Abstract 7567

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

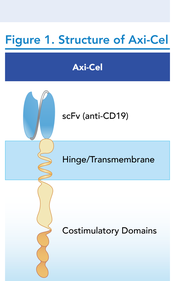
Paolo Strati, MD[1]; Lori Leslie, MD[2]; Parveen Shiraz, MD[3]; Elizabeth Budde, MD, PhD[4]; Olalekan O. Oluwole, MBBS, MPH[5]; Matthew Ulrickson, MD[6]; Aravind Ramakrishnan, MD[7]; Jennifer Sun, MS[8]; Rhine Shen, PhD[8]; Justyna Kanska, PhD[8]; Peter McCroskery, MD, MS[8]; Jinghui Dong, PhD[8]; Marco Schupp, MD[8]; Hairong Xu, MD, PhD[8]; and Krish Patel, MD[9]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]John Theurer Cancer Center, Hackensack, NJ, USA; [3]Stanford University, CA, USA; [4]City of Hope National Medical Center, Duarte, CA, USA; [5]Vanderbilt University Cancer Center, Nashville, TN, USA; [6]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [7]Texas Transplant Physician Group, Austin, TX, USA; [8]Kite, a Gilead Company, Santa Monica, CA, USA; and [9]Swedish Cancer Institute, Seattle, WA, USA

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 chemoimmunotherapy[1]
  - 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 refractory LBCL[2]
  - 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 cells[3]
  - T-cell lines transduced with anti-CD19 CAR saw strong cytotoxicity against B-cell non-Hodgkin lymphoma cell lines and lymphoma cells isolated from patients[3]
  - The addition of rituximab had a synergistic effect, without causing hematological side effects *in vivo*[3]
- ZUMA-14 is investigating the efficacy and safety of axi-cel plus rituximab in patients with refractory LBCL

Figure 1. Structure of Axi-Cel



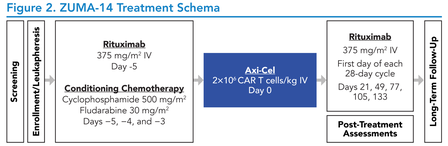
Axi-cel, axicabtagene ciloleucel; scFv, single-chain variable fragment.

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



Key Eligibility Criteria
- Histologically proven LBCL
- Prior anti-CD20 monoclonal antibody and anthracycline
- Chemotherapy-refractory disease (primary refractory, no response to ≥2L therapy, or refractory post-ASCT)

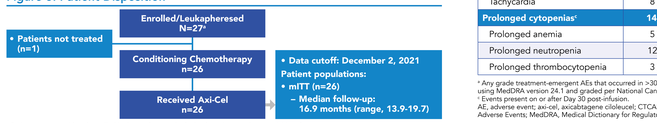
Primary Endpoint
- Investigator-assessed CR rate

Key Additional Endpoints
- ORR, DOR, PFS, OS, safety, and biomarker assessments

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

Figure 3. Patient Disposition



[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	62.5 (38–82)
≥65 years	12 (46)
Male, n (%)	14 (54)
ECOG PS of 1, n (%)	14 (54)
Disease stage, n (%)	
I/II	2 (8)/3 (12)
III/IV	5 (19)/16 (62)
Number of prior therapies, n (%)	
1	5 (19)
2	19 (73)
≥3	2 (8)
Prior transplant, n (%)	2 (8)
Extranodal disease, n (%)	16 (62)
Elevated LDH,[a] n (%)	10 (38)
aaIPI, n (%)	
0/1/2	4 (15)/13 (50)/9 (35)
Primary refractory disease, n (%)	5 (19)

[a] LDH>ULN per local laboratory reference range.
aaIPI, 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)
Serious AEs	15 (58)
Worst Grade ≥3 cytopenias	22 (85)
Worst Grade ≥3 infections	5 (19)
Deaths	6 (23)
Progressive disease	6 (23)

AE, adverse event; axi-cel, axicabtagene ciloleucel.

Table 3. Treatment-Emergent Adverse Events

	Axi-Cel + Rituximab (n=26)	
AE, n (%)	**Any Grade**	**Grade ≥3**
Any AE[a,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 (**Table 2**)
- 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]	25 (96)
Grade ≥3	0
Most common any grade symptoms of CRS, n (%)[b]	
Pyrexia	25 (100)
Hypotension	10 (40)
Sinus tachycardia	3 (12)
AE management for CRS, n (%)	
Tocilizumab	20 (77)
Steroids[c]	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. [c] No 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)

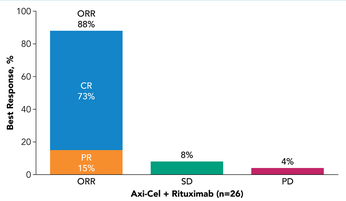
Table 5. Neurologic Events

Parameter	Axi-Cel + Rituximab (n=26)
Any grade NE, n (%)[a]	16 (62)
Grade ≥3	4 (15)
Most common any grade symptoms of NE, n (%)[b]	
Confusional state	10 (38)
Tremor	7 (27)
Agitation	5 (19)
Aphasia	3 (12)
Somnolence	3 (12)
AE management for NE, n (%)	
Tocilizumab	3 (12)
Steroids	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)

[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 (**Table 5**)
- Median time to onset of NEs was 6 days (range, 2-12), with a median duration of 7 days (range, 1-39)

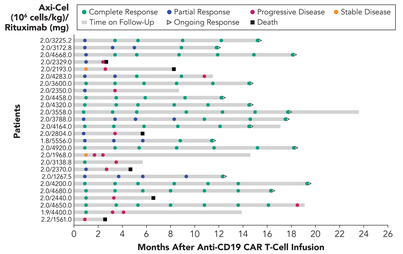
Figure 4. ORR Was 88% With a CR Rate of 73%



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

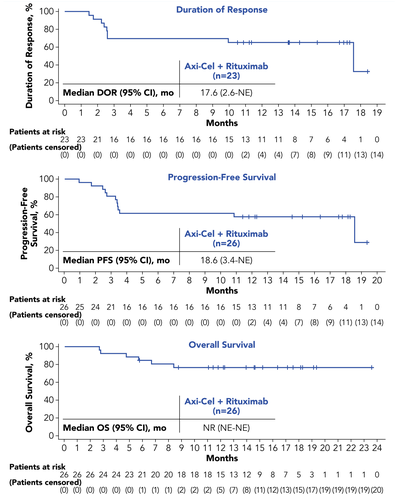
Figure 5. Swimmer Plot of Responses and Survival Status by Time



Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor.

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

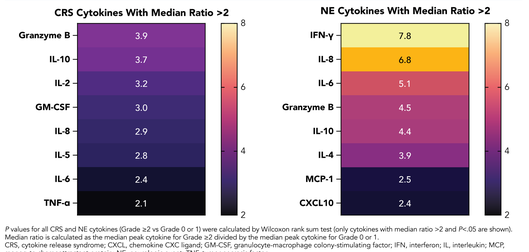
Figure 6. Duration of Response, Progression-Free Survival, and Overall Survival



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

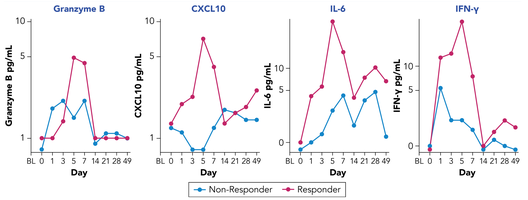
Figure 7. Association of Serum Cytokines With Safety Outcomes (CRS and NE)



P values for all CRS and NE cytokines (Grade ≥2 vs Grade 0 or 1) were calculated by Wilcoxon rank sum test (only cytokines with median ratio >2 and *P*<.05 are shown). Median ratio is calculated as the median peak cytokine for Grade ≥2 divided by the median peak cytokine for Grade 0 or 1.
CRS, cytokine release syndrome; CXCL, chemokine CXC ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; NE, neurologic event; TNF, tumor necrosis factor.

- Peak inflammatory and effector cytokines significantly associated with both Grade ≥2 CRS and NEs in ZUMA-14, including higher granzyme B, interleukin (IL)-10, IL-6, and IL-8 (**Figure 7**), were also associated with Grade ≥3 CRS and NEs in ZUMA-1 Cohorts 1+2[4]
- Interferon (IFN)-γ and monocyte chemoattractant protein-1 were also associated with higher-grade NEs in ZUMA-1 Cohorts 1+2[4]

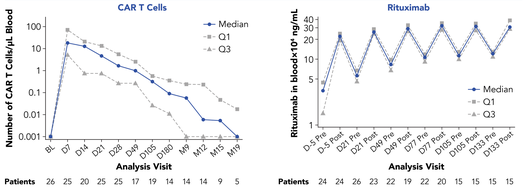
Figure 8. Key Cytokines Elevated In Responders Versus Non-Responders Post–Axi-Cel and Rituximab Infusion



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

- Immune-modulating cytokines, including IL-6, chemokine CXC ligand (CXCL)10, and 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. Peak CAR T-Cell and Rituximab Levels in Blood



Parameter, median (range)	ZUMA-14 (n=26)	ZUMA-1 C1+2 (n=98)
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)

AUC_{0-28}, area under curve (day 0 to day 28); BL, baseline; C, cohort; CAR, chimeric antigen receptor; D, day; M, month; Q, quartile.

- Peak CAR T-cell levels in ZUMA-14 were comparable to ZUMA-1 (**Figure 9**)
- Peak and area under the curve rituximab levels were elevated in responders versus non-responders (data not shown)

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-1[4]
- Overall, axi-cel in combination with rituximab in patients with R/R LBCL showed encouraging activity with a manageable safety profile

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