Axicabtagene Ciloleucel in Combination With Rituximab for the Treatment of Refractory Large B-Cell Lymphoma: Outcomes of the Phase 2 ZUMA-14 Study

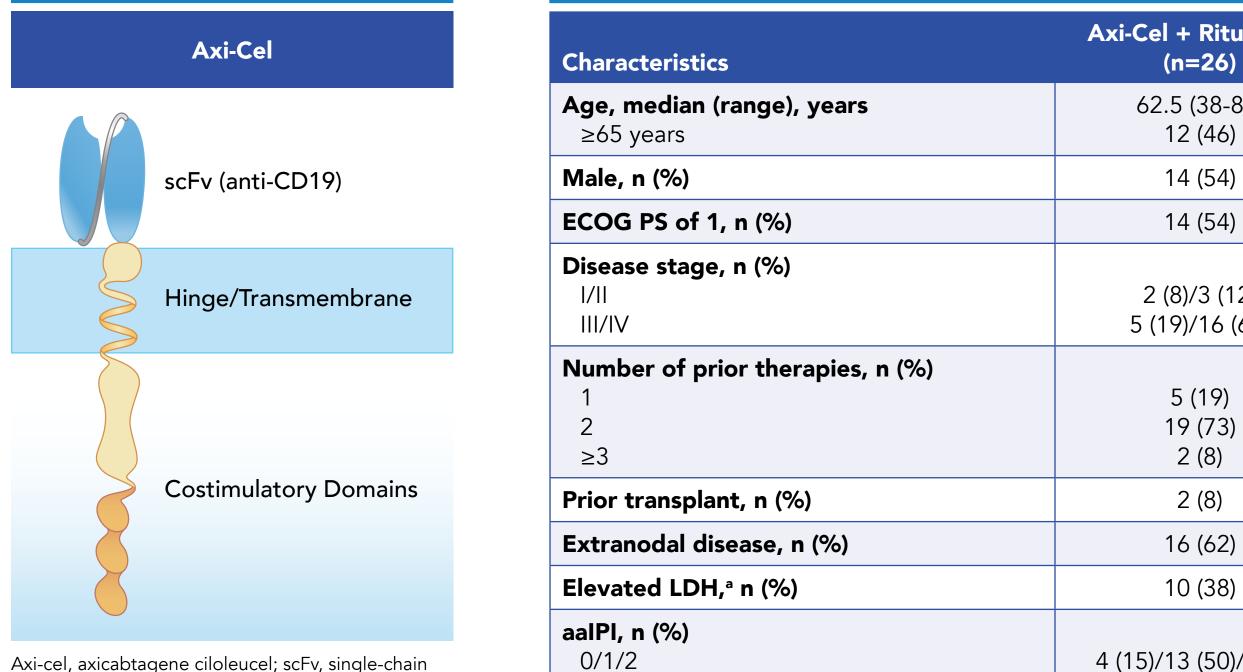
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BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (**Figure 1**) approved for the treatment of adult patients with relapsed/ refractory (R/R) large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy and most recently, in the United States, for R/R LBCL within 12 months of first-line chemoimmunotherapy¹
- With a median follow-up of 27.1 months in ZUMA-1, the objective response rate (ORR) with axi-cel was 83% (58% complete response [CR] rate) in patients with
- Axi-cel has been a successful treatment strategy for many patients; however, approximately 60% of patients have no response or relapse within ~2 years after treatment,² highlighting the need for more therapeutic strategies
- In preclinical studies rituximab augmented CD19 CAR T-cell function, increasing tumor reduction and survival in murine models via synergistic targeting with CAR T cells³ T-cell lines transduced with anti-CD19 CAR elicited strong cytotoxicity against B-cell non-Hodgkin lymphoma cell
- lines and lymphoma cells isolated from patients³ - The addition of rituximab had a synergistic effect, without causing hematological side effects in vivo³
- ZUMA-14 is investigating the efficacy and safety of axi-cel plus rituximab in patients with refractory LBCL

Figure 1. Structure of Axi-Cel



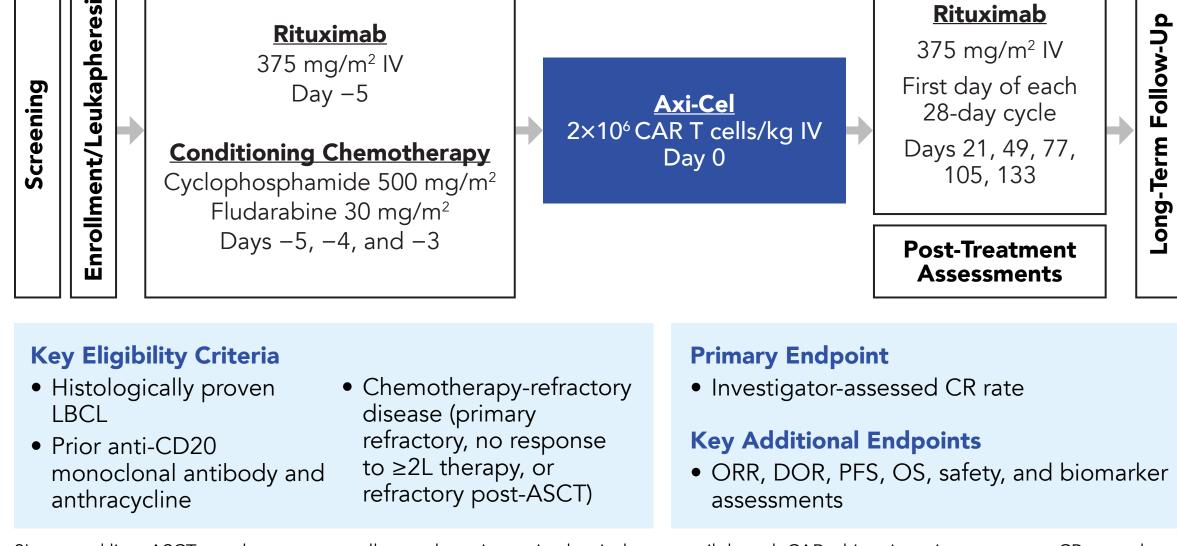
^a LDH>ULN per local laboratory reference range

OBJECTIVE

• To report outcomes of ZUMA-14, a Phase 2, multicenter study of axi-cel in combination with rituximab in patients with refractory LBCL after ≥2 lines of systemic therapy

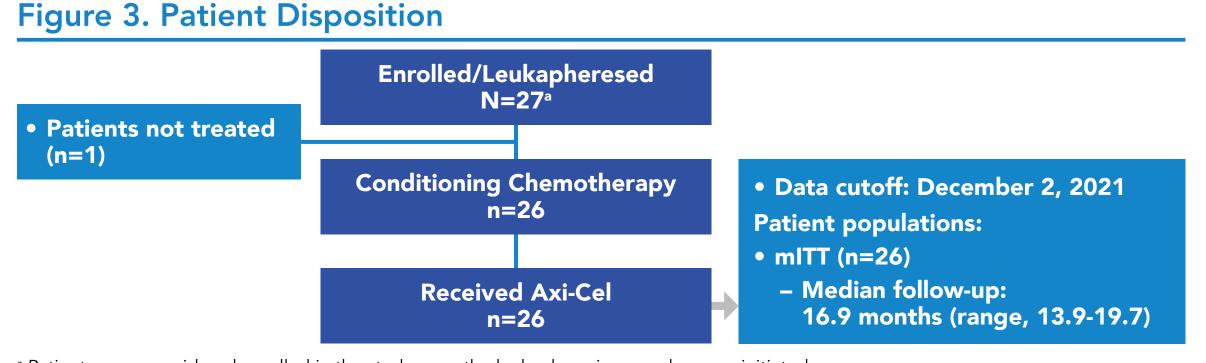
METHODS

Figure 2. ZUMA-14 Treatment Schema



2L, second line; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; IV, intravenous; LBCL, large B-cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

RESULTS



- ^a Patients were considered enrolled in the study once the leukapheresis procedure was initiated. Axi-cel, axicabtagene ciloleucel; mITT, modified intent-to-treat.
- Of the 26 patients treated with rituximab after axi-cel, 15 patients completed treatment while 11 patients did not, 1 due to an adverse event and 10 due to progressive disease - The median number of cycles of rituximab was 6 cycles

RESULTS (Continued)

Table 1. ZUMA-14 Baseline Characteristics

Characteristics	Axi-Cel + Rituximab (n=26)
Age, median (range), years ≥65 years	62.5 (38-82) 12 (46)
Male, n (%)	14 (54)
ECOG PS of 1, n (%)	14 (54)
Disease stage, n (%) / / V	2 (8)/3 (12) 5 (19)/16 (62)
Number of prior therapies, n (%) 1 2 ≥3	5 (19) 19 (73) 2 (8)
Prior transplant, n (%)	2 (8)
Extranodal disease, n (%)	16 (62)
Elevated LDH,ª n (%)	10 (38)
aalPl, n (%) 0/1/2	4 (15)/13 (50)/9 (35)
Primary refractory disease, n (%)	5 (19)

aalPI, age-adjusted International Prognostic Index; axi-cel, axicabtagene ciloleucel; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN upper limit of normal.

Table 2. Safety Summary

Parameter, n (%)	Axi-Cel + Rituximab (n=26)	Aı
Serious AEs	15 (58)	M
Worst Grade ≥3 cytopenias	22 (85)	-
Worst Grade ≥3 infections	5 (19)	,
Deaths Progressive disease	6 (23) 6 (23)	9
AE, adverse event; axi-cel, axicabtagene ciloleucel.	0 (23)	AI -

Table 3. Treatment-Emergent Adverse Events

	Axi-Cel + Rituximab (n=26)		
AE, n (%)	Any Grade	Grade ≥3	
Any AEa,b	26 (100)	24 (92)	
Pyrexia	25 (96)	0 (0)	
Neutrophil count decreased	17 (65)	16 (62)	
Hypotension	16 (62)	1 (4)	
Nausea	16 (62)	0 (0)	
Anemia	13 (50)	12 (46)	
Headache	13 (50)	0 (0)	
Confusional state	10 (38)	2 (8)	
Decreased appetite	10 (38)	1 (4)	
Fatigue	10 (38)	0 (0)	
Diarrhea	8 (31)	1 (4)	
Hypokalemia	8 (31)	1 (4)	
Tachycardia	8 (31)	1 (4)	
Prolonged cytopenias ^c	14 (54)	10 (38)	
Prolonged anemia	5 (19)	4 (15)	
Prolonged neutropenia	12 (46)	9 (35)	
Prolonged thrombocytopenia	3 (12)	3 (12)	

^a Any grade treatment-emergent AEs that occurred in >30% of patients. ^b AEs were coded using MedDRA version 24.1 and graded per National Cancer Institute CTCAE version 5.0. ^c Events present on or after Day 30 post-infusion. AE, adverse event; axi-cel, axicabtagene ciloleucel; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

- Six patients (23%) died during the study, all due to progressive disease
- Most patients (92%) experienced Grade ≥3 adverse events (AEs), and serious AEs were experienced by 58% of patients (**Table 3**) - One patient experienced a Grade 1 bacterial infection of furunculosis

Table 4. Cytokine Release Syndrome

Parameter	Axi-Cel + Rituximab (n=26)
Any grade CRS, n (%) ª Grade ≥3	25 (96) 0
Most common any grade symptoms of CRS, n (%) ^b Pyrexia Hypotension Sinus tachycardia	25 (100) 10 (40) 3 (12)
AE management for CRS, n (%) Tocilizumab Steroids ^c	20 (77) 8 (31)
Median time to onset (range), days	4 (1-7)
Median duration of events (range), days	5 (2-15)
Patients with resolved events by data cutoff, n/n (%)	25/25 (100)

^a CRS was graded per Lee DW, et al. *Blood*. 2014;124:188-195. Individual symptoms of CRS were graded per National Cancer Institute CTCAE version 5.0. b Any grade treatment-emergent AEs of interest, CRS, that occurred in >10% of patients. CNo corticosteroids were used prophylactically. AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.

 No patients experienced Grade ≥3 cytokine release syndrome (CRS; Table 4) • Median time to onset of CRS was 4 days (range, 1-7), with a median duration of 5 days (range, 2-15)

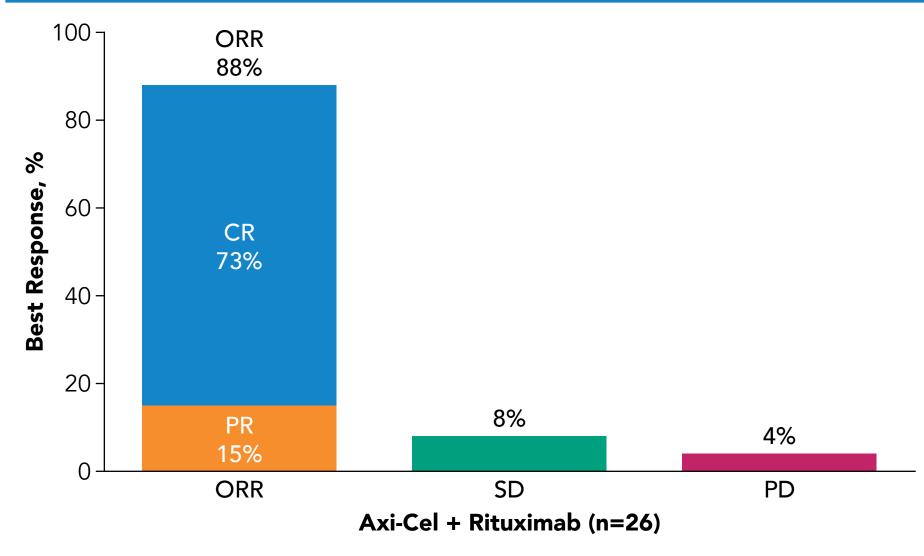
Table 5. Neurologic Events

Parameter	Axi-Cel + Rituximab (n=26)
Any grade NE, n (%)ª Grade ≥3	16 (62) 4 (15)
Most common any grade symptoms of NE, n (%) ^b Confusional state Tremor Agitation Aphasia Somnolence	10 (38) 7 (27) 5 (19) 3 (12) 3 (12)
AE management for NE, n (%) Tocilizumab Steroids	3 (12) 9 (35)
Median time to onset (range), days	6 (2-12)
Median duration of events (range), days	7 (1-39)
Patients with resolved events by data cutoff, n/n (%)	16/16 (100)
	<u>l</u>

^a AEs were coded using MedDRA version 24.1 and graded per National Cancer Institute CTCAE version 5.0. b Any grade treatment-emergent AEs of interest, NEs, that occurred in >10% of patients. AE, adverse event; axi-cel, axicabtagene ciloleucel; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NE, neurologic event.

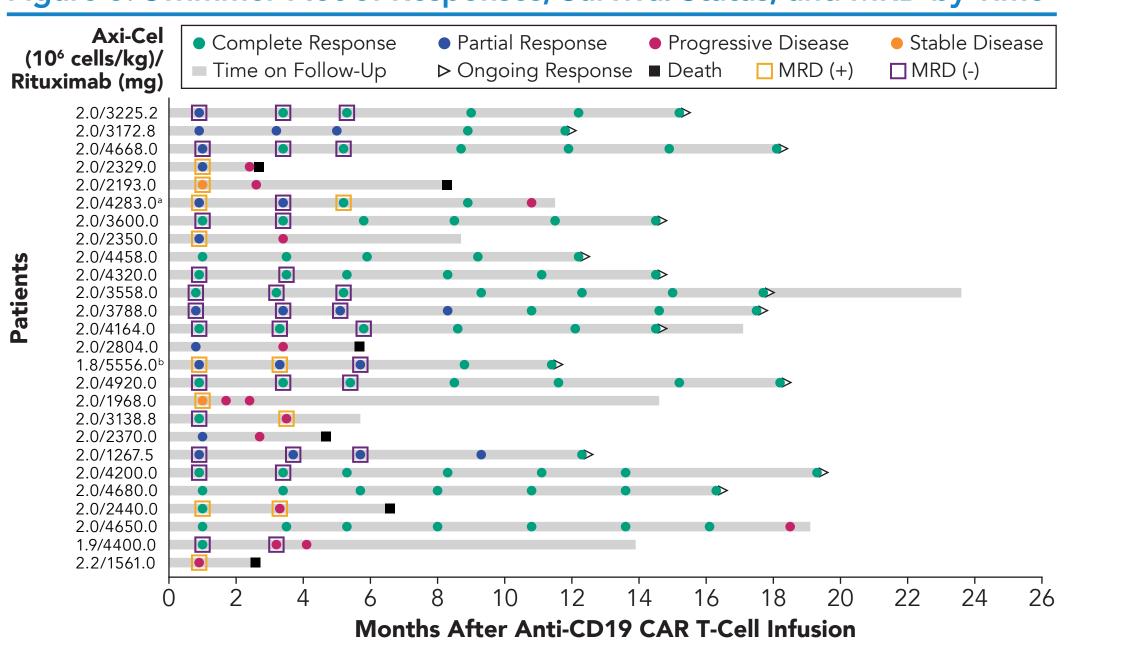
• Grade ≥3 neurologic events (NEs) occurred in 4 patients (15%), all were Grade 3 NEs • Median time to onset of NEs was 6 days (range, 2-12), with a median duration of 7 days (range, 1-39)

igure 4. ORR Was 88% With a CR Rate of 73%



Axi-cel, axicabtagene ciloleucel; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

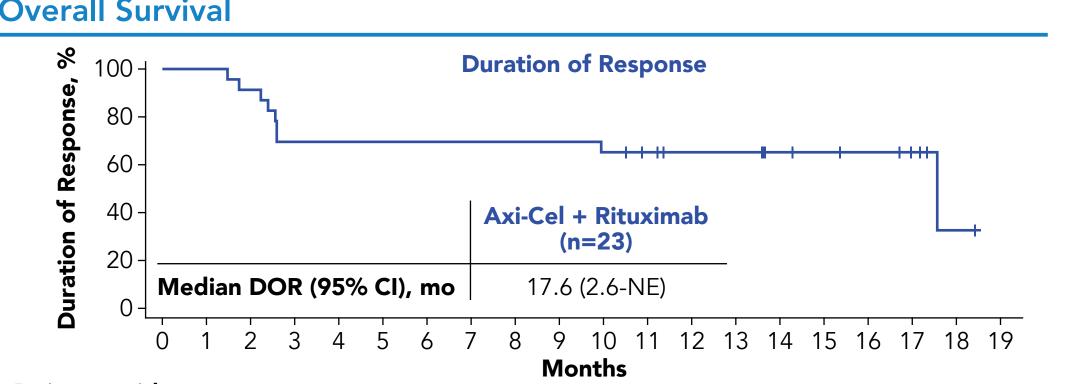
- The ORR was 88% (95% CI, 70-98), and the CR rate was 73% (95% CI, 52-88) (Figure 4)
- With a median follow-up of 16.9 months, 61% of the patients had ongoing response, all ongoing in CR



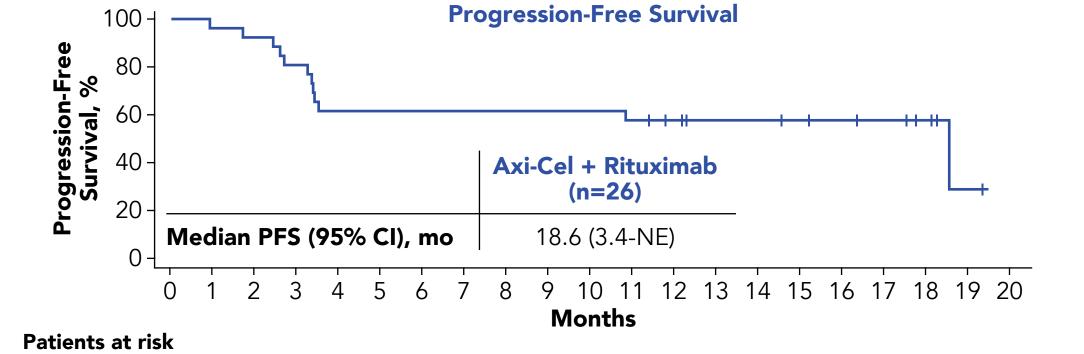
One partial response patient who converted to a complete response at Month 5 and later progressed at Month 11 had ^b MRD negativity at Month 6 in 1 partial response patient predicted a complete response conversion at Month 9. Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; MRD, minimal residual disease.

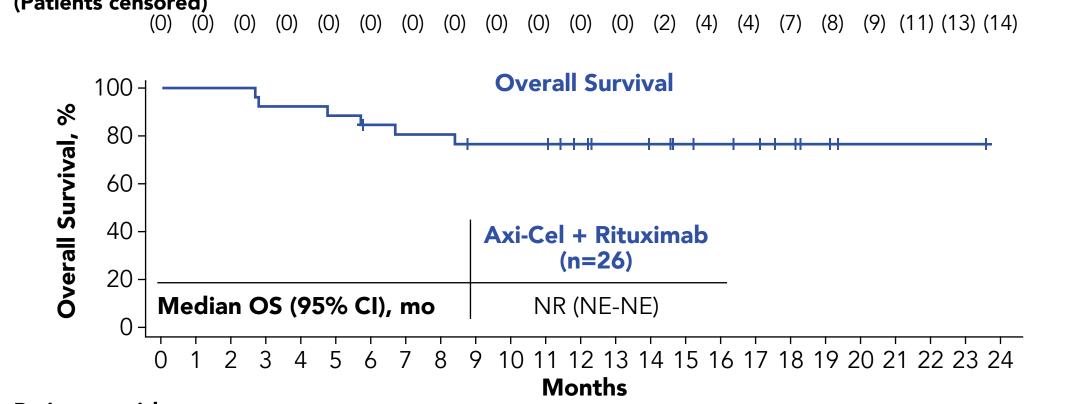
• Seven patients converted from a partial response/stable disease to CR ≥3 months post–axi-cel

Figure 6. Duration of Response, Progression-Free Survival, and



(Patients censored)

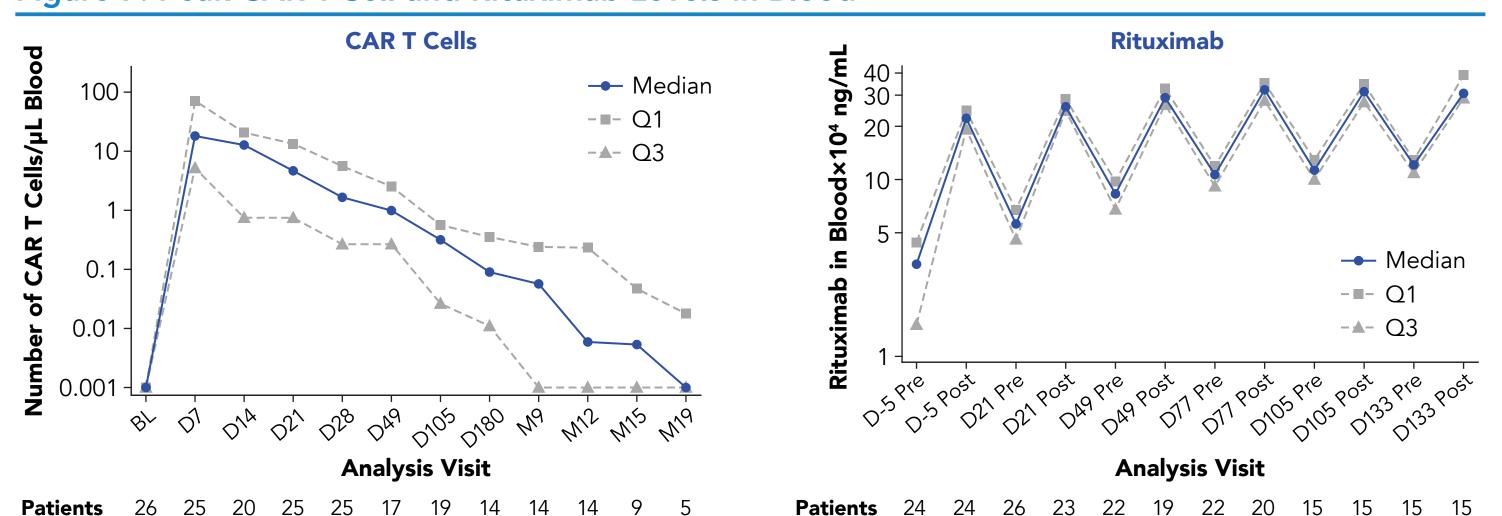




26 26 26 24 24 23 21 20 20 18 18 18 15 13 12 9 8 7 5 3 1 1 1 1 0 Axi-cel, axicabtagene ciloleucel; DOR, duration of response; mo, month; NE, not evaluable; NR, not reached; OS overall survival; PFS, progression-free survival.

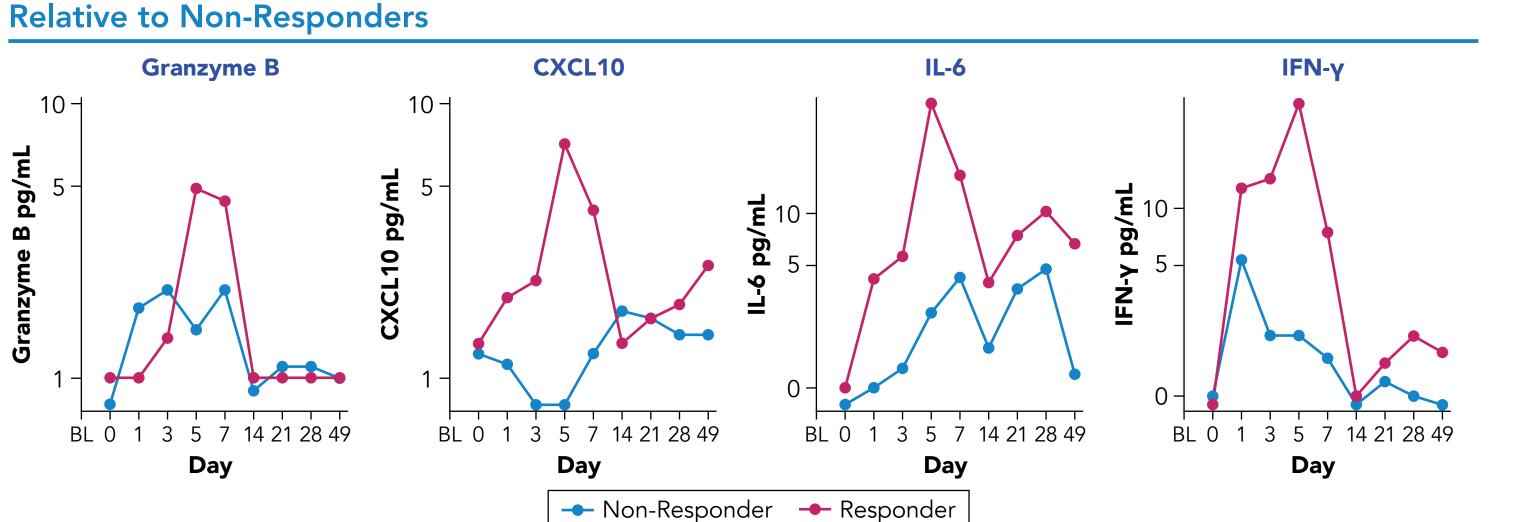
- The estimated duration of response rate at 12 months was 65% (95% CI, 42-81) • The estimated progression-free survival (PFS) rate at 12 months was 58% (95% CI, 37-74)
- The estimated 12-month overall survival rate was 77% (95% CI, 55-89), and 6 patients (23%) died of progressive disease

Figure 7. Peak CAR T-Cell and Rituximab Levels in Blood



Parameter, median (range)	ZUMA-14 (n=26) ^a	ZUMA-1 C1+2 (n=98) ^a
Peak, cells/μL	40.3 (13.6-95.9)	38.3 (14.7-83.0)
AUC ₀₋₂₈ , cells/μL×days	376.8 (136.3-895.3)	453.4 (148.7-920.3)
Time to peak, days	8 (8-8)	8 (8-15)

Figure 8. Key Cytokines Are Induced Following Axi-Cel and Rituximab Infusion in Responders

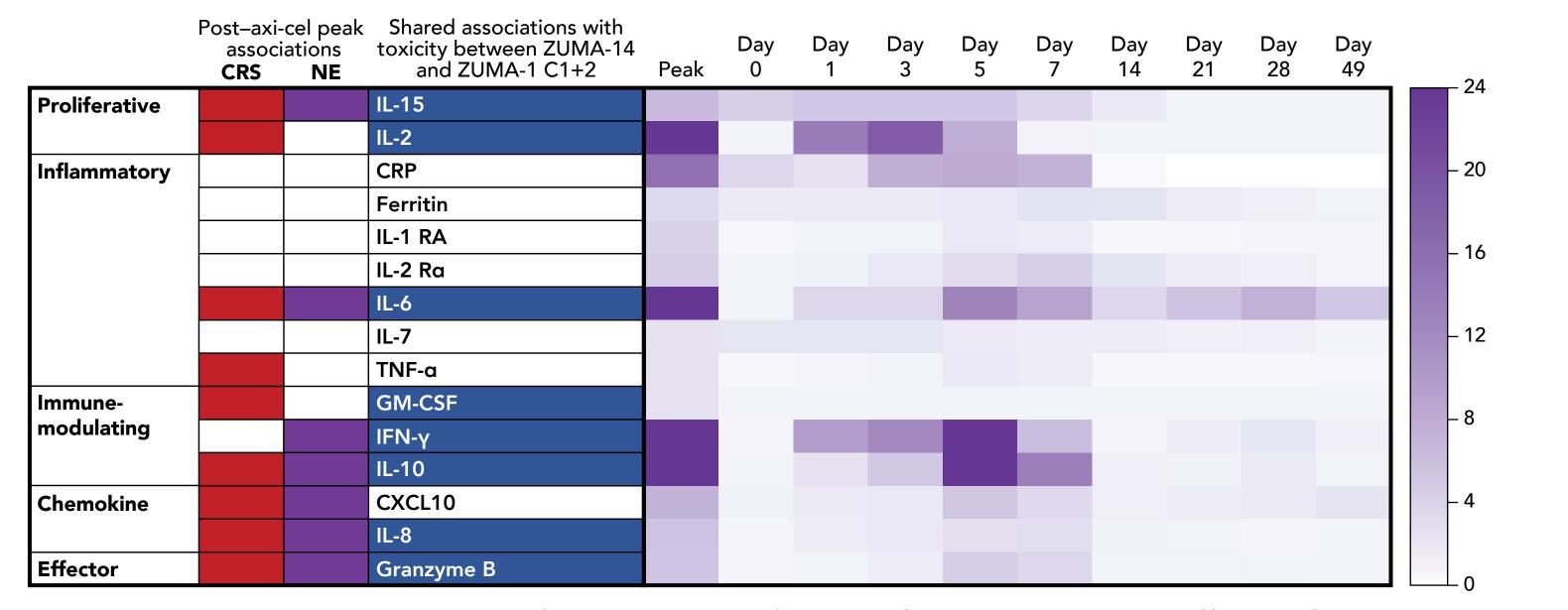


BL, baseline; CXCL, chemokine CXC ligand; IFN, interferon; IL, interleukin.

• Immune-modulating cytokines, including interleukin (IL)-6, chemokine CXC ligand (CXCL)10, and interferon (IFN)-γ, were induced in patients following axi-cel and subsequent rituximab infusion on Days 21 to 28 (Figure 8)

• In addition, granzyme B, IL-6, CXCL10, and IFN-γ were more prominently elevated in responders versus non-responders

Figure 9. Key Serum Cytokines Elevated Post Axi-Cel Infusion in Association With Safety Outcomes (CRS and NEs)



Heatmap shows serum analytes that are elevated post axi-cel infusion in >50% patients with fold change >2 from peak to baseline. The median of fold change from baseline at each post-baseline time point and peak were plotted. \dot{P} values were calculated from Wilcoxon rank sum test (only cytokines with P<.05 are shown). Axi-cel, axicabtagene ciloleucel; C, cohort; CRP, C-reactive protein; CRS, cytokine release syndrome; CXCL, chemokine CXC ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; NE, neurologic event; RA, receptor antagonist; TNF, tumor necrosis factor.

 Peak inflammatory and effector cytokines significantly associated with both Grade ≥2 CRS and NEs in ZUMA-14, including granzyme B IL-10, IL-6, and IL-8 (**Figure 9**), were also associated with Grade \geq 3 CRS and NEs in ZUMA-1 Cohorts 1+2⁴ IFN-γ was also associated with higher-grade NEs in ZUMA-1 Cohorts 1+2⁵

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CONCLUSIONS

- Results from ZUMA-14 demonstrated that axi-cel in combination with rituximab elicited a high CR rate and durable PFS in patients with refractory LBCL
- ORR was 88%, the CR rate was 73%, and the median PFS was 18.6 months
- The safety profile of axi-cel in combination with rituximab was manageable, with no new safety signals detected
- No patients experienced a Grade ≥3 CRS event, whereas Grade ≥3 NEs occurred in 15% of patients
- Peak CAR T-cell levels and pharmacodynamic findings in ZUMA-14 appear to be consistent with those observed in ZUMA-1
- Peak inflammatory and effector cytokines significantly associated with both CRS and NEs in the present study were also induced in ZUMA-14
- Overall, axi-cel in combination with rituximab in patients with R/R LBCL showed encouraging activity with a manageable safety profile

REFERENCES

Peak CAR T-cell levels in ZUMA-14

rituximab levels were elevated in

responders versus non-responders

were comparable to ZUMA-1

Peak and area under the curve

(Figure 7)

(data not shown)

1. YESCARTA® (axicabtagene ciloleucel) [Prescribing information]. Kite Pharma, Inc; 2021 2. Locke FL, et al. Lancet Oncol. 2019;20:31-42. 3. Mihara K, et al. Br J Haematol. 2010;151(1):37-46 4. Neelapu SS, et al. N Engl J Med. 2017;377(26):2531-2544. 5. Locke FL, et al. *Blood Adv.* 2020;4(19):4898-4911.

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PS: consulting or advisory role with Roche-Genentech, Hutchison Medipharma, ADC Therapeutics, TG

DISCLOSURES

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