time from leukapheresis to the delivery of KTE-X19 at the trial site was 16 days. A total of 3 patients for whom the manufacturing of KTE-X19 failed did not proceed to an additional apheresis owing to deep-vein thrombosis, death from progressive disease, or withdrawal of consent (in 1 patient each). Two patients who had successful manufacture of KTE-X19 died from progressive disease before the receipt of conditioning chemotherapy. After the receipt of conditioning chemotherapy, 1 patient with ongoing atrial fibrillation, an exclusion criterion, was deemed to be ineligible for KTE-X19 infusion. As of July 24, 2019, the median follow-up among the patients in the primary efficacy analysis was 12.3 months (range, 7.0 to 32.3).

High-risk features were common at baseline, and most patients had received at least three previous lines of therapy (Table 1 and Tables S1 and S2). All the patients had disease that was

Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

* BTK denotes Bruton's tyrosine kinase, and MCL mantle-cell lymphoma.
† The Simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) is used in patients with mantle-cell lymphoma to assess risk on the basis of age, Eastern Cooperative Oncology Group performance-status score, lactate dehydrogenase level, and white-cell count.
‡ This value was assessed at the time of diagnosis.
§ Induction plus consolidation or maintenance therapy or all treatments occurring between sequential complete responses were counted as one regimen.
¶ Patients had a relapse after or had disease that was refractory to subsequent therapies before trial entry.

refractory to BTK inhibitor therapy or had disease that had progressed during or after receipt of a BTK inhibitor. A total of 42 of 68 treated patients (62%) had disease that did not respond to BTK inhibitor therapy (primary refractory disease), and 18 (26%) had a relapse after having an initial response while receiving BTK inhibitor therapy; therefore, 88% of the treated patients had disease that was considered to be refractory to BTK inhibitor therapy. A total of 5 patients (7%) had a relapse after stopping BTK inhibitor therapy; 3 patients (4%) were unable to take ibrutinib owing to adverse events.

A total of 25 patients (37%) received bridging therapy with ibrutinib (14 patients), acalabrutinib (5), dexamethasone (12), or methylprednisolone (2) (Table S3). A total of 23 patients underwent radiologic imaging after bridging therapy; the median sum of the products of tumor diameters after bridging therapy was 3275 mm^2. The majority of the 17 patients who had assessments both before and after bridging therapy had an increase in the median tumor burden after the receipt of bridging therapy.

EFFICACY

Among the first 60 treated patients who had at least 7 months of follow-up (as specified in the protocol), 93% (95% confidence interval [CI], 84 to 98) had an objective response as assessed by the independent radiologic review committee, with 67% (95% CI, 53 to 78) having a complete response (Fig. 1A and Fig. S2). High concordance (95%) was observed between rates assessed by the independent radiologic review committee and those assessed by the investigator (Table S4). Among all 74 enrolled patients, 85% had an objective response, with 59% having a complete response. The percentages of patients with an objective response were consistent among key subgroups, including patients with high-risk features (Fig. 2). The median time to an initial response was 1.0 month (range, 0.8 to 3.1), and the median time to a complete response was 3.0 months (range, 0.9 to 9.3). Among the 42 patients who initially had a partial response or stable disease, 24 patients (57%), including 21 with an initial partial response and 3 with stable disease, subsequently had a complete response after a median of 2.2 months (range, 1.8 to 8.3) after the initial response; 17 patients were continuing to have a response as of the data-cutoff date (median follow-up, 12.3 months).

Minimal residual disease was analyzed in 29 of 74 patients (39%); 24 of these 29 patients (83% [19 patients with a complete response and 5 with a partial response]) had no detectable residual disease (i.e., <1 in 100,000 cells) at week 4, and 15 of 19 patients (79%) with available data had negative results at month 6. Two pa-

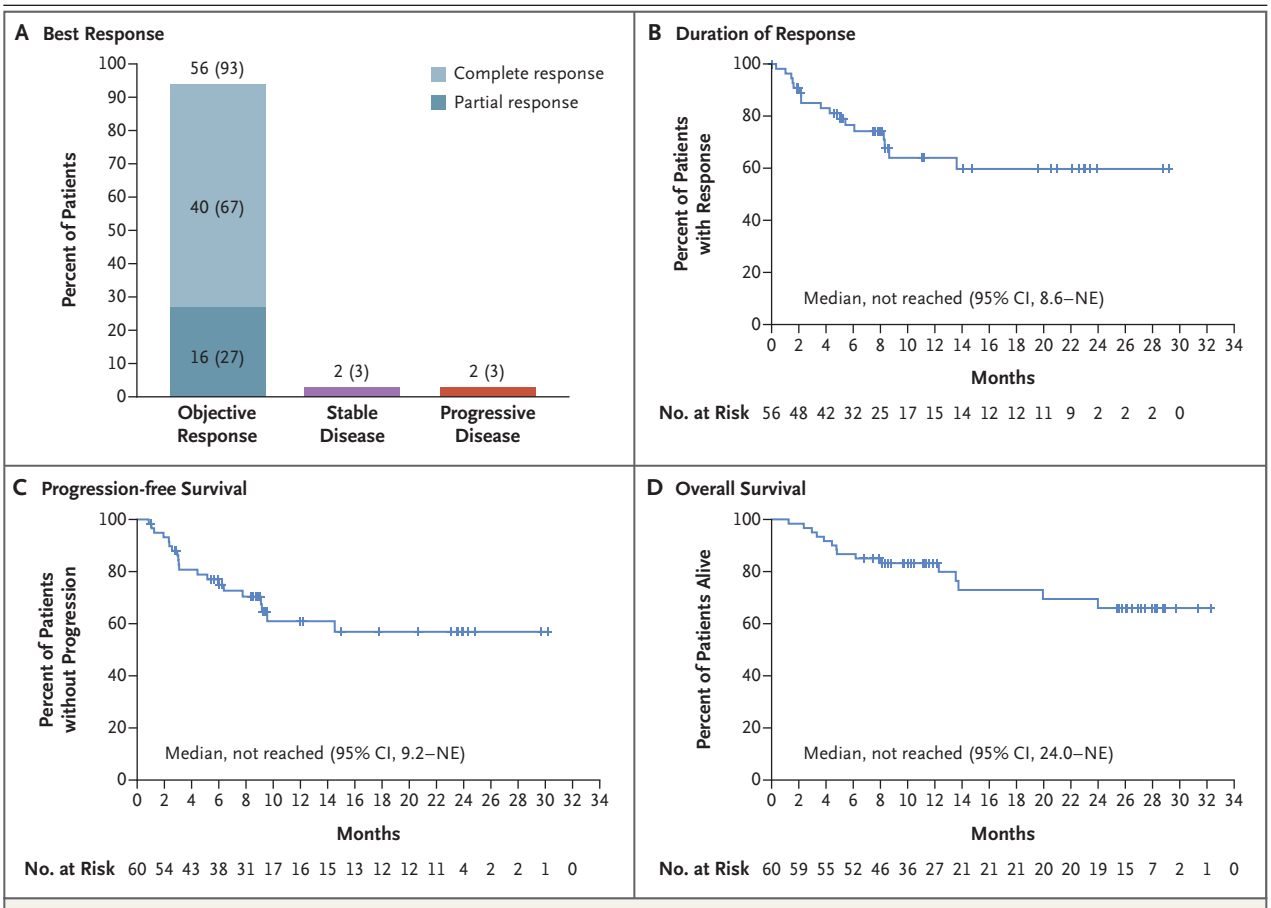

Figure 1. Objective Response, Duration of Response, Progression-free Survival, and Overall Survival.

Panel A shows the numbers and percentages of patients who had an objective response (complete response or partial response) among the 60 patients who had been treated with KTE-X19 and were included in the primary efficacy analysis. Panel B shows the Kaplan–Meier estimate of the duration of response, as assessed on the basis of review by the independent radiologic review committee, among the 56 patients in the primary efficacy analysis who had a response. Tick marks indicate censored data. Kaplan–Meier estimates of progression-free survival and overall survival among the 60 patients who were included in the primary efficacy analysis are shown in Panels C and D, respectively. NE denotes could not be estimated.

tients who had disease progression after having an objective response to KTE-X19 received a second infusion approximately 1 year and 1.3 years after the initial infusion; analysis in these patients is ongoing.

A total of 57% of all the patients in the primary efficacy analysis and 78% of the patients who had a complete response were in remission as of the data-cutoff date (Fig. 1B). The first 28 patients who were treated had a median follow-up of 27.0 months (range, 25.3 to 32.3), with 43% having a continued remission without additional therapy. The percentages of patients with an ongoing response were also consistent across key covariates (Fig. S3). The 3 patients who had CD19-negative tumors at baseline and were included in the primary efficacy analysis had a complete response and were in remission as of the data-cutoff date.

At 12 months, the estimated progression-free survival and overall survival were 61% and 83%, respectively (Fig. 1C and 1D). Subgroup analysis showed that progression-free survival at 6 months was consistent among patients with poor prognostic features, including pleomorphic morphologic characteristics, *TP53* mutation, or a Ki-67 proliferation index of 50% or higher (Figs. S4 and S5 and Table S5).

Subgroup	No. of Patients	No. of Patients with Response	Percent of Patients with Objective Response (95% CI)
All patients	60	56	93 (84–98)
Age			
<65 yr	28	26	93 (76–99)
≥65 yr	32	30	94 (79–99)
Relapsed–refractory subgroup			
Relapse after autologous SCT	26	24	92 (75–99)
Relapse after most recent previous therapy	10	10	100 (69–100)
Refractory to most recent previous therapy	24	22	92 (73–99)
Relapsed or refractory status with BTK inhibitor			
Refractory to BTK inhibitor therapy	38	35	92 (79–98)
Relapse during or after BTK inhibitor therapy	19	19	100 (82–100)
Could not receive BTK inhibitor therapy	3	2	67 (9–99)
Morphologic characteristic of MCL			
Classical MCL	35	32	91 (77–98)
Pleomorphic MCL	4	4	100 (40–100)
Blastoid MCL	14	13	93 (66–100)
Ki-67 proliferation index			
<50%	14	14	100 (77–100)
≥50%	32	30	94 (79–99)
Disease stage			
I or II	2	2	100 (16–100)
III or IV	58	54	93 (83–98)
Extranodal disease			
Yes	37	36	97 (86–100)
No	23	20	87 (66–97)
Tumor burden according to central laboratory			
<Median	27	24	89 (71–98)
≥Median	28	28	100 (88–100)
LDH relative to ULN			
<0.67× ULN	14	13	93 (66–100)
≥0.67× ULN and <ULN	21	19	90 (70–99)
≥ULN and <1.5× ULN	15	14	93 (68–100)
≥1.5× ULN	8	8	100 (63–100)
Bone marrow involvement			
Positive	35	31	89 (73–97)
Negative	21	21	100 (84–100)
Simplified MIPI risk assessment			
Low risk	25	23	92 (74–99)
Intermediate or high risk	33	31	94 (80–99)
TP53 mutation detected			
Yes	6	6	100 (54–100)
No	30	30	100 (88–100)
CD19 positive			
Yes	44	42	95 (85–99)
No	3	3	100 (29–100)
Tocilizumab use			
Yes	42	40	95 (84–99)
No	18	16	89 (65–99)
Glucocorticoid use for adverse-event management			
Yes	35	33	94 (81–99)
No	25	23	92 (74–99)
Bridging therapy use			
Yes	21	19	90 (70–99)
No	39	37	95 (83–99)

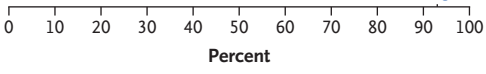

Figure 2 (facing page). Subgroup Analysis of Objective Response.

Shown is the analysis of objective response according to key baseline and clinical covariates. The Clopper–Pearson method was used to calculate the 95% confidence interval (not adjusted for multiplicity). Ki-67 is a marker of cellular proliferation, as detected by immunohistochemical testing. Tumor burden was assessed as the sum of the product diameters. The Simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) is used in patients with mantle-cell lymphoma to assess risk on the basis of age, Eastern Cooperative Oncology Group performance-status score, lactate dehydrogenase (LDH) level, and white-cell count. BTK denotes Bruton's tyrosine kinase, MCL mantle-cell lymphoma, SCT stem-cell transplantation, and ULN upper limit of the normal range.

At the time of this analysis, 76% of all 68 treated patients were alive. Among the patients who had a response, progressive disease developed in 14. One patient who had a partial response underwent allogeneic stem-cell transplantation.

SAFETY

All 68 treated patients had at least one adverse event of any grade, with adverse events of grade 3 or higher occurring in 99% of the patients (Table 2). The most common adverse events of grade 3 or higher were cytopenias (in 94% of the patients) and infections (in 32%). Grade 3 or higher cytopenias included neutropenia (in 85%

Table 2. Adverse Events among All 68 Treated Patients.*

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Any adverse event	68 (100)	0	1 (1)	11 (16)	54 (79)	2 (3)
Pyrexia	64 (94)	14 (21)	41 (60)	9 (13)	0	0
Neutropenia	59 (87)	0	1 (1)	11 (16)	47 (69)	0
Thrombocytopenia	50 (74)	9 (13)	6 (9)	11 (16)	24 (35)	0
Anemia	46 (68)	0	12 (18)	34 (50)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	13 (19)	2 (3)	0
Chills	28 (41)	17 (25)	11 (16)	0	0	0
Hypoxemia	26 (38)	2 (3)	10 (15)	8 (12)	6 (9)	0
Cough	25 (37)	14 (21)	11 (16)	0	0	0
Hypophosphatemia	25 (37)	2 (3)	8 (12)	15 (22)	0	0
Fatigue	24 (35)	10 (15)	13 (19)	1 (1)	0	0
Headache	24 (35)	15 (22)	8 (12)	1 (1)	0	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Hypoalbuminemia	23 (34)	5 (7)	17 (25)	1 (1)	0	0
Hyponatremia	22 (32)	15 (22)	0	7 (10)	0	0
Nausea	22 (32)	11 (16)	10 (15)	1 (1)	0	0
Alanine aminotransferase increased	21 (31)	13 (19)	2 (3)	5 (7)	1 (1)	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Hypokalemia	21 (31)	12 (18)	4 (6)	3 (4)	2 (3)	0
Tachycardia	21 (31)	14 (21)	7 (10)	0	0	0

* The first row (Any adverse event) shows the worst grade of adverse event in each of the 68 treated patients. All rows subsequent to the first row show adverse events of any grade that occurred in at least 30% of the patients. Severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Regarding the grade 5 events, 1 patient died from organizing pneumonia related to conditioning chemotherapy, and 1 from staphylococcus bacteremia related to conditioning chemotherapy and KTE-X19 therapy.

Table 3. Cytokine Release Syndrome and Neurologic Events among All 68 Treated Patients.*

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Symptom of cytokine release syndrome						
Any	62 (91)	20 (29)	32 (47)	8 (12)	2 (3)	0
Pyrexia	62 (91)	15 (22)	40 (59)	7 (10)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	14 (21)	1 (1)	0
Hypoxemia	23 (34)	1 (1)	10 (15)	8 (12)	4 (6)	0
Chills	21 (31)	12 (18)	9 (13)	0	0	0
Tachycardia	16 (24)	11 (16)	5 (7)	0	0	0
Headache	15 (22)	7 (10)	8 (12)	0	0	0
Alanine aminotransferase increased	10 (15)	5 (7)	1 (1)	3 (4)	1 (1)	0
Aspartate aminotransferase increased	9 (13)	4 (6)	0	5 (7)	0	0
Fatigue	9 (13)	6 (9)	2 (3)	1 (1)	0	0
Nausea	9 (13)	5 (7)	4 (6)	0	0	0
Neurologic event	43 (63)	13 (19)	9 (13)	15 (22)	6 (9)	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Confusional state	14 (21)	3 (4)	3 (4)	8 (12)	0	0
Aphasia	10 (15)	3 (4)	4 (6)	3 (4)	0	0

* Shown are events of any grade that occurred in at least 15% of the patients and events of grade 3 or higher that occurred in at least 4% of the patients. Cytokine release syndrome was graded according to Lee et al.[21] The severity of neurologic events and symptoms of cytokine release syndrome were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

of patients), thrombocytopenia (51%), and anemia (50%). A total of 26% of the patients had cytopenias of grade 3 or higher more than 90 days after the administration of KTE-X19, including neutropenia (in 16% of patients), thrombocytopenia (16%), and anemia (12%). The cytokine release syndrome occurred in 91% of the patients (Table 3). No patient died from cytokine release syndrome. Most cases were grade 1 or 2 (in 76% of patients), with cases of grade 3 or higher occurring in 15% of the patients. For the management of cytokine release syndrome, 59% of all treated patients received tocilizumab, 22% received glucocorticoids, and 16% received vasopressors. The median time after infusion to the onset of cytokine release syndrome of any grade was 2 days (range, 1 to 13); the corresponding interval to the onset of cytokine release syndrome of grade 3 or higher was 4 days (range, 1 to 9). All events resolved within a median of 11 days.

A total of 63% of patients had neurologic events (Table 3). No patient died from a neurologic event. Neurologic events of grade 1 or 2 occurred in 32% of the patients and events of grade 3 or higher in 31%. One patient had grade 4 cerebral edema and fully recovered with aggressive multimodality therapy including ventriculostomy. For the management of neurologic events, 26% of all treated patients received tocilizumab and 38% received glucocorticoids. The median time to the onset of a neurologic event of any grade was 7 days (range, 1 to 32); the corresponding interval to the onset of a neurologic event of grade 3 or higher was 8 days (range, 5 to 24). The median duration of a neurologic event was 12 days, with events fully resolving in 37 of 43 patients (86%). As of this analysis, 4 patients had ongoing symptoms, including grade 1 tremor (in 3 patients), grade 2 concentration impairment (in 1), and grade 1 dysesthesia (in 1).

A total of 68% of patients had serious adverse events (Table S6). Infection of grade 3 or higher occurred in 32% of the patients, with the most common being pneumonia (in 9%) (Table S7). Two cases of grade 2 cytomegalovirus infection occurred (3% of patients). Grade 3 hypogamma-

globulinemia and grade 3 tumor lysis syndrome occurred in 1 patient (1%) each. A total of 22 patients (32%) received intravenous immune globulin therapy. No cases of replication-competent retrovirus, Epstein–Barr virus–associated lymphoproliferation, hemophagocytic lymphohistiocytosis, or KTE-X19–related secondary cancers were reported. EQ-5D scores revealed decreases from baseline in patient-reported health-related quality of life at week 4; better scores in mobility, self-care, usual activities, and overall health (patients' perception of their overall health was assessed according to the EQ-5D visual-analogue scale) were observed by month 3, with overall health returning to baseline status or better in most patients by month 6 (Table S8).

A total of 16 patients (24%) who received KTE-X19 died, primarily from progressive disease (14 patients [21%]). Two patients (3%) had grade 5 adverse events, including organizing pneumonia related to conditioning chemotherapy (in 1) and staphylococcus bacteremia related to conditioning chemotherapy and KTE-X19 therapy (in 1).

BIOMARKER ANALYSIS

The median time to peak anti-CD19 CAR T-cell levels was 15 days (range, 8 to 31) after the infusion of KTE-X19 (Fig. S7A); cells were still detectable at 24 months in 6 of 10 patients (60%) who had samples that could be evaluated at the time of this analysis. CAR T-cell persistence in blood showed a decrease over time in patients who had an ongoing response (Fig. S8). Of the 34 patients who had an ongoing response at 6 months, B cells were detectable by flow cytometry in 21 (62%), and gene-marked CAR T cells were no longer detectable in 6 (18%). All 4 patients who did not have a response had detectable B cells at baseline; none had B-cell aplasia at any point during the trial. Of the 14 patients who had a relapse, 13 (93%) had detectable CD19 at relapse. Of the 7 patients who provided samples at the time of relapse, CAR T cells were still detectable in the blood of 5 patients at levels well below the peak of expansion and showed no evidence of a secondary expansion.

Although there was no association with baseline tumor burden, expansion was associated with response ($P=0.004$), with an area under the curve (AUC) and peak level that were more than 200 times as high among patients with a response as among those without a response; the peak level and AUC were more than 80 times as high among patients without minimal residual disease as among those with minimal residual disease at week 4. For patients with cytokine release syndrome and neurologic events, expansion was greater in those who had events of grade 3 or higher than in those who had events of grade 2 or lower, and the highest peak and AUC values were noted in patients receiving tocilizumab, with or without glucocorticoids. The median time to peak levels of cytokines was 8 days; most values resolved to baseline levels by 28 days. Elevated levels of serum granulocyte–macrophage colony-stimulating factor and interleukin-6 were associated with grade 3 or higher cytokine release syndrome and neurologic events. Elevated levels of serum ferritin were associated only with grade 3 or higher cytokine release syndrome, whereas serum interleukin-2 and interferon-γ were associated only with neurologic events of grade 3 or higher. Cerebrospinal fluid cytokine analysis revealed higher levels of C-reactive protein, ferritin, interleukin-6, interleukin-8, and vascular-cell adhesion molecule 1 in patients with grade 3 or higher neurologic events. Induction of anti-CAR antibodies was not observed in any patient. (Data are shown in Figs. S7, S9, S10, and S11.)

DISCUSSION

The treatment of patients with relapsed or refractory mantle-cell lymphoma whose disease is resistant to BTK inhibitor therapy can be a therapeutic challenge. Retrospective studies evaluating salvage therapy after the failure of BTK inhibitor therapy in patients with relapsed or refractory mantle-cell lymphoma have shown low response rates and a median overall survival of 6 to 10 months.[5,6] In the ZUMA-2 trial, among the protocol-specified 60 patients with relapsed or refractory mantle-cell lymphoma, KTE-X19 resulted in an objective response in 93% of the patients and in a complete response in 67%; the majority of these patients had disease that was refractory to or that had relapsed after the receipt of BTK inhibitor therapy. In the intention-to-treat analysis involving 74 patients, 85% of the patients had an objective response. This percentage of patients with a response, which includes 59% of those with a complete response,

after a single infusion is promising in this population of patients. A total of 57% of all the patients in the primary efficacy analysis and 78% of those who had a complete response were continuing to have a response after a median follow up of 12.3 months.

The percentages of patients with an objective response, including an ongoing response, were generally similar in the key subgroups, including patients who had high-risk features. A recent study of ibrutinib plus rituximab therapy in patients with relapsed or refractory mantle-cell lymphoma showed that 88% of the patients had an objective response and 58% had a complete response.[22] However, among patients with a Ki-67 proliferation index of 50% or higher, 50% of the patients had an objective response and 17% had a complete response, and the 3-year progression-free survival was 1%.[22,23] Similarly, patients in that study who had blastoid morphologic features and high scores (indicating high risk) on the Mantle-Cell Lymphoma International Prognostic Index (MIPI) had poor outcomes. In our trial, a high percentage of patients who had a Ki-67 proliferation index of 50% or higher had an objective response, as did patients who had blastoid or pleomorphic morphologic features or *TP53* mutation, which suggests that KTE-X19 may benefit patients who typically have a poorer prognosis than patients without these characteristics.

Although it is possible that bridging therapy could contribute to the antitumor effects observed, the majority of the patients' PET-CT scans after bridging therapy showed an increase in tumor burden. All the patients who had an objective response after CAR T-cell infusion had robust T-cell expansion and also had B-cell aplasia at the first assessment, in contrast to the patients who did not have an objective response. The percentages of patients with a response were also similar regardless of exposure to bridging therapy. As observed in earlier studies,[10,11] peak and AUC CAR T-cell levels correlated with response in the first 28 days, which suggests that higher expansion led to better and perhaps deeper responses as indicated by the peak level and AUC that were more than 80 times as high among patients without minimal residual disease than among those with minimal residual disease. Conditioning chemotherapy with fludarabine and cyclophosphamide may have contributed toward the response findings, and both agents have led to favorable responses in a study involving patients with mantle-cell lymphoma.[24] However, in that study, the median progression-free survival after the administration of these chemotherapy agents was relatively short (4.8 months), and the doses were much higher than those used for conditioning chemotherapy in our trial.[24] The correlations between the percentage of patients with a response and the peak level and AUC for CAR T cells and the prolonged duration of response in our trial, with patients alive at 24 to 30 months, suggest that any benefit conferred by the conditioning chemotherapy was probably marginal as compared with that of KTE-X19.

Data are limited regarding other treatment approaches for relapsed or refractory mantle-cell lymphoma in patients who have received a BTK inhibitor, although single-agent venetoclax and the R-BAC regimen (rituximab, bendamustine, and cytarabine) have shown efficacy. A retrospective study of venetoclax therapy, which was administered on a compassionate-use basis in 20 patients with mantle-cell lymphoma who discontinued BTK inhibitor therapy, showed that 53% of the patients had a response and 18% had a complete response; patients had a relatively short duration of response, progression-free survival, and overall survival (8.1 months, 3.2 months, and 9.4 months, respectively).[25] In a retrospective study of R-BAC therapy in 35 patients with mantle-cell lymphoma after BTK inhibitor therapy, 82% of the patients had a response (complete response plus unconfirmed complete response in 56%), with a median progression-free survival of 9.3 months and a median overall survival of 12.2 months.[26] It is difficult to draw comparisons between these studies given different study designs and end-point confirmation.

The incidence of grade 3 or higher cytokine release syndrome and neurologic events was similar to the incidence that has been reported previously with anti-CD19 CAR T-cell therapies in patients with aggressive lymphoma.[10,11] No patients died from cytokine release syndrome or neurologic events, and most symptoms occurred early and were generally reversible. Associations between toxic effects and peak levels of CAR and myeloid-cell–related serum cytokines, chemokines, and effector molecules were consistent with previously published data from studies in-

volving a similar CAR construct in B-cell lymphoma.[10,14] One case of grade 4 cerebral edema occurred; the patient had a full recovery and was in complete remission at 24 months of follow-up with no unresolved neurologic sequelae. Patient-reported outcomes suggested no long-term quality-of-life deficits after the receipt of KTE-X19 therapy.

The rapid expansion of CAR T cells and gradual decrease to undetectable levels over time are consistent with the known mechanism of action of anti-CD19 CAR T cells that have CD28 and CD3ζ costimulatory domains. B-cell recovery was observed in the majority of patients who had an ongoing response at 6 months (21 of 34 patients [62%]), and CAR T-cell levels remained detectable in 82% of those patients. The recovery of B cells in patients with mantle-cell lymphoma in our trial is consistent with that reported previously with anti-CD19 CAR T-cell therapy in patients with refractory large B-cell lymphoma, which suggests that durable responses may not depend on long-term persistence of functional CAR T cells.[9]

Finally, the manufacturing of CAR T products in patients with a highly proliferative tumor with circulating blasts and leukemic cells continues to be a challenge. In our trial, 96% of the patients had a dose successfully manufactured, with KTE-X19 delivered to the site in a median of 16 days after apheresis.

This trial showed that a single infusion of KTE-X19 was capable of inducing durable remissions in patients with relapsed or refractory mantle-cell lymphoma after the failure of BTK inhibitor therapy. The trial therapy led to serious and life-threatening toxic events that are largely consistent with those reported in previous studies of anti-CD19 CAR T-cell therapies in patients with aggressive B-cell lymphoma.[10,11]

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Appendix

The authors' full names and academic degrees are as follows: Michael Wang, M.D., Javier Munoz, M.D., Andre Goy, M.D., Frederick L. Locke, M.D., Caron A. Jacobson, M.D., Brian T. Hill, M.D., Ph.D., John M. Timmerman, M.D., Houston Holmes, M.D., Samantha Jaglowski, M.D., Ian W. Flinn, M.D., Ph.D., Peter A. McSweeney, M.D., David B. Miklos, M.D., John M. Pagel, M.D., Ph.D., Marie-Jose Kersten, M.D., Noel Milpied, M.D., Henry Fung, M.D., Max S. Topp, M.D., Roch Houot, M.D., Amer Beitinjaneh, M.D., Weimin Peng, Ph.D., Lianqing Zheng, Ph.D., John M. Rossi, M.S., Rajul K. Jain, M.D., Arati V. Rao, M.D., and Patrick M. Reagan, M.D.

The authors' affiliations are as follows: the University of Texas M.D. Anderson Cancer Center, Houston (M.W.), and Texas Oncology, Dallas (H.H.); Banner M.D. Anderson Cancer Center, Gilbert, AZ (J.M.); John Theurer Cancer Center, Hackensack, NJ (A.G.); Moffitt Cancer Center, Tampa (F.L.L.), and the University of Miami, Miami (A.B.) — both in Florida; Dana–Farber Cancer Institute, Boston (C.A.J.); Cleveland Clinic Foundation, Cleveland (B.T.H.), and the Ohio State University Comprehensive Cancer Center, Columbus (S.J.); David Geffen School of Medicine at UCLA, Los Angeles (J.M.T.), Stanford University School of Medicine, Stanford (D.B.M.), and Kite, a Gilead company, Santa Monica (W.P., L.Z., J.M.R., R.K.J., A.V.R.) — all in California; Sarah Cannon Research Institute–Tennessee Oncology, Nashville (I.W.F.); Colorado Blood Cancer Institute, Denver (P.A.M.); Swedish Cancer Institute, Seattle (J.M.P.); the Academic Medical Center, University of Amsterdam, Amsterdam, for the Lunenburg Lymphoma Phase I/II Consortium (M.-J.K.); Centre Hospitalier Universitaire (CHU) Bordeaux, Service d'Hematologie et Therapie Cellulaire, Bordeaux (N.M.), and CHU Rennes, INSERM French Blood Establishment, Rennes (R.H.) — both in France; Fox Chase Cancer Center, Philadelphia (H.F.); Universitätsklinikum Würzburg, Würzburg, Germany (M.S.T.); and the University of Rochester Medical Center, Rochester, NY (P.M.R.).

References

1. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66:443-59.
2. Cheah CY, Seymour JF, Wang ML. Mantle cell lymphoma. J Clin Oncol 2016;34:1256-69.
3. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013;369:507-16.
4. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet 2018;391:659-67.
5. Martin P, Maddocks K, Leonard JP, et al. Postibrutinib outcomes in patients with mantle cell lymphoma. Blood 2016;127:1559-63.
6. Jain P, Kanagal-Shamanna R, Zhang S, et al. Long-term outcomes and mutation profiling of patients with mantle cell lymphoma (MCL) who discontinued ibrutinib. Br J Haematol 2018;183:578-87.
7. Epperla N, Hamadani M, Cashen AF, et al. Predictive factors and outcomes for ibrutinib therapy in relapsed/refractory mantle cell lymphoma — a "real world" study. Hematol Oncol 2017;35:528-35.
8. Robinson SP, Boumendil A, Finel H, et al. Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation in patients with mantle cell lymphoma: a retrospective study from the EBMT Lymphoma Working Party. Bone Marrow Transplant 2018;53:617-24.
9. Locke FL, Ghobadi A, Jacobson CA,

et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
10. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-44.
11. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56.
12. Abramson JS, Siddiqi T, Palomba ML, et al. High durable CR rates and preliminary safety profile for JCAR017 in R/R aggressive B-NHL (TRANSCEND NHL 001 Study): a defined composition CD19-directed CAR T-cell product with potential for outpatient administration. J Clin Oncol 2018;36:Suppl:120. abstract.
13. Neelapu SS, Rossi JM, Jacobson CA, et al. CD19-Loss with preservation of other B cell lineage features in patients with large B cell lymphoma who relapsed post-axi-cel. Blood 2019;134:Suppl:203. abstract.
14. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol 2017;35:1803-13.
15. Sabatino M, Choi K, Chiruvolu V, Better M. Production of anti-CD19 CAR T cells for ZUMA-3 and -4: phase 1/2 multicenter studies evaluating KTE-C19 in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (R/R ALL). Blood 2016;128:Suppl:1227. abstract.
16. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. Mol Ther 2017;25:285-95.
17. Shah BD, Bishop MR, Oluwole OO, et al. End of phase I results of ZUMA-3, a phase 1/2 study of KTE-X19, anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in adult patients (pts) with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). J Clin Oncol2019;37: Suppl:7006. abstract.
18. Lee DW, Wayne AS, Huynh V, et al. ZUMA-4 preliminary results: phase 1 study of KTE-C19 chimeric antigen receptor T cell therapy in pediatric and adolescent patients (pts) with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). Ann Oncol 2017;28:Suppl:1008PD. abstract.
19. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.
20. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25: 579-86.
21. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-95.
22. Jain P, Romaguera J, Srour SA, et al. Four-year follow-up of a single arm, phase II clinical trial of ibrutinib with rituximab (IR) in patients with relapsed/refractory mantle cell lymphoma (MCL). Br J Haematol 2018;182:404-11.
23. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol 2016;17:48-56.
24. Cohen BJ, Moskowitz C, Straus D, Noy A, Hedrick E, Zelenetz A. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001;42:1015-22.
25. Eyre TA, Walter HS, Iyengar S, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica 2019; 104(2):e68-e71.
26. McCulloch RV, Frewin R, Phillips N, et al. R-BAC maintains high response rate in mantle cell lymphoma following relapse on BTK inhibitor therapy. Blood 2019;134: Suppl 1:3989. abstract.