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Original Article

Outpatient axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma: ZUMA-24 primary analysis

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Abstract: ZUMA-24 is a Phase 2, open-label, multicenter study that investigated safety and efficacy of axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, administered in the outpatient setting to patients with relapsed or refractory large B-cell lymphoma (R/R LBCL) with ≥1 prior lines of therapy. Patients underwent leukapheresis and received lymphodepleting chemotherapy, axi-cel infusion (2×10^6 CAR T cells/kg), and prophylactic steroids. Patients were monitored daily ≥7 days after infusion per institutional outpatient monitoring guidelines. The primary endpoint was incidence and severity of cytokine release syndrome (CRS) and neurologic events (NEs). Median follow-up was 13 months for 30 patients treated with outpatient axi-cel. Grade 1-2 CRS was reported in 90% of patients, with no grade ≥3 CRS. NEs of any grade were reported in 80% of patients (grade ≥3, 23%; no patients died due to NEs). Median time to onset was 4 days for CRS and 7 days for NEs, with a median duration of 5 days and 6 days, respectively. All patients experienced AEs of any grade (grade ≥3, 83%). After axi-cel, 93% of patients were hospitalized, with 4 days median time to first hospitalization (8 days median stay), and 4 patients (13%) were admitted to the ICU (for 2-7 days). Among patients evaluable for efficacy (n=29), the objective response rate was 93% (complete response, 76%), with a median duration of response of 11.4 months. These results support safety and feasibility of outpatient administration of axi-cel. This trial is registered at ClinicalTrials.gov: #NCT05459571.

Keywords: Large B-cell lymphoma, chimeric antigen receptor, CAR-T, outpatient, phase 2, clinical trial

Introduction

Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for adults with relapsed or refractory (R/R) large B-cell cell lymphoma (LBCL) [1, 2]. Approval was based on clinical benefit demonstrated in the second line in ZUMA-7 and third or later lines of therapy in ZUMA-1 [3, 4]. In ZUMA-7, axi-cel showed improved overall survival (OS) compared with platinum-based chemotherapy and autologous stem cell transplantation at 47.2 months median follow-up (hazard ratio [HR], 0.73; 95% CI, 0.54-0.98; stratified 2-sided log-rank *P*=.03) [5]. The incidence of grade ≥3 cytokine release syndrome (CRS) was 6%, and 21% of patients experienced grade ≥3 neurologic

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Table 1. List of study sites

Center	No. of Patients
John Theurer Cancer Center	6
Colorado Blood Cancer Institute/Sarah Cannon Research Institute	6
Greco-Hainsworth Tennessee Oncology Centers for Research	5
Methodist Hospital - San Antonio	5
City of Hope - Duarte	4
Intermountain Healthcare	3
Virginia Commonwealth University	2
Barbara Ann Karmanos Cancer Center Wayne State University	1
Huntsman Cancer Institute and Hospital	1
Prisma Health Cancer Institute - Eastside	1
University of California Los Angeles	1

events. However, prior axi-cel trials like ZUMA-7 were conducted in the inpatient setting, with prolonged hospital stays observed (median 16 days) and 25% of patients admitted to the intensive care unit (ICU) [3, 4].

After initial clinical experience with axi-cel, efforts in the clinical trial and real-world settings were undertaken to optimize safety outcomes. In a safety management cohort of ZUMA-1 (Cohort 6), prophylactic corticosteroids and early corticosteroid and/or tocilizumab were evaluated, showing a delay in median time to onset of CRS (5 days), with no grade ≥3 CRS events [6]. Median time to onset of neurologic events was 6 days, with a lower rate of patients experiencing grade ≥3 events compared with ZUMA-1 pivotal cohorts (Cohorts 1 and 2). Similarly, in a real-world assessment of outpatient axi-cel, early toxicity management for patients with R/R LBCL showed an improvement in safety outcomes, including shorter time to CRS resolution (4 vs 5 days for early vs late management, respectively) [7].

As the FDA-approved indications for axi-cel and other CAR T-cell therapies continue to increase, so will the demand on treatment centers [2]. Prolonged hospitalization with inpatient treatment may increase healthcare costs. Improved safety outcomes with prophylactic steroid use, combined with careful patient monitoring and the timely escalation of care, may enable outpatient treatment, with hospitalization only when clinically indicated. Here we report the primary analysis of the prospective, Phase 2 ZUMA-24 trial evaluating the safety and feasibility of outpatient administration of axi-cel with prophylactic corticosteroids and early toxicity intervention in patients with R/R LBCL.

Materials and methods

Patients and trial design

ZUMA-24 is a Phase 2, open-label, multicenter study evaluating the safety and efficacy of outpatient axi-cel, conducted at 11 sites with outpatient programs throughout the United States (**Table 1**). Eligible patients were aged ≥18 years with histologically confirmed LBCL type defined by World Health Organization 2016 classification [8] (diffuse large B-cell lymphoma [DLBCL] not otherwise specified, high-grade B-cell lymphoma [HGBL] with or without *MYC* and *BCL2* and/or *BCL6* rearrangement; DLBCL associated with chronic inflammation; Epstein-Barr virus + DLBCL, primary mediastinal [thymic] LBCL, primary cutaneous DLBCL [leg type], and transformed follicular lymphoma); and ≥1 measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma [9]. Patients had R/R disease after ≥1 prior lines of therapy, including an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen, and had an ECOG performance status (PS) of 0 or 1. Patients could not have had prior CD19-targeted therapy, autologous or allogeneic stem cell transplantation, or CAR or other genetically modified T-cell therapy, and patients were excluded if, based on investigator's judgment, they were unlikely to complete all protocol-required study visits and procedures.

All patients provided written informed consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board or independent ethics committee at each study site. The sponsor funded medical writing assistance. All au-

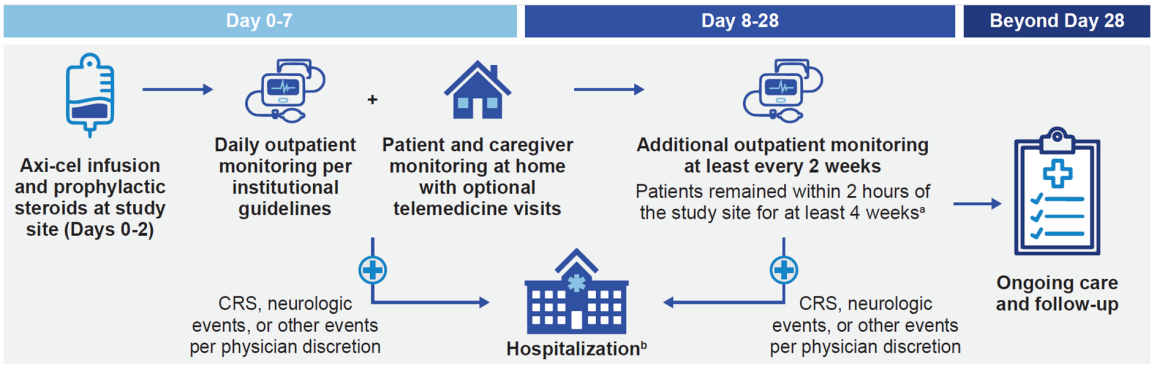

Figure 1. Safety management protocol. The figure shows institutional outpatient monitoring guidelines. [a]An electronic wearable device was available for continuous temperature monitoring, worn up to 4 weeks per investigator discretion. [b]For grade 1-2 CRS and grade 1 neurologic events, patients may have been admitted for outpatient observation per physician discretion. If symptoms persisted or recurred, patients were to be admitted to the inpatient setting. Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome.

thors had access to the data and contributed to the data analysis and interpretation.

Procedures

Patients underwent leukapheresis to obtain mononuclear cells for axi-cel manufacturing at enrollment. Lymphodepleting chemotherapy (cyclophosphamide and fludarabine) was administered on Days -5, -4, and -3. Bridging therapy was optional and could be administered, per investigator discretion, after leukapheresis and no later than 7 days before initiating lymphodepleting chemotherapy. On Day 0, a single infusion of axi-cel was administered at a target dose of 2×10^6 cells/kg. Prophylactic dexamethasone 10 mg was given before axi-cel infusion and on Days 1 and 2 after infusion.

Patients were monitored daily at a healthcare facility for ≥7 days in the outpatient setting after axi-cel infusion for toxicity, including symptoms of CRS and neurologic events (**Figure 1**). A complete set of vital signs and neurologic assessment were obtained according to institutional guidelines and as needed during waking hours, with an optional telemedicine visit at the end of the day. The clinic was to be notified by patient or caregiver if there were any prespecified or new abnormalities outside of the hospital setting. After 7 days of daily outpatient monitoring, patients were allowed to follow up at longer intervals, per investigator's discretion. Patients were expected to remain within 2 hours of the study site for ≥4 weeks after axi-cel infusion.

Guidelines for hospitalization included any grade CRS, any grade neurologic events, and other criteria at the discretion of covering physician. However, per physician discretion, patients with grade 1 neurologic events or grade 1 or 2 CRS (eg, fever, hypotension responsive to fluids, or hypoxia responsive to O_2) could be monitored in an outpatient observation unit.

Electronic wearable devices were deployed, per investigator discretion and patient consent. The device had a continuous temperature monitoring patch. Devices were to be checked for proper functioning on Days -5, -4, and -3, and were to be worn for up to 4 weeks. The data collected were for research purposes only and were blinded to the patient and center.

Endpoints and assessments

The primary endpoint was the incidence and severity of CRS and neurologic events following outpatient administration of axi-cel. Key secondary endpoints were time to onset and duration of CRS and neurologic events, hospitalization after axi-cel infusion, duration of initial hospitalization after axi-cel infusion, proportion of patients admitted to the ICU, duration of ICU admission during first hospitalization after axi-cel infusion, other safety outcomes, patient-reported outcomes by changes in EuroQoL 5-dimension 5-level (EQ-5D-5L) from baseline to Month 6, efficacy, and blood levels of serum analytes (including cytokines) and axi-cel CAR T-cells over time. Efficacy measures included objective response rate (ORR), complete

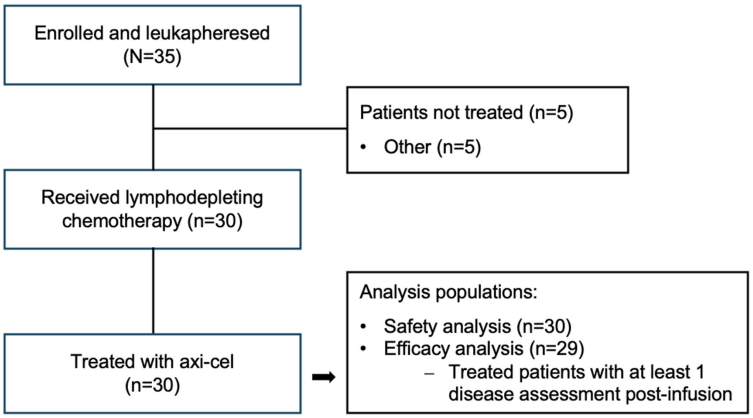

Figure 2. Consort diagram. Axi-cel, axicabtagene ciloleucel.

response (CR) rate, duration of response (DOR), progression-free survival (PFS), and event-free survival (EFS), all based on investigator assessment, and OS. Exploratory endpoints included time from axi-cel infusion to initial CRS and progression to higher grade CRS, and cumulative corticosteroid dosing.

CRS was defined and graded according to modified Lee et al. criteria [10]. Neurologic events were identified according to Topp et al. [11] and graded per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Other adverse events (AEs) were coded based on MedDRA v27.1 and graded according to CTCAE v5.0. All AEs, serious AEs, and AEs of special interest (neurologic events, hematologic events, autoimmune disorders, infections, and new malignancies) that occurred from enrollment through 90 days after infusion were reported. After 90 days, only AEs of special interest were collected for 24 months or until disease progression, whichever was first.

Investigator-assessed ORR (CR plus partial response [PR]) was based on the Lugano Classification [9]. PET-CT disease assessment was performed at baseline, Week 4, every 3 months between Month 3 and Month 18, and Month 24, or until disease progression, whichever came first. If a patient's disease had not progressed by Month 24, disease assessments continued per standard of care. DOR was defined as time from first objective response to disease progression or death from any cause. PFS was defined as time from axi-cel infusion to disease progression or death from any cause, EFS was time from axi-cel infusion to progression, initiation of new anti-lymphoma therapy, or death of any cause, and OS was time from axi-cel infusion to death. CAR T-cell expansion was assessed as previously described [12].

Statistical analysis

All statistical analyses were descriptive, with no formal hypothesis testing. The target sample size for the study was approximately 30 patients. Safety and pharmacokinetic analyses were measured in all patients treated with any dose of axi-cel, and efficacy analyses included all patients treated with axi-cel at the target dose of 2×10^6 cells/kg with ≥1 disease assessment following axi-cel administration. Time-to-event endpoints were analyzed using Kaplan-Meier estimates and 2-sided 95% confidence intervals using the Clopper-Pearson method. Time to onset of CRS and neurologic events were defined as the earliest start date of the event minus axi-cel infusion date, plus 1 day. EQ-5D-DL analysis was conducted by time of assessment, response category, and health states most applicable for oncology economic analyses (progression-free, progressed disease, and death). Progression-free health state included patients who were in CR, PR, and stable disease (SD). Progressed disease health state included patients with progressive or relapsed disease (PD).

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, and access can be requested by contacting medinfo@kitepharma.com.

Results

Patients

Thirty-five patients were enrolled between 08/30/2022 and 03/07/2024 and were leukapheresed. Thirty patients subsequently received lymphodepleting chemotherapy and were treated with axi-cel in the outpatient setting (**Figure 2**). Five patients did not receive

Table 2. Demographics and baseline disease characteristics

Characteristics	Treated Patients (N=30)
Median age (range), years	62 (24-76)
≥70 years, n (%)	8 (27)
Male, n (%)	20 (67)
Ethnicity, n (%)	
Hispanic or Latino	2 (7)
Not Hispanic or Latino	23 (77)
Not reported	5 (17)
Race, n (%)	
Asian	3 (10)
Black or African American	2 (7)
White	22 (73)
Other or missing	3 (10)
ECOG performance status 1, n (%)	10 (33)
Disease type, n (%)	
DLBCL not otherwise specified	23 (77)
HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement	1 (3)
PMBCL	2 (7)
TFL	4 (13)
Disease stage at study entry, n (%)	
I/II	11 (37)
III	5 (17)
IV	14 (47)
IPI score, n (%)[a]	
0-1	25 (83)
2	2 (7)
4	1 (3)
Number of prior chemotherapy regimens, n (%)	
1	28 (93)
2	2 (7)
Best response to last prior therapy, n (%)	
CR	13 (43)
PR	11 (37)
PD	5 (17)
Not evaluable	1 (3)
Relapse <12 mo of completion of 1L therapy, n (%)[b]	23 (77)
Median LDH at baseline, U/L (range)[c]	198 (102-1136)
Median SPD at baseline, mm^2 (range)[d]	2316 (221-17,843)

[a]IPI score was missing for 2 patients. [b]2L patients with available data only (n=27). [c]The upper limit of normal was 190 U/L. [d]As measured by the sum of the product of dimensions of all target lesions at baseline. 1L, first-line; 2L, second-line; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; SPD, sum of the product diameters; TFL, transformed follicular lymphoma.

treatment due to entry into an expanded access program (n=4) and physician decision (n=1). Median time from leukapheresis to axi-cel administration was 27 days (range, 21-58). Of the patients who were treated with axi-cel, 15 received bridging therapy after leukapheresis. As of the data cutoff date of 09/20/2024, median follow-up in treated patients was 13 months (range, 6-24).

Median age of treated patients was 62 years (range, 24-76; **Table 2**). Sixty-seven percent of

Table 3. Incidence and severity of cytokine release syndrome and neurologic events

Parameter	Treated Patients (N=30)	
	CRS	Neurologic Events
Any grade, n (%)[a]	27 (90)	24 (80)
Grade 1	12 (40)	9 (30)
Grade 2	15 (50)	8 (27)
Grade 3	0	6 (20)
Grade 4	0	1 (3)
Grade 5	0	0
Median time to onset, days (95% CI)	4 (NE-NE)	7 (6-14)
Median duration of event, days (95% CI)	5 (3-6)	6 (3-46)
Steroids used for treatment of AE, n (%)	9 (30)	14 (47)
Tocilizumab used for treatment of AE, n (%)	26 (87)	0

Medians of time-dependent outcomes were measured using Kaplan-Meier estimates. Time to onset of CRS or neurologic events was defined as the earliest start date of the event - the infusion date + 1. For patients who withdrew consent, it was censored at the end of study date. [a]CRS was graded per Lee at al. 2014. Neurologic events were graded per CTCAE 5.0. AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NE, not estimable.

Table 4. Common adverse events

AEs, n (%)[a]	Treated Patients (N=30)	
	Any Grade	Grade ≥3
Any grade, n (%)	30 (100)	25 (83)
Pyrexia	26 (87)	1 (3)
Hypotension	18 (60)	3 (10)
Chills	14 (47)	0
Neutrophil count decreased	12 (40)	12 (40)
Confusional state	12 (40)	4 (13)
Fatigue	11 (37)	0
Headache	11 (37)	0
Platelet count decreased	11 (37)	5 (17)
White blood cell count decreased	10 (33)	9 (30)
Cough	9 (30)	0
Anemia	8 (27)	3 (10)
Constipation	8 (27)	0
Aphasia	7 (23)	3 (10)
Diarrhea	7 (23)	0
Hypogammaglobulinemia	7 (23)	0
Agitation	6 (20)	1 (3)
Dizziness	6 (20)	0
Neutropenia	6 (20)	4 (13)
Tachycardia	6 (20)	0

AEs were coded using MedDRA Version 27.1 and graded per CTCAE 5.0. [a]AEs shown are those of any grade that occurred in ≥20% of patients. AE; adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

patients (n=20) were male, 33% of patients (n=10) had an ECOG PS of 1, and 10% of patients (n=3) had an IPI score of ≥2. Most patients (77%, n=23) had DLBCL not otherwise specified. Sixty-three percent of patients (n=19) had Stage III/IV disease at study entry and median tumor burden (measured by sum of product diameters) was 2316 mm^2. Ninety-three percent of patients (n=28) had 1 prior chemotherapy regimen.

Safety

Grade 1-2 CRS events were reported in 90% of patients (n=27) and there were no grade ≥3 CRS events (**Table 3**). The most common CRS symptoms of any grade were pyrexia (96%), hypotension (52%), and chills (26%). Eighty percent of patients (n=24) experienced neurologic events of any grade, including 17 patients (57%) with grade 1-2 events, 6 patients with grade 3 events (20%; most commonly confusional state [n=4; 13%] and aphasia [n=3; 10%]), and 1 patient (3%) with grade 4 events (agitation and depressed level of consciousness). No patients died due to neurologic events. Median time to onset for CRS was 4 days (95% CI, not estimable [NE]-NE) with a median duration of 5 days (95% CI, 3-6), and median time to onset for neurologic events was 7 days (95% CI, 6-14) with a median duration of 5.5 days (95% CI, 3-46). At data cutoff, all CRS events had resolved and 5 patients had ongoing or unresolved neurologic events, including 1 with grade 2 encephalopathy (unrelated to axicel) that was unresolved on

Table 5. Treatment-emergent adverse events of interest

AEs, n (%)	Treated Patients (N=30)	
	Any Grade	Grade ≥3
Neutropenia	18 (60)	17 (57)
Thrombocytopenia	13 (43)	6 (20)
Anemia	8 (27)	3 (10)
Cardiac arrhythmias	14 (47)	3 (10)
Infections	11 (37)	4 (13)
Hypogammaglobulinemia	9 (30)	0
Hemophagocytic lymphohistiocytosis	1 (3)	0
Tumor lysis syndrome	0	0

AE, adverse event.

Table 6. Hospital toxicity management

Parameter	Treated Patients (N=30)
Outpatient hospitalized after infusion, n (%)	28 (93)
Patients admitted through the emergency department, n (%)	13 (43)
Median time to first hospitalization, days (range)	4 (2-9)
Median duration of first hospitalization, days (range)	8 (2-44)
Reasons for first hospitalization[a]	
Grade 1 CRS	18 (60)
Grade 2 CRS	9 (30)
Grade 1 neurologic event	3 (10)
CRS and neurologic event	3 (10)
Other[b]	1 (3)
Patients admitted to ICU, n (%)[c]	4 (13)
Escalation from grade 1 to grade 2 CRS, n (%)	7 (23)

[a]Per Kite medical adjudication. [b]Arrhythmia. [c]ICU admission details are as follows: Patient 1, arrhythmia (Day 1 ICU admission, 2-day stay) and large intestine perforation (Day 12 ICU admission, 8-day stay); Patient 2, other reason (Day 2 ICU admission, 7-day stay); Patient 3, pyrexia (Day 4 ICU admission, 6-day stay); Patient 4, agitation and aphasia (Day 7 ICU admission, 7-day stay) with additional aphasia and depressed level of consciousness developing on Day 8. CRS, cytokine release syndrome; ICU, intensive care unit.

their date of death, 1 with grade 2 confusional state and grade 1 lethargy (related to axi-cel) that were unresolved on their date of death, 1 with hypoesthesia and paresthesia (both grade 1 and unrelated to axi-cel) unresolved at death, 1 with ongoing grade 1 disturbance in concentration (unrelated to axi-cel), and 1 with ongoing grade 1 tremor (unrelated to axi-cel). No unresolved neurologic events were of high grade and none required hospitalization.

Excluding prophylaxis, corticosteroids were used to treat AEs in 20 patients, including 9 with CRS and 14 with neurologic events. The median cumulative systemic corticosteroid dose including prophylaxis was 2817 mg (n=30). Among those with CRS and/or neurologic events (n=19), the median cumulative steroid dose was 4695 mg. Tocilizumab was used to treat 27 patients, including 26 patients with CRS, 1 patient with grade 3 arrhythmia on Day 1 (related to axi-cel), and no patients with neurologic events.

All patients (n=30) experienced an AE of any grade, and 83% of patients (n=25) experienced grade ≥3 AEs (**Tables 4**, **5**). The most common AEs of any grade were pyrexia (87%), hypotension (60%), chills (47%), confusional state (40%), and decreased neutrophil count (40%). Common grade ≥3 AEs were mainly cytopenias. Serious AEs of any grade occurred in 80% of patients (n=24), most commonly pyrexia (60%), confusional state (20%), febrile neutropenia (13%), and aphasia (10%). There were no reported cases of tumor lysis syndrome (**Table 5**). New malignancies occurred in 2 patients (unknown malignant neoplasm on Day 318 and invasive squamous cell carcinoma of the skin on Day 373), none were considered related to axi-cel.

After treatment with axi-cel, 93% of patients (n=28) were hospitalized (**Table 6**). Median time to first hospitalization was 4 days (range, 2-9), with a median duration of 8 days (range, 2-44). Reasons for hospitalization included grade 1 CRS in 60% of patients (n=18), grade 2 CRS in 30% (n=9), and grade 1 neurologic events in 10% (n=3). Seven patients (23%) who were admitted with grade 1 CRS had the event subsequently worsen to grade 2. CRS remained the same or was downgraded for the remaining patients. A total of 4 patients (13%) were admitted to the ICU after axi-cel treatment, with length of stay lasting 2 to 7 days. In total, 5

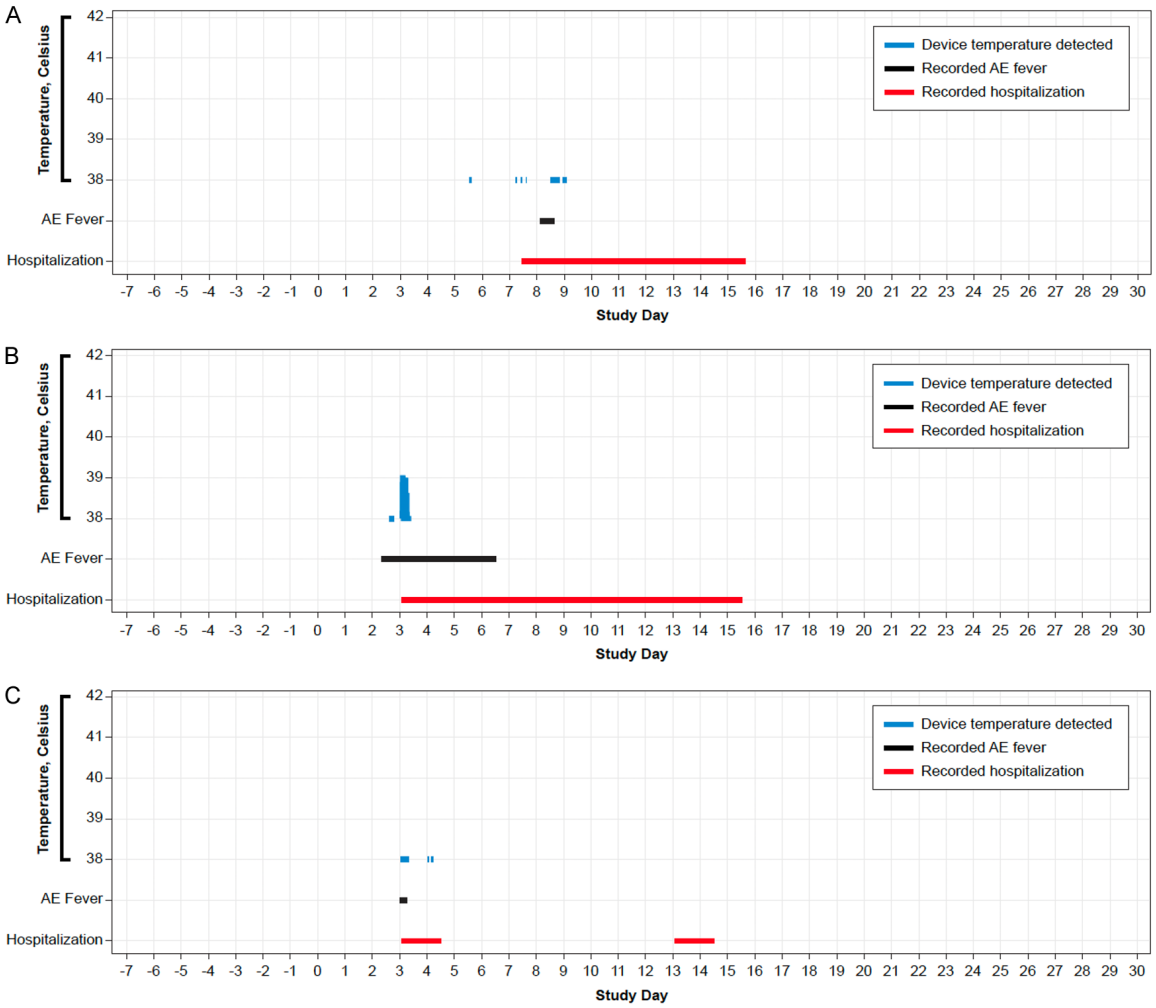

Figure 3. Device data: (A) Patient 1; (B) Patient 2; (C) Patient 3. Temperature recordings from wearable devices for 3 evaluable patients with a detectable temperature ≥38 degrees Celsius, with fever event and hospitalization by day on study. AE, adverse event.

patients died: 1 patient (3%) due to a grade 5 AE (sepsis), 3 patients (10%) from PD, and 1 patient (3%) because of a motorcycle accident. No patients died due to a new malignancy.

Temperature data were collected by a wearable device for 5 patients, 3 of whom had a detectable temperature ≥38 degrees Celsius. For these 3 patients, the device detected the elevated temperature at or before the fever event was reported and before the patient was hospitalized (**Figure 3**).

Efficacy

In patients evaluable for efficacy (n=29), the ORR was 93% (n=27; 95% CI, 77-99), with a CR rate of 76% (n=22; 95% CI, 57-90) and PR rate of 17% (n=5; 95% CI, 6-36; **Figure 4A**). Median time to response was 1.0 month (range, 1-3) from axi-cel infusion. Median DOR was 11.4 months (95% CI, 3.0-NE) among patients with an objective response (n=27; **Figure 4B**), with ongoing response at data cutoff in 14 patients (52%). Median EFS was 8.9 months (95% CI, 3.8-NE; **Figure 5A**) and median PFS was 8.9 months (95% CI, 3.8-NE; **Figure 5B**). At 6 months, EFS and PFS rates were both 66%. Median OS was not reached (95% CI, 12.5-NE). At 6 months the OS rate was 97%. Median OS was not yet reached in all treated patients (n=30), and 83% of treated patients were alive at data cutoff (**Figure 5C**). Among 8/30 treated patients (27%) who received subsequent therapy, 3 were treated with epcoritamab

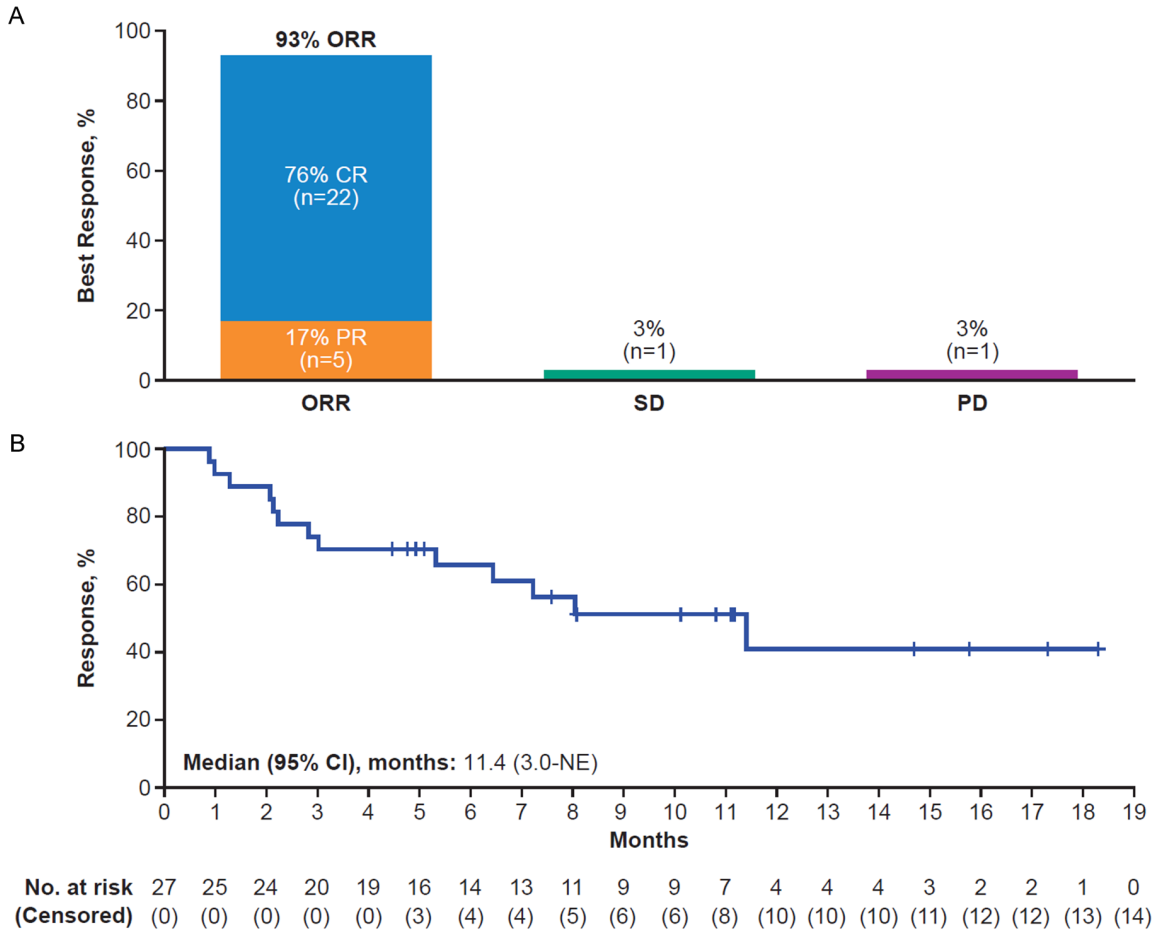

Figure 4. Objective response rate (A) and Duration of Response (B). The graphs show ORR per investigator assessment for efficacy evaluable patients (n=29; A) and Kaplan-Meier estimates of DOR in patients with an objective response (n=27; B). Axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

and 2 were treated with investigational CAR T-cell therapy.

Among patients who received bridging therapy (n=15), all responded (100%, n=15; 95% CI, 78.2-100), with a CR rate of 73% (n=11; 95% CI, 44.9-92.2) and PR rate of 27% (n=4; 95% CI, 7.8-55.1). Median PFS was 8.5 months (95% CI, 2.2-NE; **Table 7**) in patients receiving bridging.

Patient-reported outcomes

Quality of life (QOL) data were available for 23 patients at screening and following axi-cel infusion at Week 4. One patient completed initial patient-reported outcomes (PRO) assessment after lymphodepleting chemotherapy and therefore did not have an evaluable baseline assessment. For 22 patients with evaluable data, the mean EuroQol 5-dimension 5-level visual analogue scale (EQ-5D-5L VAS; overall QOL score ranging from 0 to 100, with higher scores indicating better state of health) was 77.2 at baseline, decreased slightly to 75.1 at Week 4, and subsequently increased above the baseline mean to 82.1 (n=17) at Month 3 and 83.2 (n=14) at Month 6. The mean change in VAS score from baseline was 4.0 (95% CI, -7.8-15.8) and 7.7 (95% CI, -7.1-22.5) for Month 3 and Month 6, respectively. The mean EQ-5D-5L index score (overall QOL score ranging from 0 to 1, with higher scores indicating better state of health) showed a decrease between baseline and Week 4 and between baseline and Month 3, with an increase of 0.0270 (95% CI, -0.018-0.072) between baseline and Month 6. The same patterns were seen in mean VAS

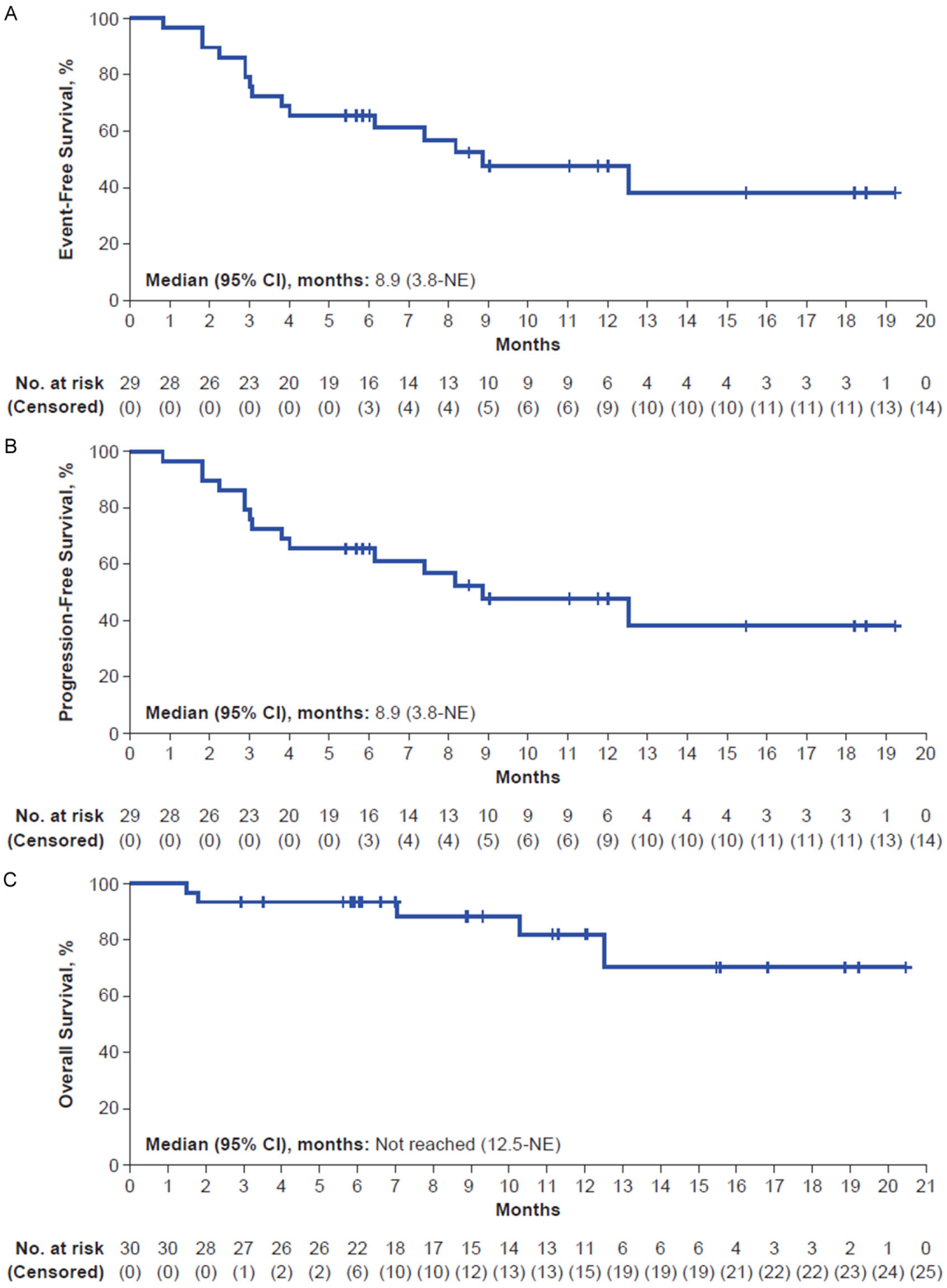

Figure 5. EFS (A), PFS (B), and OS (C). The figure shows Kaplan-Meier estimates of EFS per investigator assessment in efficacy-evaluable patients (n=29; A), PFS in efficacy-evaluable patients (n=29; B), and OS in treated patients (n=30; C). EFS, event-free survival; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Table 7. Efficacy outcome for patients who received bridging therapy

Outcome	Patients With Bridging Therapy (n=15)
ORR, n (%) [95% CI]	15 (100) [78.2-100]
CR	11 (73) [44.9-92.2]
PR	4 (27) [7.8-55.1]
SD	0
PD	0
PFS, median mo (95% CI)	8.5 (2.2-NE)

ORR = CR + PR. CR, complete response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 8. Patient reported quality of life outcomes by best overall response

	Best Overall Response	
	CR (n=17)	CR + PR + SD (n=22)
Screening		
EQ-5D-5L VAS, n	17	22
Median (95% CI)	85 (66-89)	80 (68-86)
EQ-5D-5L index score, n	17	22
Median (95% CI)	0.932 (0.691-0.929)	0.936 (0.735-0.921)
Week 4		
EQ-5D-5L VAS, n	17	22
Median (95% CI)	80 (61-83)	80 (66-83)
EQ-5D-5L index score, n	17	22
Median (95% CI)	0.836 (0.495-0.881)	0.891 (0.583-0.888)
Month 3		
EQ-5D-5L VAS, n	16	17
Median (95% CI)	80 (75-87)	80 (76-88)
EQ-5D-5L index score, n	16	18
Median (95% CI)	0.840 (0.548-0.912)	0.840 (0.569-0.895)
Month 6		
EQ-5D-5L VAS, n	13	14
Median (95% CI)	90 (76-91)	88 (76-90)
EQ-5D-5L index score, n	13	14
Median (95% CI)	0.904 (0.686-0.944)	0.890 (0.688-0.927)

CR, complete response; EQ-5D-5L, EuroQol 5-dimension 5-level; PR, partial response; SD, stable disease VAS, visual analogue scale.

and index scores for patients who achieved a CR (n=17) and when patients achieved a best response of CR, PR, and SD were combined (**Table 8**).

Pharmacokinetics

For patients with available samples (n=29), the median peak and area under the curve for CAR T-cell expansion were 40.8 cells/μL (range, 3.9-696.7) and 337.7 cells/μL × days (range, 43.9-4969.4), respectively (**Figure 6**). Median time to peak CAR T-cell levels was 8 days (range, 8-15).

Discussion

CAR T-cell therapies like axi-cel are highly efficacious and have transformed the treatment landscape for several hematologic malignancies [13]; however, anticipated growth in indications may place an increased demand on inpatient care settings, potentially leading to capacity constraints and limited resources for care. Additionally, there remain barriers to access CAR T-cell therapy, with a continued need for improved safety outcomes and reduced hospitalization time [14]. Among 30 patients treated with outpatient axi-cel in ZUMA-24, there were no grade ≥3 CRS events, and grade ≥3 neurologic events were reported in 23% of patients, demonstrating manageable rates of severe CAR T-cell-related toxicities. CAR T-cell expansion was robust and axi-cel demonstrated an ORR and durability of response consistent with the inpatient setting, supporting the feasibility and safety of outpatient administration.

Overall safety and efficacy profiles of outpatient axi-cel were largely consistent with those observed in the inpatient setting, but it should be noted that there are inherent limitations in comparing outcomes across different trials [3, 6]. As observed in the safety management cohort of ZUMA-1 (Cohort 6), no high-grade CRS events occurred in ZUMA-24 with the improved safety management [6]. Rates of high-grade neurologic events were similar to ZUMA-7, despite differences in patient populations between trials [3]. We also observed a low rate of escalation from grade 1

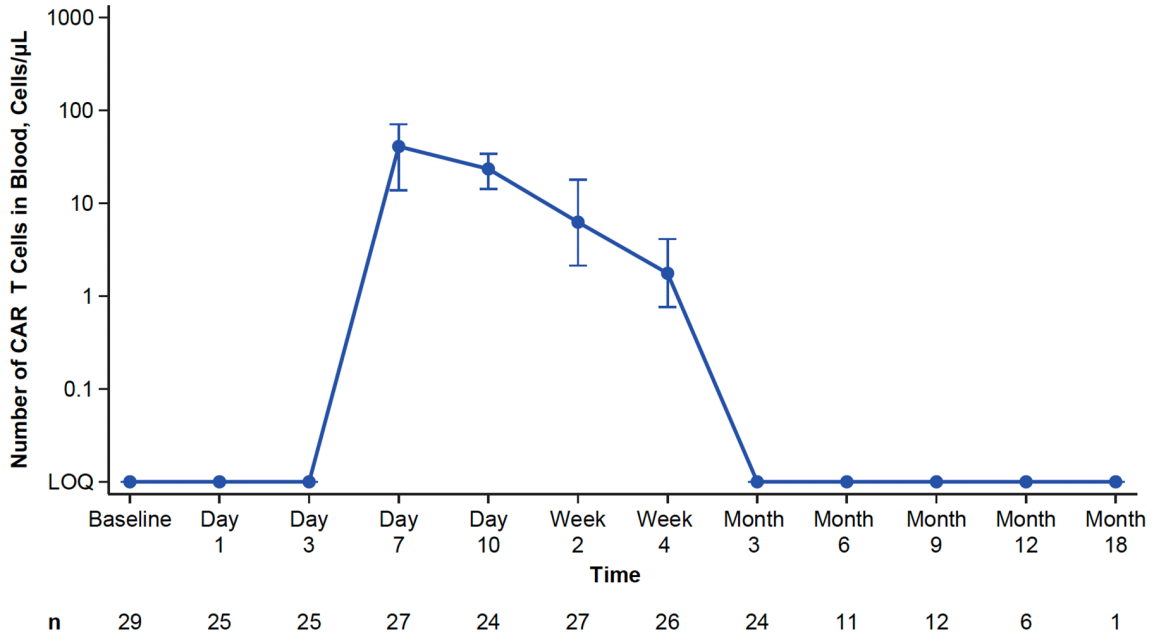

Figure 6. CAR T-cell expansion over time. The graph shows median and interquartile range. CAR T-cell levels in blood were measured using droplet digital polymerase chain reaction analysis. CAR, chimeric antigen receptor.

to grade 2 CRS in ZUMA-24, further suggesting that prophylactic steroids and early safety intervention can facilitate outpatient therapy with axi-cel. Outpatient administration of axi-cel demonstrated responses and CAR T-cell expansion that were consistent with trials of axi-cel in the inpatient setting, indicating that prophylactic corticosteroid use with axi-cel administration did not compromise its activity [3, 4].

Patients who were hospitalized after axi-cel infusion in ZUMA-24 were admitted mostly for grade 1 CRS. Importantly, patients who required hospitalization after infusion had a median duration of hospitalization of 8 days, and 13% of patients were admitted to the ICU. This is lower than what was observed with inpatient axi-cel in ZUMA-7, suggesting outpatient treatment with prophylactic steroids and early safety intervention may be associated with reduced burden on treatment centers [3, 5, 6]. Toxicity management in the inpatient care setting has been associated with increased costs with CAR T-cel therapy [15]. Though inpatient axi-cel was previously shown to be cost-effective compared with standard-of-care treatment, it still required prolonged hospitalization [16, 17]. In a preliminary healthcare resource utilization analysis from ZUMA-24, short-term costs with outpatient axi-cel were manageable, with hospitalization driving most of the short-term costs [15]. As most hospitalizations in ZUMA-24 were due to grade 1 events, increased experience in managing these low-grade toxicities may lead to a future decrease in hospitalizations post-CAR T-cell therapy. ZUMA-24 results were consistent with a systemic literature review showing outpatient CAR T-cell therapy provided similar efficacy and safety compared with inpatient administration, but with lower healthcare utilization and cost, leading to more efficient use of resources [18].

This trial builds on prior real-world experience of single centers with outpatient CAR T-cell administration demonstrating the safety and feasibility of outpatient axi-cel. Factors shown to influence successful administration of outpatient CAR T-cell therapy include adequate infrastructure and staff trained in managing CAR T-cell-related toxicities, well-defined guidelines for monitoring patients, clear criteria for hospital admission, and a caregiver who can provide 24-hour support at home [14, 18, 19]. In one such study at Vanderbilt University Medical Center, 13 serially treated patients were administered outpatient axi-cel or brexucabtagene autoleucel and were subsequently

monitored twice daily with in-person visits and an overnight telemedicine visit for 14 days; patients were admitted for in-patient treatment for grade ≥2 CRS or any grade neurologic events and early tocilizumab was used for low-grade CRS [20]. At some centers, including the University of Oklahoma Health Sciences Center and Johns Hopkins University, the CAR T-cell program was structured as an outpatient program from inception [21, 22]. The Johns Hopkins University study demonstrated the feasibility of outpatient CAR T-cell therapy, even in older patients, albeit with closer monitoring due to more frequent and higher-grade ICANS seen in older patients. The Mayo Clinic outpatient experience further demonstrated the importance of early intervention for improving safety outcomes [7]. Overall, these studies demonstrated similar incidence of high-grade CRS and neurologic events and shorter duration of hospitalization with outpatient axi-cel compared with registrational trials, due in part to close monitoring, clear guidelines, and early and appropriate intervention [23]. Of note, patients treated with CAR T-cell therapies like axi-cel in the real world have characteristics that would have excluded them from this study, including ECOG PS of ≥2. We acknowledge that exclusion of patients with poorer performance status may limit some real-world applicability of this data.

The early PRO data for outpatient axi-cel in this trial were similar to previous studies, with an initial decrease in QOL measures after infusion, followed by clinically meaningful improvement in QOL [24-26]. In ZUMA-7, mean QOL scores decreased between baseline and Day 100, increased by Day 150, and exceeded baseline scores thereafter [24]. Additionally, a recent real-world study at Moffitt Cancer Center reported a decrease in mean EQ-5D-5L VAS scores at 7 days post-axi-cel infusion, followed by improvements thereafter through 1 year of follow-up [26]. The follow-up for the current study is relatively short and results with longer follow-up are needed to confirm and extend these findings.

Neurologic events and cytopenias remain common and concerning classes of CAR T-cell associated toxicities. Beyond management of initial toxicity with prophylactic steroids, management of immune effector cell-associated hematotoxicity (ICAHT) that appears early (within 30 days) with CAR T-cell therapy, including use of growth factor support, transfusions, and anti-infectious prophylaxis, may address severe cytopenias, the risk of infection, and other complications [27]. In addition, there may be an association between tumor burden and prevalence and severity of ICAHT, suggesting that proactive use of other active agents (eg bridging therapies) could help to mitigate these events. Neurotoxicity is a complicated class that includes life-threatening events, and there is an unmet need for addressing underlying mechanisms for toxicity and managing events [28]. Notably, though safety observed in this trial was consistent with ZUMA-1 Cohort 6, rates reported here were based on CTCAE grading; rates might be lower if graded according to the newer grading system for neurologic events proposed by the American Society for Transplantation and Cellular Therapy [3, 29].

Other challenges associated with outpatient administration of CAR T-cell therapy are caregiver support and monitoring for AEs. Caregivers are often the first to observe toxicities in those treated with CAR T-cell therapy, and as patients may not drive themselves, they rely on caregiver for transportation to the treatment center or hospital [30]. Some centers have addressed AE monitoring with the use of devices to record patients' vital signs [31, 32]. In this trial, the feasibility of central monitoring was investigated through the voluntary use of a wearable device to monitor body temperature and serve as an early warning for the potential onset of AEs. There were challenges with remote monitoring at the sites and, while the device was predictive of AEs, the data were limited due to small sample size and some false positive/false negative results; therefore, interpretations of these data are limited. In another study, 40 patients who were treated with outpatient CAR T-cell therapy were provided wearable devices that transmitted vital signs, including skin temperature, pulse, respiratory rate, and O_2 saturation, which were monitored remotely by nurses [32]. Wearable adherence in that study was 79%-89%, and helped establish an integrated outpatient safety management process for the first 30 days post-infusion.

In conclusion, this trial demonstrated that outpatient administration of axi-cel was feasible in a multicenter setting. Prophylactic corticoste-

roids coupled with early intervention, including hospitalization for AE management, resulted in relatively low rates of high-grade toxicities. Hospital length of stay was shorter than in previous clinical trials with inpatient administration of axi-cel, which could translate to more efficient use of healthcare resources and alleviate capacity constraints on care. Overall, the results were largely consistent with previous clinical trials and real-world studies and further support the feasibility of outpatient administration of axi-cel.

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Disclosure of conflict of interest

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