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Original Article

Impact of debulking therapy on the clinical outcomes of axicabtagene ciloleucel in the treatment of relapsed or refractory large B-cell lymphoma

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Abstract: Axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor T-cell therapy, was approved for relapsed/refractory (R/R) large B-cell lymphoma (LBCL) based on the results from pivotal Cohorts 1+2 of ZUMA-1 (NCT02348216). ZUMA-1 was expanded to investigate safety management strategies aimed at reducing the incidence and severity of cytokine release syndrome (CRS) and neurologic events (NEs). Prospective safety expansion Cohort 5 evaluated the impact of debulking therapy, including rituximab-containing immunochemotherapy regimens and radiotherapy, in axi-cel-treated patients; the CRS and NE management strategy paralleled those in Cohorts 1+2. Among the 50 patients in Cohort 5 who received axi-cel, 40% received ≥3 prior lines of chemotherapy, and 40% had disease that progressed while on the most recent chemotherapy. Forty-eight patients (96%) received debulking therapy, 14 (28%) radiotherapy only, and 34 (71%) systemic immunochemotherapy. Median decrease in tumor burden (per sum of product of diameters of target lesions) relative to screening was 17.4% with R-ICE/R-GDP, 4.3% with other debulking chemotherapies, and 6.3% with radiotherapy only. All patients were followed for ≥8 months. CRS was reported in 43 patients (86%), with 1 patient (2%) experiencing grade ≥3. NEs were reported in 28 patients (56%), with 6 (12%) experiencing grade ≥3. Cytopenias were the most frequent grade ≥3 adverse event (AE); 19 (38%) and 18 (36%) treated patients had any and grade ≥3 prolonged thrombocytopenia, respectively, and 25 (50%) and 24 (48%) patients had any and grade ≥3 prolonged neutropenia, respectively. Overall, patients who received debulking chemotherapy had higher incidences of serious treatment-emergent AEs than those who received radiotherapy only. At the 24-month analysis, objective response rate was 72%, and complete response rate was 56%. Median duration of response, progression-free survival, and overall survival were 25.8, 3.1, and 20.6 months, respectively. These results from exploratory Cohort 5 demonstrate the feasibility of debulking prior to axi-cel, and together with current real-world evidence, suggest that debulking regimens may help minimize the frequency and severity of CRS and NEs in patients with R/R LBCL. The incidence of other AEs observed in Cohort 5 suggest the risk/benefit profile was not improved via the debulking regimens studied here.

Keywords: Large B-cell lymphoma, axi-cel, chimeric antigen receptor T cell, cytokine release syndrome, neurotoxicity, debulking

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Introduction

Chimeric antigen receptor (CAR) T-cell therapy has become an invaluable treatment strategy for patients with B-cell malignancies [1]. The most common acute toxicities associated with CAR T-cell therapy are cytokine release syndrome (CRS) and neurologic events (NEs), both of which can be severe and life-threatening [2, 3]. Ongoing efforts aim to improve the safety profile of CAR T-cell therapy without compromising durable clinical benefit to provide a greater benefit/risk profile to patients.

Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (R/R LBCL) [4-7]. Initial approval in third-line or later treatment was based on safety and efficacy demonstrated in the pivotal Cohorts 1+2 of the phase 1/2 ZUMA-1 study (NCT02348216) [8]. At the 5-year follow-up of ZUMA-1, the objective response rate was 83%, the complete response rate was 58%, the median overall survival was 25.8 months, and the 5-year overall survival rate was 43% [9]. Grade ≥3 CRS and NEs were reported in 11% and 30% of patients, respectively [9].

Strategies to minimize the incidence and/or severity of CRS and NEs with axi-cel have been evaluated in safety management Cohorts 3-6 that were added to the ZUMA-1 study (Supplementary Figure 1) [10-12]. Cohort 3 (N=34), which evaluated the impact of prophylactic use of tocilizumab and levetiracetam, found a lower rate of grade ≥3 CRS but no improvement in incidence of grade ≥3 NEs [10]. Cohort 4 (N=41) evaluated the impact of levetiracetam prophylaxis in addition to earlier corticosteroid and tocilizumab intervention. Grade ≥3 CRS and grade ≥3 NEs occurred in 2% and 17% of patients, respectively [12, 13]. The objective response rate was 73% and the complete response rate was 51% at a median follow-up of 14.8 months [12]. Finally, Cohort 6 (N=40) evaluated the addition of prophylactic corticosteroids to the Cohort 4 toxicity management protocol, further reducing grade ≥3 CRS and grade ≥3 NEs to 0% and 13%, respectively. The objective response and complete response rates in Cohort 6 at a median follow-up of 26.9 months were 95% and 80%, respectively, and the median duration of response was 25.9 months (95% confidence interval [CI], 7.8 to not estimable) [14], suggesting that this toxicity management strategy can improve rates of grade ≥3 CRS and grade ≥3 NEs without negatively impacting efficacy.

Patients in ZUMA-1 Cohorts 1+2 were not permitted to receive any anticancer therapy (i.e., bridging or debulking therapy) between leukapheresis and lymphodepleting chemotherapy [8]. Thus, safety expansion Cohort 5 prospectively evaluated the impact of debulking therapy on the incidence and severity of CRS and NEs in patients treated with axi-cel. Here we report the Cohort 5 primary analysis and an updated analysis with at least 2 years of follow-up.

Methods

Patients

Eligibility criteria for Cohort 5 were similar to the pivotal ZUMA-1 Cohorts 1+2 [8]. Patients were ≥18 years with histologically confirmed R/R LBCL after two or more lines of therapy. Refractory disease was defined as progressive disease (PD) or stable disease (SD) as the best response to the most recent therapy regimen or PD or relapse within 12 months after autologous stem cell transplantation. Other key requirements are detailed in the Supplementary Methods. The study was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization and was approved by the institutional review board at each site. All patients provided informed consent before being included in the study.

Treatment

Patients in Cohort 5 received debulking therapy after leukapheresis and prior to administration of lymphodepleting chemotherapy and axi-cel. Debulking regimens were meant to reduce lymphoma burden, and the choice of debulking therapy was made by the investigator from a list of options that included rituximab-containing immunochemotherapy regimens and radiotherapy (**Table 1**). Other debulking treatment options may have been considered in select cases after discussion with the Kite medical

Table 1. Debulking therapy regimens

Type	Proposed Regimen[a]	Timing/Washout
R-CHOP	Rituximab 375 mg/m^2 Day 1 Doxorubicin 50 mg/m^2 Day 1 Prednisone 100 mg Day 1 through Day 5 Cyclophosphamide 750 mg/m^2 Day 1 Vincristine 1.4 mg/m^2 Day 1	Should have been administered after leukapheresis/enrollment and should have been completed at least 14 days prior to the start of lymphodepleting chemotherapy
R-ICE	Rituximab 375 mg/m^2 Day 1 Ifosfamide 5 g/m^2 24 h-CI Day 2 Carboplatin AUC5 Day 2 maximum dose 800 mg Etoposide 100 mg/m^2/d Days 1 through 3	
R-GEMOX	Rituximab 375 mg/m^2 Day 1 Gemcitabine 1000 mg/m^2 Day 2 Oxaliplatin 100 mg/m^2 Day 2	
R-GDP	Rituximab 375 mg/m^2 Day 1 (or Day 8) Gemcitabine 1000 mg/m^2 on Day 1 and Day 8 Dexamethasone 40 mg on Day 1 through Day 4 Cisplatin 75 mg/m^2 on Day 1 (or carboplatin AUC5 on Day 1)	
Radiotherapy[b]	Per local standard up to 20 to 30 Gy	Should have been administered after leukapheresis/enrollment and should have been completed at least 5 days prior to the start of lymphodepleting chemotherapy

[a]Other debulking treatment options may have been used but had to be discussed with the medical monitor. Supportive care with hydration, antiemetic, mesna, growth factor support, and tumor lysis prophylaxis according to local standard may have been used. More than one cycle was allowed. [b]At least one target lesion should have remained outside of the radiation field to allow for tumor measurements. AUC5, area under the curve value of 5 mg/mL/min; CI, continuous infusion; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-GEMOX, rituximab, gemcitabine, and oxaliplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide.

monitor. Consistent with ZUMA-1 Cohorts 1+2 [8], patients received lymphodepleting chemotherapy for 3 days (cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day on Days -5, -4, and -3) prior to a single intravenous infusion of axi-cel (target dose, 2×10^6 anti-CD19 CAR T cells/kg) on Day 0. Cohort 5 followed the safety management strategy of Cohorts 1+2, which was no prophylactic or earlier steroids; however, in contrast to Cohorts 1+2, patients in Cohort 5 received prophylactic levetiracetam (750 mg oral or intravenous twice daily) starting on Day 0 to manage potential NEs after axi-cel treatment.

Endpoints

The descriptive primary endpoints were the incidence and severity of CRS and NEs. CRS was defined and graded per modified Lee 2014 criteria [15]. NEs were identified by a search term list per Topp et al. [16] and graded for severity per Common Terminology Criteria for Adverse Events version 4.03 [17]. Secondary endpoints included investigator-assessed objective response rate (complete response and partial response) based on revised International Working Group Response Criteria for Malignant Lymphoma [18], duration of response, progression-free survival, overall survival, incidence of adverse events, and levels of anti-CD19 CAR T cells and cytokines in blood (Supplementary Methods). CIs for objective response rates were generated by the Clopper-Pearson method. CIs and landmark estimates of duration of response, progression-free survival and overall survival were generated using the Kaplan-Meier survival method. For duration of response and progression-free survival, disease assessment after the initiation of new anticancer therapy, not including stem cell transplantation, was not included in the derivation. Exploratory endpoints included biomarker analyses.

Statistical analyses

Similar to other ZUMA-1 safety management cohorts [11, 12], Cohort 5 was not designed for formal hypothesis testing and all analyses were

descriptive. The primary analysis was conducted when all 50 patients treated were followed for ≥6 months after axi-cel infusion; in addition, an updated analysis was performed when each patient had been followed for ≥24 months. The safety analysis set included all patients treated with any dose of axi-cel, and the modified intent-to-treat (mITT) population comprised those treated with axi-cel at a target dose of at least 1×10^6 CAR T cells/kg and was used for efficacy-based endpoints. For post hoc debulking subgroup analyses, outcomes between patients receiving chemotherapy versus radiotherapy only were assessed. In addition, chemotherapy regimens were grouped into two categories: more intensive regimens, including rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) or rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP; R-ICE/R-GDP group), and other less aggressive debulking chemotherapies. Tumor burden was measured by sum of product of diameters of target lesions [18]. Descriptive *P* values, calculated by Wilcoxon 2-sample test, were generated to compare pharmacokinetic parameters with toxicity severity. Exploratory, retrospective propensity score matching (PSM) analysis was performed to descriptively compare results of the primary analysis for Cohort 5 with those of Cohorts 1+2 (Supplementary Methods).

Results

Patients

Patients were enrolled in Canada (30%), France (26%), Netherlands (26%), and Germany (18%) between December 2018 and December 2019. Of the 58 patients enrolled and leukapheresed, 54 (93%) received debulking therapy, 51 (88%) received lymphodepleting chemotherapy, and 50 patients received axi-cel at the target dose (Supplementary Figure 2). Eight enrolled patients who underwent leukapheresis did not receive axi-cel due to failure to meet eligibility criteria (n=3), adverse event related to refractory disease (n=1), withdrawn consent (n=1), and death due to disease progression (n=3). At the data cutoff for the primary (September 10, 2020) and 24-month (January 10, 2022) analyses, the median follow-up was 15.1 months (range, 8.0-18.8) and 31.1 months (range, 24.0-34.8), respectively. Among patients who were treated with axi-cel (mITT population), the median age was 57.5 years (range, 29-74), most patients (74%) had stage III or IV disease, 40% had received 3 or more prior lines of chemotherapy, and 40% had PD as the best response to the most recent chemotherapy (**Table 2**).

Forty-eight patients treated with axi-cel (96%) received debulking therapy; 34 (71%) received systemic chemotherapy and 14 (28%) received radiotherapy only. Among the patients receiving debulking chemotherapy, 17 patients (34%) received intensive chemotherapy regimens (R-ICE/R-GDP), and 17 (34%) received other less aggressive debulking chemotherapies (including R-GEMOX [rituximab, gemcitabine, and oxaliplatin] and R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone]). Two patients received more than one type of debulking regimen: one received radiotherapy and R-CHOP, and one received R-GEMOX and prednisone. The median time from leukapheresis to axi-cel delivery at the study site was 31 days (range, 23-71) in Europe and 21 days (range, 18-22) in Canada. The median time from leukapheresis to axi-cel infusion was 33 days (range, 25-71) in Europe and 33 days (range, 27-51) in Canada. No significant differences in manufacturing times were observed based on type of debulking therapy.

Safety

Primary analysis: In the primary analysis, all 50 patients (100%) experienced at least one treatment-emergent adverse event (TEAE), and 25 patients (50%) had at least one serious TEAE. The most common any-grade TEAEs were pyrexia (86%), hypotension (52%), neutrophil count decreased (50%), anemia (38%), headache (34%), platelet count decreased (34%), and neutropenia (32%). All 50 patients (100%) experienced grade ≥3 TEAEs, the most common of which were neutrophil count decreased (48%), anemia (30%), and neutropenia (30%) (**Table 3** and Supplementary Table 1). Grade 4 adverse events were reported in 70% of patients, and 10% of patients had grade 5 adverse events. Serious TEAEs were more common among patients who received intensive chemotherapy debulking (R-ICE/R-GDP) versus other less aggressive chemotherapies (including R-GEMOX and R-CHOP) or radiotherapy only, and incidence of grade ≥3 infections were high-

Table 2. Patient and disease characteristics at baseline

Parameter	Overall[a] (N=50)
Disease type, n (%)	
DLBCL	36 (72)
TFL	7 (14)
HGBCL	7 (14)
Age	
Median (range), years	57.5 (29-74)
≥65 years, n (%)	15 (30)
Male sex, n (%)	36 (72)
ECOG performance status score of 1, n (%)	23 (46)
Disease stage, n (%)	
I or II	13 (26)
III or IV	37 (74)
IPI score, n (%)	
0-2	25 (50)
3-4	25 (50)
Number of prior lines of chemotherapy, n (%)	
1	4 (8)
2	26 (52)
3	16 (32)
4	2 (4)
5	2 (4)
Prior autologous SCT, n (%)	16 (32)
PD as best response to most recent chemotherapy, n (%)	20 (40)
Median (range) tumor burden by SPD, mm^2	1652 (0-36,409)
Median (range) LDH, U/L	262 (225-479)
Median (range) ferritin, ng/mL	602 (35-6646)
Refractory subgroup, n (%)	
Primary refractory	4 (8)
Refractory ≥2nd-line therapy	24 (48)
Relapsed ≥2nd-line therapy	6 (12)
Relapsed post-ASCT	12 (24)
Missing	4 (8)
Any debulking therapy, n (%)	48 (96)
R-GEMOX	9 (18)
R-ICE	9 (18)
R-GDP	8 (16)
R-CHOP	2 (4)
Other[b]	7 (14)
Radiotherapy only	15 (30)

Medications onset during retreatment period are excluded. [a]All patients treated with at least 1×10^6 CAR T cells/kg. [b]Other debulking therapies include rituximab and dexamethasone (n=2); bendamustine, rituximab, and prednisone (n=1); bridging chemotherapy, rituximab, and bendamustine (n=1); R-GDP without cisplatin (n=1); dexamethasone, methylprednisolone, prednisone, and IGEV (ifosfamide, gemcitabine, vinorelbine, and prednisolone) (n=1); and prednisone (n=1). ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PD, progressive disease; SPD, sum of the products of diameters; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-GEMOX, rituximab, gemcitabine, and oxaliplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; TFL, transformed follicular lymphoma.

Table 3. Treatment-emergent adverse events of any grade and grade ≥3 adverse events occurring in ≥15% of patients (primary analysis)

n (%)	Any	Any grade ≥3
Any	50 (100)	50 (100)
Pyrexia	43 (86)	7 (14)
Hypotension	26 (52)	3 (6)
Neutrophil count decreased	25 (50)	24 (48)
Anemia	19 (38)	15 (30)
Headache	17 (34)	0 (0)
Platelet count decreased	17 (34)	14 (28)
Neutropenia	16 (32)	15 (30)
Chills	14 (28)	0 (0)
Tremor	14 (28)	1 (2)
White blood cell count decreased	13 (26)	13 (26)
Fatigue	12 (24)	1 (2)
Nausea	12 (24)	0 (0)
Diarrhea	11 (22)	0 (0)
Hypokalemia	10 (20)	2 (4)
Thrombocytopenia	9 (18)	9 (18)
Aphasia	9 (18)	3 (6)
Lymphocyte count decreased	8 (16)	8 (16)
Leukopenia	8 (16)	7 (14)
Confusional state	8 (16)	2 (4)
Constipation	8 (16)	0 (0)
Dizziness	8 (16)	0 (0)

er in patients who received R-ICE/R-GDP versus other debulking therapies (**Table 4**).

CRS was reported in 43 patients (86%), all with severity grade 1 or 2 except one patient (2%) who received ifosfamide, gemcitabine, vinorelbine, and corticosteroid debulking and experienced grade 4 CRS (**Table 5**). The most frequently reported any-grade CRS symptoms were pyrexia (n=41, 95%), hypotension (n=24, 56%), chills (n=10, 23%), and nausea (n=9, 21%). The median time to CRS onset was 2 days (range, 1-9 days) after axi-cel infusion and among the 42 patients whose CRS resolved, the median duration was eight days (range, 1-19). One patient had grade 4 hypoxia reported on Day 17 and grade 2 tachycardia reported on Day 31 that were ongoing at the time of death due to grade 5 pneumonia influenza type A (related to lymphodepleting chemotherapy) on Day 42. Any-grade CRS was more common among patients who received intensive chemotherapy debulking (R-ICE/R-GDP; 17/17 patients [100%]) and radiotherapy only (14/14 patients [100%]) versus other less aggressive debulking chemotherapy (11/17 patients [65%]; **Table 4**).

The overall incidence of NEs was 56% (n=28), with 12% (n=6) of patients experiencing grade ≥3 events (**Table 5**). The most frequent any-grade NEs were tremor (n=14, 28%), aphasia (n=9, 18%), and confusional state (n=8, 16%). The median time to NE onset was eight days (range, 1-17) after axi-cel infusion, and among the 23 patients whose NEs resolved, the median duration was 12 days (range, 1-99). At primary data cutoff, five patients had unresolved NEs, three of whom had died (n=1 each due to PD, septic shock [related to axi-cel], and pneumonia influenza type A [aforementioned]). Any-grade NEs occurred at similar incidence across debulking groups (**Table 4**).

Overall, 26 patients (52%) received corticosteroids for the management of CRS (14 patients; 28%), NEs (14 patients; 28%), and/or other reasons (10 patients; 20%). The median cumulative cortisone-equivalent corticosteroid dose received was 3599.5 mg (range, 125.2-138,725.2). Of the 26 patients who received corticosteroids, 25 also received tocilizumab. Thirty-nine patients (78%) received tocilizumab for the treatment of CRS (37 patients; 74%) and/or NEs (5 patients; 10%).

Infections occurred in 19 patients (38%), including four patients (8%) with grade 3 infections and four patients (8%) with grade 5 infections (Supplementary Table 2). Grade 5 infections included three patients (6%) with septic shock, reported on Days 27, 40, and 144, and one (2%) with pneumonia influenza type A, related to lymphodepleting chemotherapy reported on Day 42. One patient (2%) developed COVID-19 (grade 3). The median time to onset of infection was 10 days (range, 2-282). In general, any-grade infections were more common among patients who received debulking radiotherapy versus debulking chemotherapy regimens, with grade ≥3 events most common among those who received intensive chemotherapy regimens (R-ICE/R-GDP; **Table 4**). Hypogammaglobulinemia was reported in four patients (8%); all events were grade 1 or 2 (Supplementary Table 3). Intravenous immunoglobulin therapy was administered to three

Table 4. Treatment-emergent adverse events by debulking regimen (primary analysis)

n (%)	R-ICE/R-GDP (n=17)		Other debulking chemotherapies (n=17)		Radiotherapy only (n=14)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	17 (100)	17 (100)	17 (100)	17 (100)	14 (100)	14 (100)
Serious TEAE	11 (65)	11 (65)	8 (47)	6 (35)	6 (43)	4 (29)
CRS	17 (100)	0	11 (65)	1 (6)	14 (100)	0
NE	9 (53)	2 (12)	9 (53)	3 (18)	8 (57)	1 (7)
Infection	6 (35)	5 (29)	5 (29)	1 (6)	7 (50)	2 (14)
Hypogammaglobulinemia	2 (12)	0	1 (6)	0	1 (7)	0

CRS, cytokine release syndrome; NE, neurologic event; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; TEAE, treatment-emergent adverse event.

Table 5. Incidence, severity, onset, and duration of CRS and NEs

TEAE	Overall (N=50)
CRS	
Any, n (%)	43 (86)
Grade 1, n (%)	19 (38)
Grade 2, n (%)	23 (46)
Grade 3, n (%)	0
Grade 4, n (%)	1 (2)
Grade 5, n (%)	0
Grade ≥3, n (%)	1 (2)
Median (range) time to onset of any-grade CRS, days	2 (1-9)
Median (range) duration, days	8 (1-19)
NEs	
Any, n (%)	28 (56)
Grade 1, n (%)	13 (26)
Grade 2, n (%)	9 (18)
Grade 3, n (%)	5 (10)
Grade 4, n (%)	1 (2)
Grade 5, n (%)	0
Grade ≥3, n (%)	6 (12)
Median (range) time to onset of any-grade NEs, days	8 (1-17)
Median (range) duration, days	12 (1-99)

CRS was graded per the revised grading system proposed by Lee et al. [15]. NEs were identified based on Topp et al. [16]. CRS, cytokine release syndrome; NE, neurologic event.

patients (6%), around 1 month after axi-cel infusion in all 3 cases. The incidence of grade ≥3 prolonged cytopenias (i.e., present on or after Day 30 following axi-cel infusion) was 52% (n=26), the most common being neutropenia (n=24, 48%), followed by thrombocytopenia (n=18, 36%), and anemia (n=7, 14%; Supplementary Table 4).

New malignancies were reported in two patients. Both patients developed grade 3 myelodysplastic syndrome (MDS), one on Day 363 and the other on Day 496 (evolved to grade 5 on Day 884), that were considered related to lymphodepleting chemotherapy per investigator assessment.

A total of 23 of 50 treated patients (46%) died during the primary analysis period. TEAE-related deaths were the four grade 5 infections noted above. Of the remaining 19 deaths, 17 were due to PD, one due to respiratory failure (in the setting of disease progression), and one due to sepsis that was secondary to lymphoma.

Updated analysis: 24-month follow up: The 24-month safety results were similar to those of the primary analysis. Seven serious TEAEs were reported in three patients after the primary analysis, including 2 new malignancies. The first patient experienced 5 events, including pyrexia (grade 1) and neutropenia (grade 3) on Day 272, cellulitis (grade 3) on Day 275, sepsis (grade 4) on Day 548, and MDS (grade 4; related to lymphodepleting chemotherapy) on Day 485 that evolved to grade 5 on Day 552. The second patient experienced pneumonia (grade 3) on Day 559. Finally, the third patient reported a new malignancy of acute myeloid leukemia on Day 668 which was ongoing at the 24-month data cutoff date. None of these TEAEs were considered related to axi-cel treat-

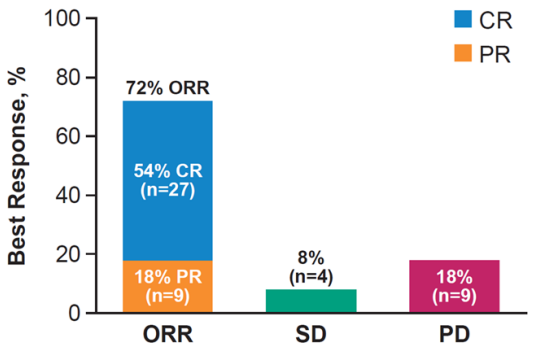

Figure 1. Best overall response (primary analysis). One patient died 27 days after axi-cel infusion and did not have a response assessment. CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

ment per investigator assessment, except the case of neutropenia.

Overall, five deaths occurred between the primary and 24-month data cutoffs: two from PD, two from MDS (both aforementioned, one in primary analysis and one in the updated 24-month analysis), and one from ischemic bowel followed by septic shock, none of which were deemed related to axi-cel treatment.

No additional cases of CRS or NEs were reported after the primary analysis. Of the two patients who were alive with unresolved NEs at primary data cutoff, one had grade 2 lethargy and died on Day 552 (due to development of MDS) and the other was alive at the 24-month data cutoff with unresolved grade 1 amnesia. Neither NE was related to any study treatment per investigator assessment. The incidence of any-grade infection was the same at 24 months as the primary analysis, though grade ≥3 infections were increased by one patient (grade 4 sepsis reported on Day 548 and resolved on Day 552). No additional intravenous immunoglobulin therapy was administered after the primary analysis. B cells were detectable in two of 16 evaluable patients (13%) at Month 3 after axi-cel infusion and in five of 12 evaluable patients (42%) at 24 months (Supplementary Table 5). Anti-axi-cel antibodies were not detected, and no case of replication-competent retrovirus was reported.

Efficacy

Primary analysis: Among the 48 patients who received debulking therapy, the median tumor burden was reduced from 2058.0 mm^2 at screening to 1390.0 mm^2 at postdebulking baseline. Median decrease in tumor burden relative to screening was 17.4% with intensive debulking chemotherapy regiments (R-ICE/R-GDP; from 3136.0 mm^2 at screening to 1896 mm^2 at postdebulking baseline), 4.3% with other less aggressive debulking chemotherapies (from 1452.0 mm^2 to 980.0 mm^2), and 6.3% with radiotherapy only (1932.0 mm^2 to 1652.0 mm^2). At primary data cutoff, the objective response rate was 72% (95% CI, 58%-84%), with a complete response rate of 54% (95% CI, 39%-68%) (**Figure 1**). At a median follow-up of 11.4 months, the median duration of response was not reached (95% CI, 2.2 months, not estimable), with 21 of 36 patients (58%) in ongoing response (**Figure 2A**); 21 patients (42%) remained in ongoing response at data cutoff. Median progression-free survival and overall survival were 3.1 months (95% CI, 2.9 months-not estimable) (**Figure 2B**) and 14.6 months (95% CI, 12.5 months-not estimable), respectively (**Figure 2C**). Efficacy outcomes appeared improved for patients who received debulking chemotherapy regimens (R-ICE/R-GDP or other less aggressive debulking chemotherapies) versus those who received debulking by radiotherapy only; although, results should be interpreted with caution due to the small number of patients included in the different groups. Objective response rate were 76%, 71% and 64% for patients treated with intensive chemotherapy regimens (R-ICE/R-GDP), other less aggressive debulking chemotherapies, and radiotherapy only, respectively. Complete response rates were 71%, 53%, and 36% for the same groups. The 6-month progression-free survival estimates were 53 months for both chemotherapy groups and 21 months for the radiotherapy-only group. Median overall survival was not reached (95% CI, 4.7-not estimable), 14.6 months (95% CI, 12.5-not estimable), and 11.6 (95% CI, 4.6-not estimable) for patients treated with R-ICE/R-GDP, other debulking chemotherapies, and radiotherapy only, respectively (Supplementary Table 6). Two patients achieved complete response after debulking and went on to receive axi-cel; both patients remained in complete response until last assessment on study.

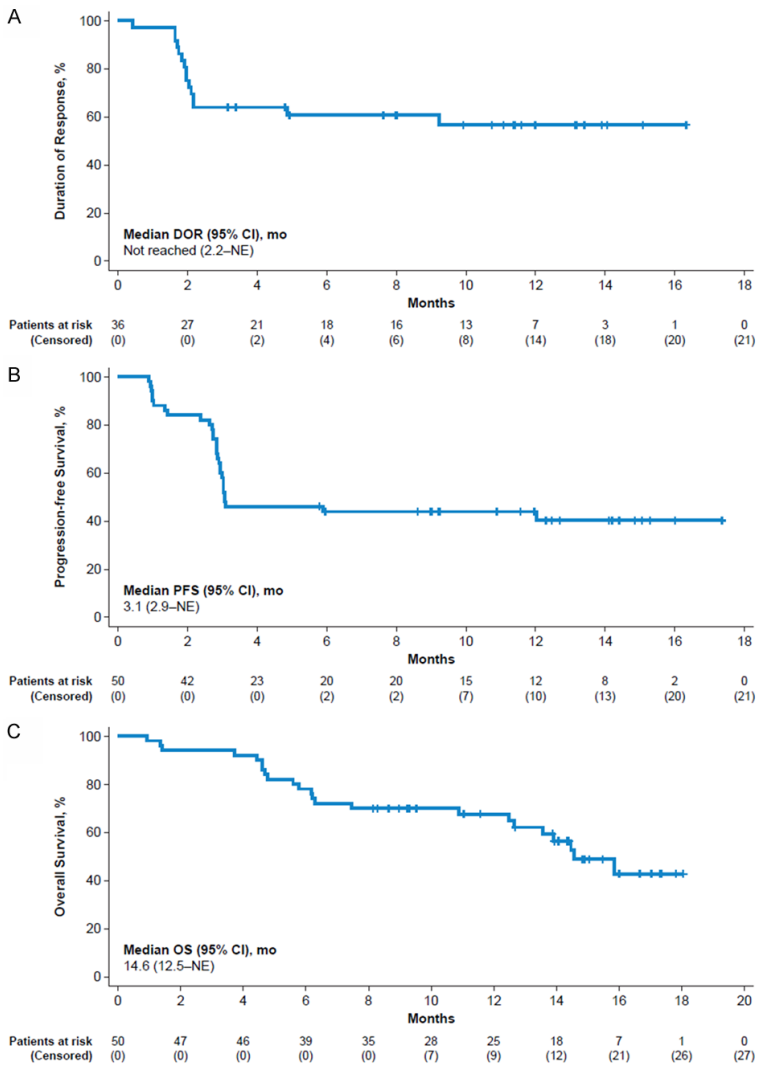

Figure 2. Duration of response, progression-free survival, and overall survival (primary analysis). A. Duration of response. B. Progression-free survival. C. Overall survival. Disease assessment after initiation of new anticancer therapy (not including stem cell transplant) was not included in the duration of response or progression-free survival derivations. DOR, duration of response; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Updated analysis: 24-month follow up: At the 24-month analysis, the objective response rate was unchanged from the primary analysis; as one patient converted from partial response to complete response at the Month 30 visit (on Day 908), the complete response rate increased to 56%. Median duration of response was 25.8 months (95% CI, 2.2 months-not estimable) (**Figure 3A**), and 18 patients (36%) were in ongoing response at time of data cutoff. Median progression-free survival was 3.1 months (95% CI, 2.9-29.1) and median overall survival was 20.6 months (95% CI, 12.6 months-not estimable) (**Figure 3B**, **3C**).

Translational analyses

Primary analysis: Pre-infusion product characteristics are reported in Supplementary Table 7. In summary, the median number of infused T cells was 277.7×10^6 cells (range, 161.3-941.2) and the median number of infused CAR T cells was 160.0×10^6 cells (range, 80.0-200.0). Of these, the median percentage of viable cells was 94.0% (range, 82.0-97.0). The median peak levels and $AUC_{0\text{-}28}$ of anti-CD19 CAR T cells were 26.63 cells/μL (range, 0.05-692.89) and 184.75 cells/μL × days (range, 0.16-4613.91), respectively. At 24 months, the median level of anti-CD19 CAR T cells in the blood was 0.13 cells/μL (range, 0-0.65) (**Figure 4A**).

A potential association between anti-CD19 CAR T-cell peak with frequency of grade ≥2 CRS and grade ≥3 NEs was observed (Supplementary Figure 3). Median peak level was higher for patients with grade ≥2 CRS compared with patients with grade ≤1 CRS (52.18 vs 17.48 cells/μL; descriptive P=0.0143), and peak level was also higher for patients with grade ≥3 NEs compared with patients with grade ≤2 NEs (135.84 vs 24.29 cells/μL; descriptive P=0.2035). These results should be interpreted with caution due to the small number of patients with grade ≥3 NEs. The median time-to-peak for 18 preselected serum analytes was between six and eight days after axi-cel infusion, except for granulocyte-macrophage colony-stimulating factor (GM-CSF) (3 days), interleukin (IL)-15 (4 days), IL-2 (5 days), IL-7 (4 days), and perforin (29 days). With the exception of intercellular adhesion molecule 1 (ICAM-1), perforin, vascu-

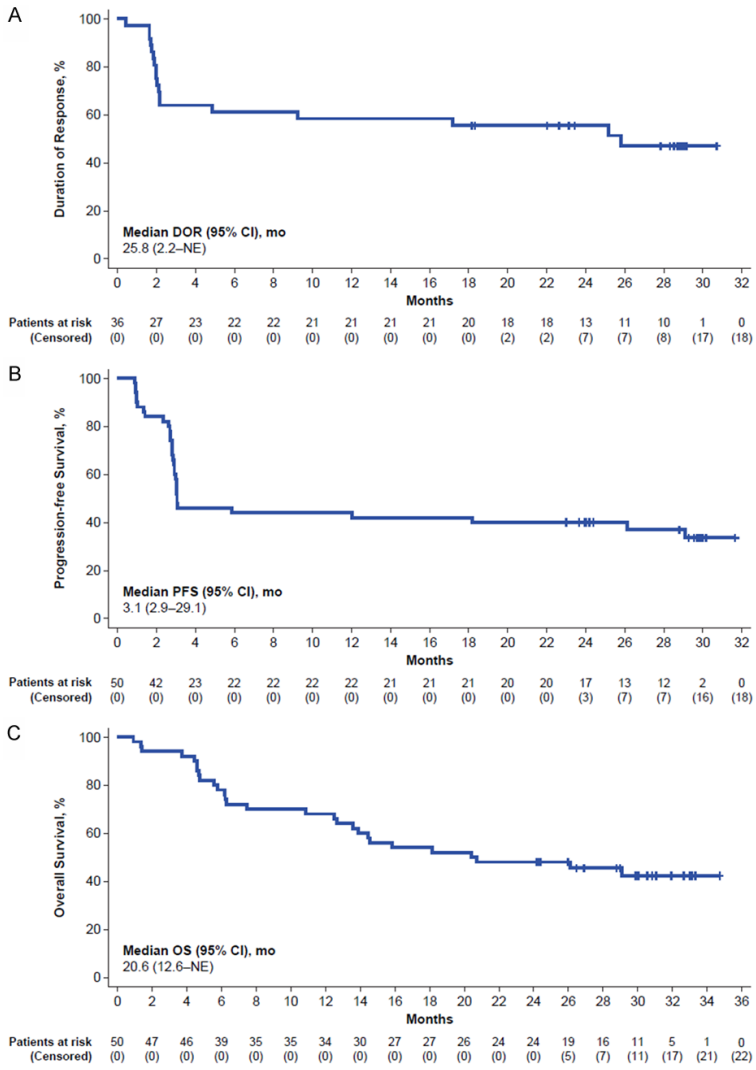

Figure 3. Duration of response, progression-free survival, and overall survival (24-month analysis). A. Duration of response. B. Progression-free survival. C. Overall survival. Disease assessment after initiation of new anticancer therapy (not including stem cell transplant) were not included in the duration of response or progression-free survival derivations. DOR, duration of response; NE, not estimable; OS, overall survival; PFS, progression-free survival.

lar cell adhesion protein 1 (VCAM-1), and GM-CSF, analytes were elevated by at least 2-fold at peak compared with baseline in at least 50% of patients (Supplementary Table 8).

Updated analysis: 24-month follow up: Peak CAR T-cell levels in the blood were numerically higher among patients in ongoing response or among nonresponders at 24 months versus those who relapsed by the data cutoff date; these differences were not significant, possibly due to the small number of patients (**Figure 4B**). Moreover, peak pharmacokinetic expansion did not appear to be altered by debulking compared with ZUMA-1 Cohorts 1+2.

Propensity score matching

After PSM, patient characteristics at baseline were balanced between Cohorts 1+2 and Cohort 5, with variations within 0.2 standardized mean difference (Supplementary Table 9). Of the 50 patients in Cohort 5, nine could not be matched to patients in Cohort 1+2 because their propensity scores were outside the prespecified boundary. Although CAR T-cell peak was similar in the two groups, the $AUC_{0\text{-}28}$ was lower in Cohort 5 than Cohorts 1+2. Responses were more frequently observed in Cohorts 1+2, including objective response rate (92.7% vs 70.7%) and complete response (61.0% vs 51.2%) (Supplementary Table 10). Grade ≥3 CRS was more frequent in Cohorts 1+2 compared with Cohort 5 (9.8% vs 2.4%), with a similar time to onset in both groups (median onset time was 6 and 7 days for Cohort 1+2 and Cohort 5, respectively). Similarly, grade ≥3 NEs were more frequent in Cohorts 1+2 compared with Cohort 5 (26.8% vs 14.6%), with a similar time to onset in both groups (median onset time was 7 and 7.5 days for Cohort 1+2 and Cohort 5, respectively). Steroid and tocilizumab were used in approximately twice as many patients in Cohort 5 compared with Cohorts 1+2, but Cohort 5 was associated with lower cumulative steroid use and higher cumulative tocilizumab use. A similar peak of CD8 T cells was observed in both groups, but a higher naive T-cell peak was observed in Cohort 5 (16.80% vs 31.35%). Regarding product characteristics, the transduction rate was also slightly higher in Cohort 5 (Supplementary Table 10).

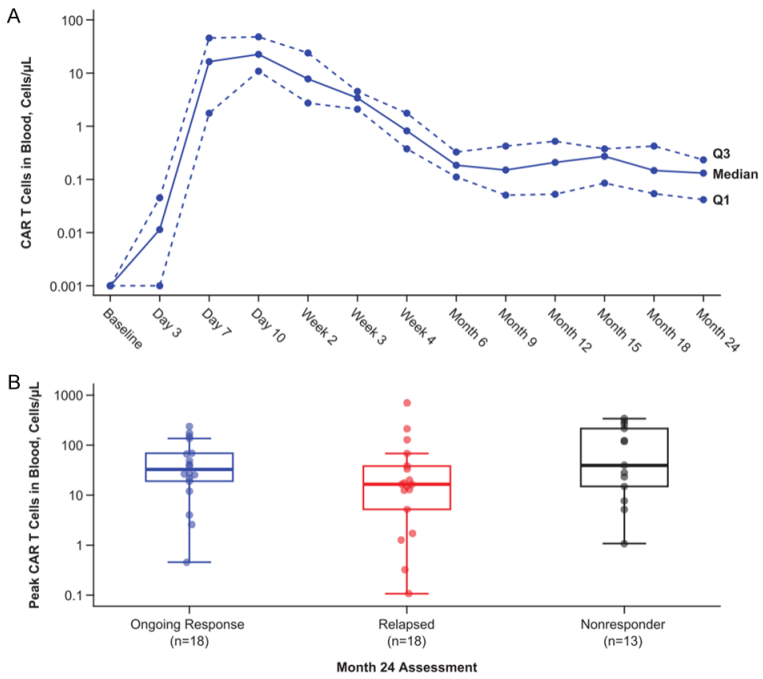

Figure 4. CAR T-cell expansion. A. CAR T-cell expansion through 24 months. B. Association of CAR T-cell peak expansion with ongoing response at 24 months. Peak was defined as the maximum number of CAR T cells measured post infusion. Responses were determined by study investigators per the revised International Working Group Response Criteria for Malignant Lymphoma [16]. Ongoing response was defined as responders (CR/PR) who did not have PD or die by the data cutoff. Relapse was defined as responders who had documented PD or died by the data cutoff. Nonresponder was defined as those who did not have either CR or PR by the data cutoff. Patients who were responders (CR/PR) and had the following events by the data cutoff were not included for the ongoing response assessment: allogeneic stem cell transplantation, started new anticancer therapy, withdrawal of consent, lost to follow-up, or other reasons listed for end of study. CAR, chimeric antigen receptor; CR, complete response; PD, progressive disease; PR, partial response.

Discussion

Debulking treatments prior to CAR T-cell therapy may be needed in some patients in clinical practice to limit disease progression or reduce tumor burden during the manufacturing process. Further, evidence from ZUMA-1 Cohorts 1+2 suggested that lower tumor burden prior to axi-cel infusion was associated with better efficacy and safety outcomes [19]. The analysis of ZUMA-1 Cohort 5 aimed to provide some clarity on the impact of debulking therapy on the clinical outcomes of patients treated with axi-cel, which we contextualize with the more recent treatment landscape.

Based on unmatched comparisons, the incidences of grade ≥3 CRS and NEs were lower in Cohort 5 (at time of primary analysis) than in ZUMA-1 Cohorts 1+2. The median time to onset and duration of CRS was two days and eight days, respectively, in both Cohort 5 and 1+2. NEs developed more slowly and resolved in a similar time frame in Cohort 5 (median time to onset, 8 days; median duration, 12 days) compared with Cohorts 1+2 (median time to onset, 5 days; median duration, 13 days). Lower incidences of grade ≥3 CRS and NEs in Cohort 5 versus Cohorts 1+2 may have been influenced by several factors, including lower baseline tumor burden, lower CAR T-cell expansion for patients in Cohort 5, the use of prophylactic levetiracetam, or greater clinical experience among treatment teams in managing these toxicities. Additionally, corticosteroid use was higher in Cohort 5 (52% vs 27% in Cohorts 1+2), which may reflect greater confidence among investigators in using corticosteroids with CAR T-cell therapy. Generally, the safety profile was similar in Cohort 5 compared with Cohorts 1+2, but there were some hematologic adverse events that were more frequent and more severe in Cohort 5, such as prolonged neutropenia, prolonged thrombocytopenia, and infections [8]; similar trends persisting through the 24-month follow-up. Finally, a similar incidence of deaths due to adverse events was observed in Cohort 5 and Cohorts 1+2.

Although this was an exploratory cohort and not designed for formal hypothesis testing, the debulking regimens used in Cohort 5 did not appear to have a negative impact on efficacy outcomes. While the objective response rate in the 24-month analysis of ZUMA-1 Cohort 5 was numerically lower than that of Cohorts 1+2 (72% and 83%, respectively), the median duration of response in Cohort 5 was longer than that of Cohorts 1+2 (25.2 months vs 11.1

months) [20]. Complete response rates in the primary analyses of Cohort 5 and Cohorts 1+2 were comparable (54% vs 52%) [8]. Median progression-free survival was 3.1 months for Cohort 5 and 5.9 months for Cohorts 1+2, and the 24-month estimated overall survival was 48% and 50.5%, respectively.

The usefulness of bridging therapy remains controversial [21-23]. In a recent publication, including single-institution real-world evidence of the use of radiotherapy and other bridging therapies in patients with LBCL undergoing CAR T-cell therapy, authors observed no significant survival or safety differences between those that did or did not receive bridging therapy [22]. A separate retrospective study found no significant difference in rates of CRS and NEs between patients treated with axi-cel who achieved complete metabolic response with bridging therapy versus those with stable response, partial response, or progressive disease [21]. In addition, no significant progression-free survival differences were found (median follow-up, 26 months) [21]. In contrast, another study showed that complete or partial response to bridging therapy may reduce disease progression and death in patients treated with axi-cel or especially tisagenlecleucel [23]. Moreover, real-world data show that bridging regimens, particularly radiotherapy or rituximab-bendamustine-polatuzumab, do not have a negative impact on the safety or efficacy of axi-cel or other CAR T-cell therapy [22-26].

Subgroup analyses by type of debulking therapy yielded small sample sizes and should be interpreted with caution, with validation in larger studies. In general, outcomes in this study were more favorable for patients who received debulking chemotherapy regimens compared with patients who received radiotherapy only. Patients who received chemotherapy experienced more serious TEAEs but a lower rate of infections compared with patients who received radiotherapy only. In contrast, radiotherapy was associated with better efficacy outcomes and similar toxicity levels compared with systemic bridging therapy or no bridging therapy in a separate real-world study of patients with LBCL who received commercial axi-cel [22]. In our study, median duration of response and progression-free survival were longer among patients who received debulking chemotherapy versus radiotherapy, with ongoing response rates that were 2.5 times higher in the former group. Despite the differences between our results and real-world experience [22], the use of debulking therapy did not negatively impact overall efficacy outcomes. Notably, bridging therapy should not be considered a definitive therapy. Despite observing complete responses to bridging therapy (as with 2 patients herein), CAR T cells should be administered regardless of the result of bridging therapy if the clinical intent is to treat the patient with CAR T-cell therapy, as demonstrated by promising efficacy and safety outcomes among such patients [23, 27].

This study has several limitations as the treatment landscape and product manufacturing have evolved since conduct of the trial. Specifically, Cohort 5 enrolled patients in 2018-2019 and the treatment landscape for LBCL has evolved with respect to bridging, debulking regimens, and safety management, which may preclude generalizing these findings to the current landscape. Additionally, median time from leukapheresis to product delivery at study site, which did not appear to be impacted by the debulking regimens, was longer in European Union countries, with a median time of 31 days in this study, versus 21 days for Canada in this study, or 17 days for ZUMA-1 Cohorts 1+2 [8]. Notably, the manufacturing metrics observed in this study, with patient enrolment between 2018-2019, is not representative of today's manufacturing experience with axi-cel [28].

Furthermore, since initiation of the study, alternative safety management strategies have also been explored and brought into practice [29-33]. For example, retrospective, single-center studies have shown improvement of CRS and neurotoxicity in patients who received anakinra and axi-cel or tisagenlecleucel for LBCL or other CD19-postive hematologic malignancies [33, 34]; however, more recent studies suggest that prophylactic anakinra may have limited effects on reducing NEs. In addition, the safety management strategy in Cohort 5 followed that of Cohorts 1+2. Safety Cohort 4 of ZUMA-1 showed that earlier intervention with corticosteroid and tocilizumab administration improved the rates and severity of CRS and NEs, with no impact on responses [12, 13]. Safety Cohort 6 showed that the addition of prophylactic corti-

costeroids to earlier corticosteroid and/or tocilizumab intervention resulted in no grade ≥3 CRS and a lower rate of grade ≥3 NEs compared with earlier Cohorts 1+2 safety management strategy, while maintaining high objective response rates.

In conclusion, the debulking regimens used in Cohort 5 reduced tumor burden prior to axi-cel infusion and demonstrated the feasibility of debulking prior to CAR T-cell therapy in a prospective cohort. However, given the incidence of additional adverse events beyond CRS and NEs, the debulking strategies used in Cohort 5 did not appear to improve the overall benefit/risk profile of axi-cel. It is possible that debulking would have had a more favorable overall impact in a patient population with a higher tumor burden prior to debulking, which is consistent with the findings that tumor burden impacts outcomes in third-line or later treatment of R/R LBCL [35]. Additional studies are needed to determine whether current debulking strategies would improve efficacy and safety of axi-cel in this population.

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Disclosure of conflict of interest

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Supplementary methods

Additional inclusion and exclusion criteria

Prior therapy must have included treatment with an anti-CD20 monoclonal antibody (unless the tumor was CD20 negative) and an anthracycline-containing regimen. An Eastern Cooperative Oncology Group performance status of 0 or 1, absolute neutrophil count ≥1000/μL, platelet count ≥75,000/μL, absolute lymphocyte count ≥100/μL, and adequate renal, hepatic, pulmonary, and cardiac function were also required. Patients with central nervous system involvement and active infections were excluded.

Pharmacokinetic and pharmacodynamic analyses

Blood samples for anti-CD19 chimeric antigen receptor (CAR) T cells and serum cytokines/chemokines and other soluble biomarkers were collected and assessed as previously described [1, 2]. Product cells were characterized by flow cytometry and coculture with CD19-expressing target cells, followed by ELISA or Meso Scale Discovery [2]. Percent transduction was defined as percentage of product cells expressing CAR transgene.

Propensity score-based matching comparison with Cohorts 1+2

Propensity score-based matching (PSM) analysis was used previously to compare ZUMA-1 safety Cohorts to pivotal Cohorts 1+2 [3, 4]. This statistical method allows for balanced comparisons between two groups by reducing potential confounding effects of measured or unmeasured baseline characteristics [5, 6]. Thus, PSM analysis can help estimate the effects of treatment on outcomes and reduce bias in comparisons between groups in the absence of a randomized trial [5, 6]. In this post hoc analysis, ZUMA-1 Cohort 5 and Cohorts 1+2 were compared descriptively to evaluate if the numerical trends observed in the primary analysis held in propensity score matched subgroups. The following key baseline disease characteristics were used for 1:1 PSM analysis: tumor burden, baseline lactate dehydrogenase level, disease stage, ECOG performance status, age, prior platinum-containing chemotherapy regimen, International Prognostic Index score, and number of prior chemotherapies. These five covariates are established predictive and prognostic markers for LBCL as well as for axi-cel clinical outcomes in ZUMA-1 Cohorts 1+2 [1, 7] and in other studies [8-10]. To assess covariate balance between the 2 groups, the standardized mean difference was limited to ±0.2, and the caliper (maximum difference between groups) used was 0.5 [6, 11].

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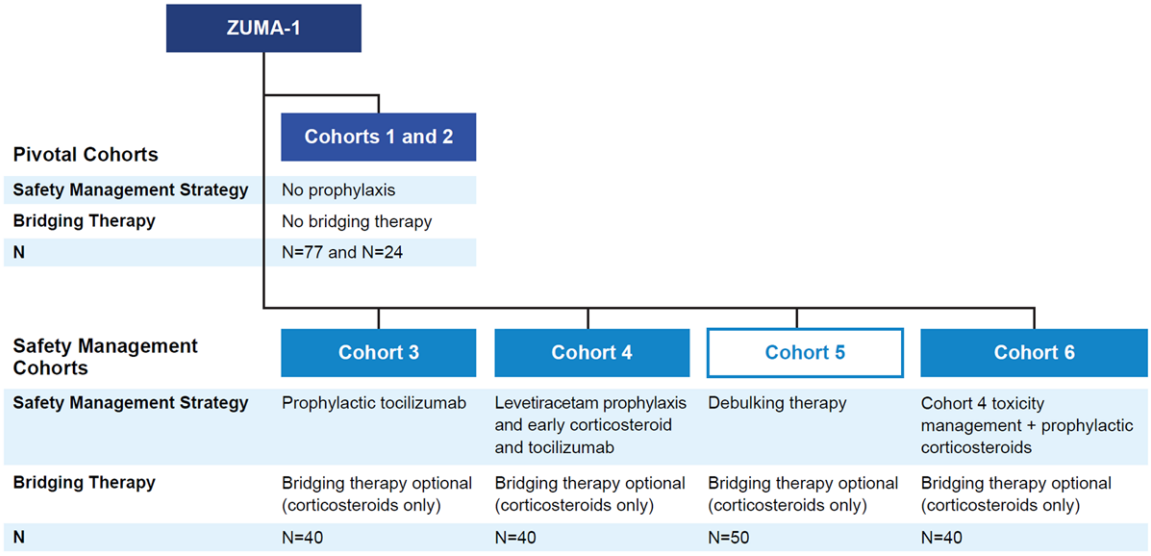
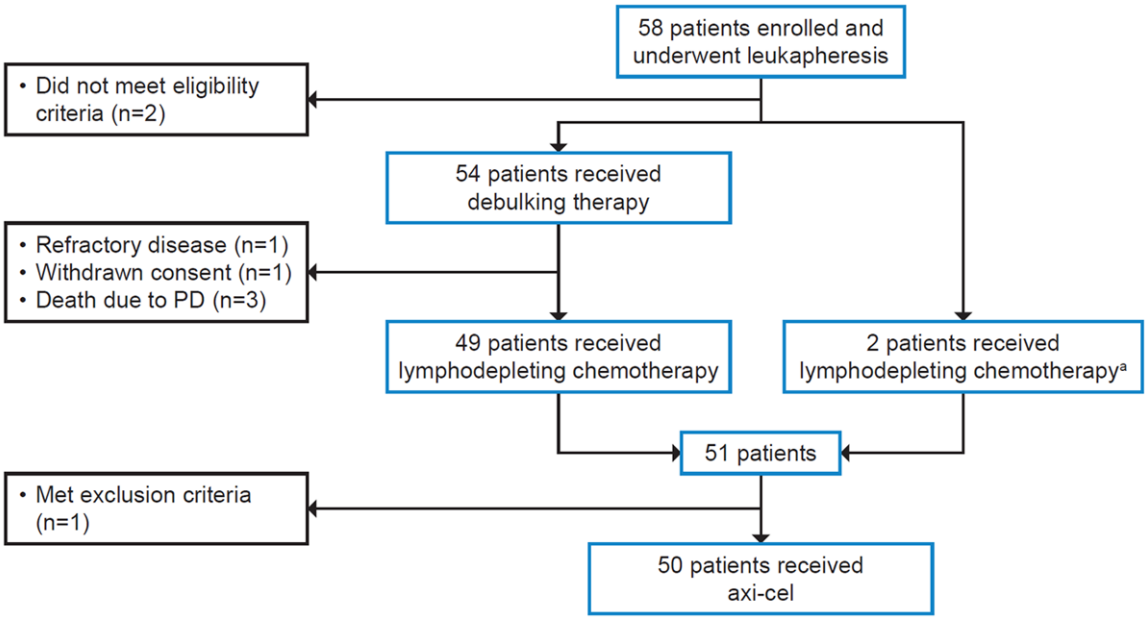


Supplementary Figure 1. Diagram with the key differences on safety management strategies in the ZUMA-1 cohorts.



Supplementary Figure 2. Patient disposition. [a]Per investigator decision, these 2 patients did not receive debulking therapy as each had low tumor burden at the time of leukapheresis. Axi-cel, axicabtagene ciloleucel; PD, progressive disease.

Supplementary Table 1. Incidence of grade ≥3 treatment-emergent adverse events that occurred in ≥5% of patients by preferred term and worst grade (primary analysis)

n (%)	Any grade ≥3	Worst grade 3	Worst grade 4	Worst grade 5
Any	50 (100)	10 (20)	35 (70)	5 (10)
Neutrophil count decrease	24 (48)	2 (4)	22 (44)	0 (0)
Anemia	15 (30)	15 (30)	0 (0)	0 (0)
Neutropenia	15 (30)	5 (10)	10 (20)	0 (0)
Platelet count decreased	14 (28)	4 (8)	10 (20)	0 (0)
White blood cell count decreased	13 (26)	2 (4)	11 (22)	0 (0)
Thrombocytopenia	9 (18)	3 (6)	6 (12)	0 (0)
Lymphocyte count decreased	8 (16)	6 (12)	2 (4)	0 (0)
Leukopenia	7 (14)	2 (4)	5 (10)	0 (0)
Pyrexia	7 (14)	6 (12)	1 (2)	0 (0)
Aphasia	3 (6)	2 (4)	1 (2)	0 (0)
Febrile neutropenia	3 (6)	3 (6)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	3 (6)	3 (6)	0 (0)	0 (0)
Hypophosphatemia	3 (6)	2 (4)	1 (2)	0 (0)
Hypotension	3 (6)	3 (6)	0 (0)	0 (0)
Hypoxia	3 (6)	2 (4)	1 (2)	0 (0)
Septic shock	3 (6)	0 (0)	0 (0)	3 (6)

Supplementary Table 2. Treatment-emergent infections starting from axi-cel infusion (primary analysis)

n (%)	Overall (N=50)
Any infection	19 (38)
Grade 1	3 (6)
Grade 2	8 (16)
Grade 3	4 (8)
Grade 4	0 (0)
Grade 5	4 (8)
Grade ≥3	8 (16)

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Adverse events were coded using Medical Dictionary for Regulatory Activities version 24.1; severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Axi-cel, axicabtagene ciloleucel.

Supplementary Table 3. Summary of treatment-emergent hypogammaglobulinemia (primary analysis)

n (%)	Overall (N=50)
Any hypogammaglobulinemia	4 (8)
Grade 1	2 (4)
Grade 2	2 (4)
Grade ≥3	0 (0)

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Supplementary Table 4. Summary of cytopenias present on or after day 30 after axi-cel infusion (primary analysis)

n (%)	Overall (N=50)	
	Any grade	Grade ≥3
Any prolonged cytopenia	28 (56)	26 (52)
Prolonged thrombocytopenia[a]	19 (38)	18 (36)
Platelet count decreased	12 (24)	11 (22)
Thrombocytopenia	8 (16)	8 (16)
Prolonged neutropenia[b]	25 (50)	24 (48)
Neutrophil count decreased	16 (32)	15 (30)
Neutropenia	10 (20)	10 (20)
Prolonged anemia	11 (22)	7 (14)
Anemia	11 (22)	7 (14)

Prolonged thrombocytopenia/neutropenia/anemia were defined as thrombocytopenia/neutropenia/anemia that was present on or after 30 days from axi-cel infusion. AEs were coded using MedDRA Version 23.0 and graded per CTCAE Version 4.03. Thrombocytopenia was identified using the SMQ hematopoietic thrombocytopenia (narrow). Neutropenia was identified using MedDRA search terms prespecified by Kite. Anemia was identified using the SMQ hematopoietic erythropenia (broad). [a]Includes the following preferred terms: thrombocytopenia and platelet count decreased. [b]Includes the following preferred terms: neutropenia and neutrophil count decreased. AE, adverse event; Axi-cel, axicabtagene ciloleucel; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Query.

Supplementary Table 5. Summary of B-cell aplasia among patients in ongoing response at 24 months

n (%)	Ongoing response (n=18[a])
B cells tested at baseline	14 (78)
No B cells	5 (36)
With B cells	9 (64)
B cells tested at month 3	16 (89)
No B cells	14 (88)
With B cells	2 (13)
B cells tested at month 6	18 (100)
No B cells	17 (94)
With B cells	1 (6)
B cells tested at month 12	14 (78)
No B cells	10 (71)
With B cells	4 (29)
B cells tested at month 15	14 (78)
No B cells	11 (79)
With B cells	3 (21)
B cells tested at month 18	15 (83)
No B cells	9 (60)
With B cells	6 (40)
B cells tested at month 24	12 (67)
No B cells	7 (58)
With B cells	5 (42)

[a]Included responders who did not have progressive disease or die by 24 months post axi-cel infusion. Axi-cel, axicabtagene ciloleucel.

Supplementary Table 6. Efficacy outcomes by debulking therapy (primary analysis)

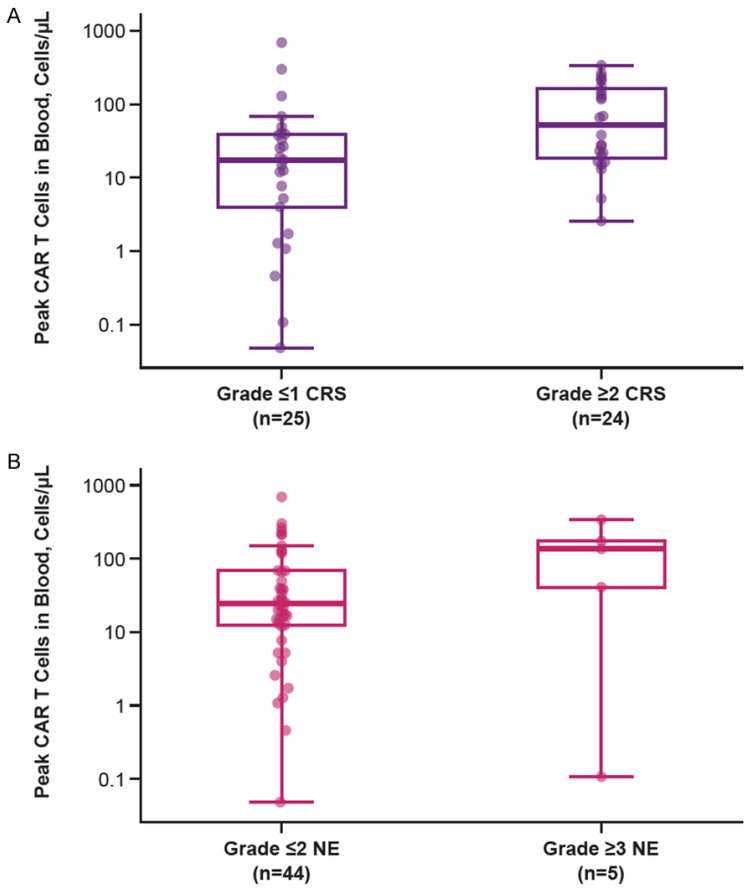
	R-ICE/R-GDP (n=17)	Other debulking chemotherapies (n=17)	Radiotherapy only (n=14)
ORR (CR + PR), n (%)	13 (76)	12 (71)	9 (64)
CR, n (%)	12 (71)	9 (53)	5 (36)
PR, n (%)	1 (6)	3 (18)	4 (29)
SD, n (%)	1 (6)	2 (12)	1 (7)
PD, n (%)	2 (12)	3 (18)	4 (29)
Not done, n (%)	1 (6)	0	0
Median DOR[a] (95% CI), months	NR (2.2-NE)	NR (1.9-NE)	2.0 (0.4-NE)
6-month DOR (95% CI), months	69 (37-87)	75 (41-91)	30 (5-61)
Ongoing response, n (%)	9 (53)	9 (53)	3 (21)
Median PFS (95% CI), months	NR (2.7-NE)	NR (2.9-NE)	2.8 (1.3-5.9)
6-month PFS (95% CI), months	53 (28-73)	53 (28-73)	21 (5-45)
Median OS (95% CI), months	NR (4.7-NE)	14.6 (12.5-NE)	11.6 (4.6-NE)
6-month OS (95% CI), months	71 (43-87)	88 (61-97)	71 (41-88)

[a]The analysis of median duration of response included 13 patients treated with R-ICE/R-GDP, 12 patients treated with other therapies, and 9 patients treated with radiotherapy. CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-ICE; rituximab, ifosfamide, carboplatin, and etoposide; SD, stable disease.

Supplementary Table 7. Summary of product characteristics

Parameter median (min-max)	Overall (N=50)
Total number of T cells infused ×10^6	277.7 (161.3-941.2)
Total number of CAR T cells infused ×10^6	160.0 (80.0-200.0)
Percent transduction, %	62.5 (17.0-82.0)
IFN-γ level in coculture, pg/mL	5987.0 (496.0-2.1×10^4)
Viability, %	94.0 (82.0-97.0)
CD4/CD8 ratio	1.1 (0.1-12.5)
Naive (CCR7+CD45RA+) T cells[a], %	32.2 (6.9-78.0)
Central memory (CCR7+CD45RA-) T cells[a], %	19.3 (0.0-49.0)

[a]Data are reported as the percentage of viable CD3+ cells. CAR, chimeric antigen receptor; IFN, interferon; max, maximum; min, minimum.



Supplementary Figure 3. Peak of anti-CD19 CAR T cells in blood (cells/µL) by grade of CRS and NE. A. Peak of anti-CD19 CAR-T cells in blood (cells/µL) by grade ≥2 vs grade ≤1 CRS. B. Peak of anti-CD19 CAR T cells in blood (cells/µL) by grade ≥3 vs grade ≤2 NE. CAR, chimeric antigen receptor; CRS, cytokine release syndrome; NE, neurologic event.

Supplementary Table 8. Summary of cytokine levels

Cytokine	Peak median (min-max)[a] N=50	AUC median (min-max)[b] N=50	Time to Peak median (min-max)[c] N=50
CRP (mg/L)	74.84 (1.81-496.00)	534.58 (3.46-6550.33)	6 (1-42)
CXCL10 (pg/mL)	1746.15 (349.80-2000.00)	2.31×10^4 ($9640.65-5.95\times10^4$)	7 (1-58)
Ferritin (ng/mL)	1516.11 (89.29-3.16×10^4)	3.56×10^4 ($1466.08-5.31\times10^5$)	8 (1-35)
Granzyme B (pg/mL)	27.90 (1.00-375.76)	227.10 (28.00-1594.55)	6 (1-58)
ICAM-1 (ng/mL)	636.74 (361.38-4835.93)	1.49×10^4 ($3763.26-7.07\times10^4$)	8 (1-35)
IFN-γ (pg/mL)	314.90 (7.50-1876.00)	2278.40 (210.00-1.59×10^4)	6 (1-35)
IL-1RA (pg/mL)	908.00 (229.00-9000.00)	1.46×10^4 ($3888.00-3.74\times10^4$)	6 (1-35)
IL-10 (pg/mL)	14.45 (0.70-300.90)	110.30 (24.30-1106.05)	6 (1-35)
IL-15 (pg/mL)	34.15 (1.40-140.00)	452.70 (128.90-1748.40)	4 (1-40)
IL-2 (pg/mL)	11.85 (0.90-142.70)	84.75 (25.20-331.95)	5 (1-35)
IL-2Rα (ng/mL)	7.82 (1.36-83.60)	138.42 (28.12-1800.86)	8 (2-35)
IL-6 (pg/mL)	97.95 (1.60-976.00)	956.90 (52.80-1.19×10^4)	6 (1-35)
IL-7 (pg/mL)	29.80 (1.40-65.20)	587.00 (314.95-1169.65)	4 (1-35)
IL-8 (pg/mL)	75.10 (5.80-750.00)	806.70 (175.15-8193.80)	6 (1-35)
Perforin (ng/mL)	10.85 (2.53-100.00)	205.82 (52.43-2424.58)	29 (4-44)
TNF-α (pg/mL)	5.25 (1.40-33.30)	93.25 (27.65-310.05)	6 (1-35)
VCAM-1 (ng/mL)	854.63 (476.60-6501.14)	1.84E+04 ($4627.26-1.07\times10^5$)	8 (1-35)
GM-CSF (pg/mL)	2.90 (1.90-35.60)	62.70 (53.20-168.80)	3 (0-35)

[a]Peak was defined as the maximum level of cytokine from baseline to week 4. [b]AUC measured the total levels of cytokine overtime and was defined as the area under curve in a plot of levels of cytokine against scheduled visit from baseline (i.e., Day -5) to Day 28. [c]Time-to-peak was defined as number of days from infusion to the date when the cytokine first reached the maximum post-baseline level. AUC, area under the curve; CRP, C-reactive protein; CXCL, chemokine C-X-C motif ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Supplementary Table 9. ZUMA-1 Phase 2 Cohorts 1+2 versus Cohort 5 descriptive statistics for selected baseline characteristics before and after propensity score matching

Baseline characteristics	Before matching			After matching		
	Cohorts 1+2 (N=101)	Cohort 5 (N=50)	SMD	Cohorts 1+2 (caliper =0.5) (N=41)	Cohort 5 (caliper =0.5) (N=41)	SMD
Age, median (IQR), years	58.0 (51.0-64.0)	57.5 (53.0-67.0)	0.17	61.0 (55.0-65.0)	57.0 (52.0-65.0)	0.12
Tumor burden, median (IQR), mm^2	3723 (2200-7138)	1652 (469-3860)	0.17	2971 (1724-6167)	2260 (504-6511)	0.07
ECOG PS 1, n (%)	59 (58.4)	23 (46.0)	0.25	24 (58.5)	23 (56.1)	0.05
IPI score ≥3, n (%)	46 (45.5)	25 (50.0)	0.09	19 (46.3)	19 (46.3)	0.00
Stage ≥3, n (%)	86 (85.1)	37 (74.0)	0.28	32 (78.1)	31 (75.6)	0.06
Number of prior lines of chemotherapy, n (%)						
≤2	31 (30.7)	30 (60.0)	0.62	24 (58.5)	21 (51.2)	0.15
3	29 (28.7)	16 (32.0)	0.07	15 (36.6)	16 (39.0)	0.05
≥4	41 (40.6)	4 (8.0)	0.82	2 (4.9)	4 (9.8)	0.12
Patients with prior treatment with platinum, n (%)	90 (89.1)	46 (92.0)	0.10	38 (92.7)	38 (92.7)	0.00
LDH, median (IQR), U/L	356.0 (219.0-743.0)	261.5 (225.0-479.0)	0.36	329.0 (238.0-480.0)	272.0 (225.0-492.0)	0.01
CRP, median (IQR), mg/L	22.30 (4.20-65.78)	20.35 (3.30-59.00)	NA[a]	25.60 (3.05-63.00)	27.00 (10.04-61.00)	NA[a]

[a]CRP was not used as a matching variable; thus, the SMD value is not applicable. CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NA, not applicable; SMD, standardized mean difference (absolute value).

Supplementary Table 10. Comparison of efficacy and safety outcomes and CAR T-cell and soluble serum biomarker levels between patients in ZUMA-1 Phase 2 Cohorts 1+2 and Cohort 5 before and after propensity score matching

	Before matching		After matching	
	Cohorts 1+2	Cohort 5	Cohorts 1+2 (caliper =0.5)	Cohort 5 (caliper =0.5)
Sample size	101	50	41	41
CAR T cells, median (IQR)				
CAR T-cell peak, cells/μL	34.41 (13.18-81.28)	26.63 (12.52-117.53)	33.15 (17.21-84.92)	26.93 (12.49-96.48)
CAR T-cell $AUC_{0\text{-}28}$, cells/μL*day	448.40 (146.41-917.48)	184.75 (106.33-647.44)	501.57 (226.51-917.48)	183.21 (99.46-646.98)
Efficacy, n (%)				
Objective response	83 (82.2)	36 (72.0)	38 (92.7)	29 (70.7)
Ongoing response	42 (41.6)	21 (42.0)	19 (48.7)	18 (43.9)
Best response				
CR	55 (54.5)	27 (54.0)	25 (61.0)	21 (51.2)
PR	28 (27.7)	9 (18.0)	13 (31.7)	8 (19.5)
Nonresponders	18 (17.8)	14 (28.0)	3 (7.3)	12 (29.3)

Safety				
Worst grade of NE, n (%)				
Worst grade ≥3	28 (27.7)	6 (12.0)	11 (26.8)	6 (14.6)
Worst grade ≥2	42 (41.6)	15 (30.0)	17 (41.5)	15 (36.6)
Time to onset for NE, median (IQR), days				
Any grade	5.0 (3.0, 7.0)	8.0 (5.0, 11.5)	6.0 (2.0, 7.0)	8.0 (5.0, 11.0)
Grade ≥3	6.5 (5.0, 7.0)	7.5 (6.0, 14.0)	7.0 (6.0, 8.0)	7.5 (6.0, 14.0)
Grade ≥2	5.5 (3.0, 7.0)	7.0 (6.0, 11.0)	6.0 (3.0, 6.0)	7.0 (6.0, 11.0)
Worst grade of CRS events, n (%)				
Worst grade ≥3	13 (12.9)	1 (2.0)	4 (9.8)	1 (2.4)
Worst grade ≥2	57 (56.4)	24 (48.0)	22 (53.7)	20 (48.8)
Time to onset for CRS, median (IQR), days				
Any grade	2.0 (2.0, 4.0)	2.5 (2.0, 6.0)	2.0 (2.0, 4.0)	2.0 (2.0, 6.0)
Grade ≥3	6.0 (5.0, 7.0)	7.0 (7.0, 7.0)	6.0 (4.5, 7.0)	7.0 (7.0, 7.0)
Grade ≥2	4.0 (2.0, 5.0)	5.5 (2.0, 8.0)	3.0 (2.0, 5.0)	6.5 (2.0, 8.5)
Steroid and tocilizumab use				
Patients with steroid use, n (%)[a]	27 (26.7)	26 (52.0)	11 (26.8)	21 (51.2)
Cumulative steroid use, median (IQR), mg	5699 (2504-15760)	3600 (563-9785)	6638 (1565-15760)	3756 (1252-13772)
Patients with tocilizumab use, n (%)[a]	43 (42.6)	39 (78.0)	14 (34.2)	31 (75.6)
Cumulative tocilizumab use, median (IQR), mg	1300 (800-2068)	1600 (800-2250)	976.00 (751-1770)	1600 (800-2304)
Peak cytokines and product characteristics, median (IQR)				
CRP, mg/L	214.24 (141.36-353.39)	74.84 (43.86-126.54)	185.19 (127.06-335.28)	98.91 (47.41-145.77)
Ferritin, ng/mL	3001.44 (1325.60-6683.49)	1516.11 (586.76-2999.23)	2738.00 (1330.40-6224.98)	1606.38 (592.26-3036.36)
GM-CSF, pg/mL	7.30 (1.90-16.07)	2.9 (1.9-10.2)	5.55 (1.90-13.70)	1.90 (1.90-7.90)
IFN-γ, pg/mL	477.40 (196.30-1096.70)	314.90 (86.00-758.50)	367.59 (137.30-1094.33)	315.80 (110.20-758.50)
IL-15, pg/mL	52.90 (34.70-72.10)	34.15 (24.10-54.10)	47.23 (34.70-64.80)	31.60 (24.10-53.00)
IL-2, pg/mL	21.70 (10.16-37.80)	11.85 (6.10-44.10)	24.50 (10.20-40.59)	11.90 (6.1-35.40)
IL-6, pg/mL	83.29 (23.26-347.50)	97.95 (23.80-535.60)	31.40 (16.10-164.80)	103.10 (24.80-535.60)
IL-8, pg/mL	93.59 (46.60-329.30)	75.10 (31.30-172.50)	118.40 (36.98-212.20)	78.40 (34.10-164.90)
MCP-1, pg/mL	1500.00 (900.11-1500.00)	1124.90 (705.70-1500.00)	1429.48 (948.95-1500.00)	1049.20 (705.70-1500.00)
TNF-α, pg/mL	7.90 (5.70-11.95)	5.25 (4.10-9.40)	6.90 (5.30-11.23)	5.50 (4.20-9.80)
IFN-γ by coculture, pg/mL	5925.00 (3408.50-8326.00)	5987.00 (3195.00-9229.00)	6384.00 (3519.00-8078.00)	5911.00 (3195.00-8852.00)
Peak CD8 T cells, % of viable CD3+ cells	53.80 (35.10-65.10)	47.85 (31.95-60.50)	54.10 (39.10-67.10)	48.65 (27.75-62.85)
Peak naive T cells, % of viable CD3+ cells	13.90 (8.20-24.40)	32.20 (20.10-43.70)	16.80 (7.50-32.80)	31.35 (19.30-43.70)
Transduction rate, %	52.55 (44.10-63.85)	62.50 (53.00-68.00)	53.80 (46.50-64.40)	62.00 (52.00-68.00)

[a]Post treatment (axi-cel) until hospitalization discharge. AUC_{0-28}, area under the curve from days 0 to 28; CAR, chimeric antigen receptor; CR, complete response; CRP, C-reactive protein; CRS, cytokine release syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; IQR, interquartile range; MCP-1, monocyte chemoattractant protein 1; NE, neurologic event; PR, partial response; TNF, tumor necrosis factor.