3-Year Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma

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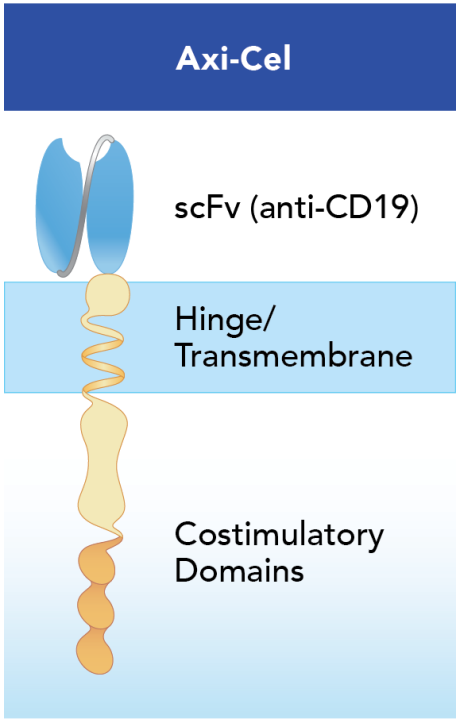
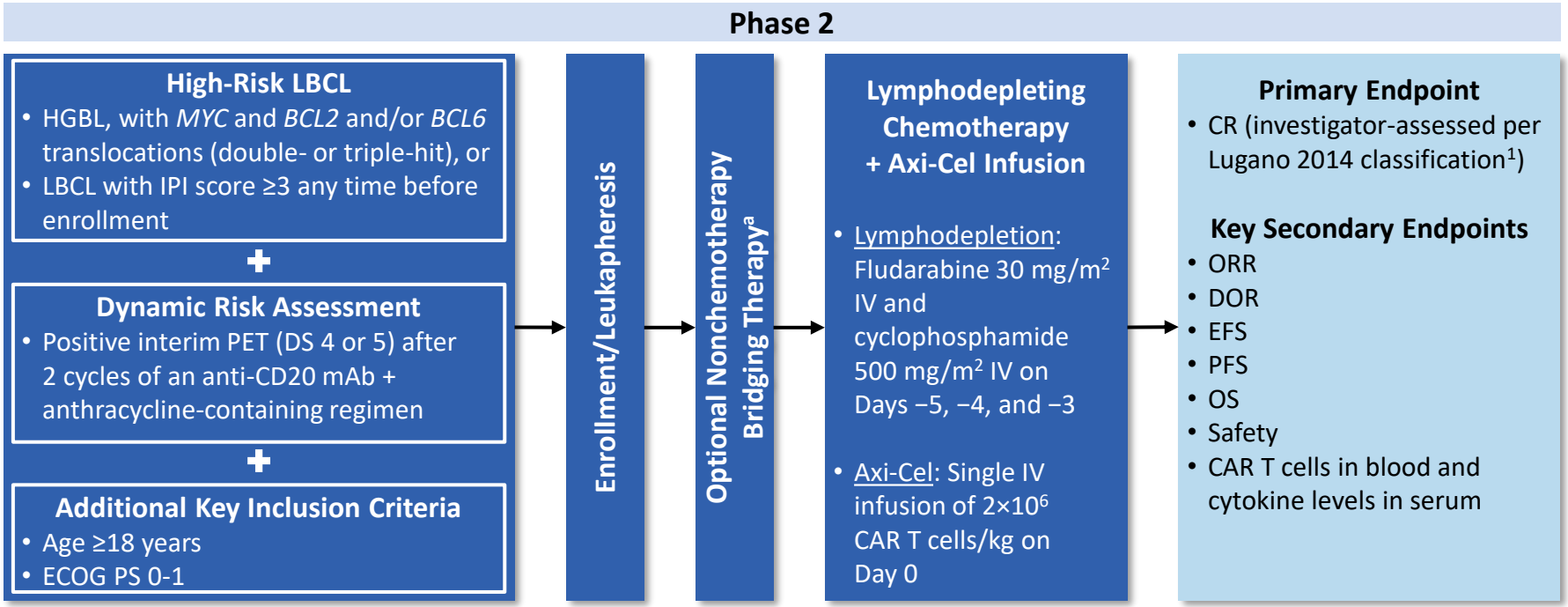
Background

- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of R/R LBCL[1,2]
- ZUMA-12 is a Phase 2, multicenter, open-label, single-arm study of axi-cel as part of first-line treatment in patients with high-risk LBCL[3]
  - In the primary efficacy analysis (n=37; median follow-up of 15.9 months), axi-cel demonstrated a high rate of durable responses with an investigator-assessed CR rate of 78% (95% CI, 62-90) and an ORR of 89% (95% CI, 75-97)[3]
  - Axi-cel also had a manageable safety profile, with no new safety signals observed in the first-line setting[3]
  - A higher frequency of CCR7+CD45RA+ T cells in axi-cel product and greater CAR T-cell expansion was observed in ZUMA-12, compared with ZUMA-1[3,4]
- Here we present updated efficacy and safety outcomes from ZUMA-12 in all patients treated with axi-cel after a median follow-up of ≥40 months



1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2022. 2. YESCARTA® (axicabtagene ciloleucel) [Summary of Product Characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2022. 3. Neelapu SS, et al. *Nat Med*. 2022;28:735-742. 4. Neelapu SS, et al. ASH 2021. Abstract 739.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CCR7, C-C chemokine receptor type 7; CR, complete response; LBCL, large B-cell lymphoma; ORR, objective response rate; R/R, relapsed/refractory; scFv, single-chain variable fragment.

ZUMA-12 Study Design



[a] Administered after leukapheresis and completed prior to initiating lymphodepleting chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

Study Analysis

Data Cutoff and Follow-Up

- Data cutoff date of the updated analysis: May 3, 2023
- The updated analysis occurred when the median follow-up in patients treated with axi-cel (n=40) was ≥40 months
  - At data cutoff, median follow-up for all patients treated with axi-cel was 40.9 months (range, 29.5-50.2)

Efficacy

- Assessed by investigators per Lugano classification[1] and reported in 37 patients who were efficacy-evaluable
  - The efficacy-evaluable analysis set consisted of enrolled patients who were treated with axi-cel at a dose of at least 1×10^6 anti-CD19 CAR T cells/kg and had a centrally confirmed disease type DHL/THL or LBCL with an IPI score ≥3

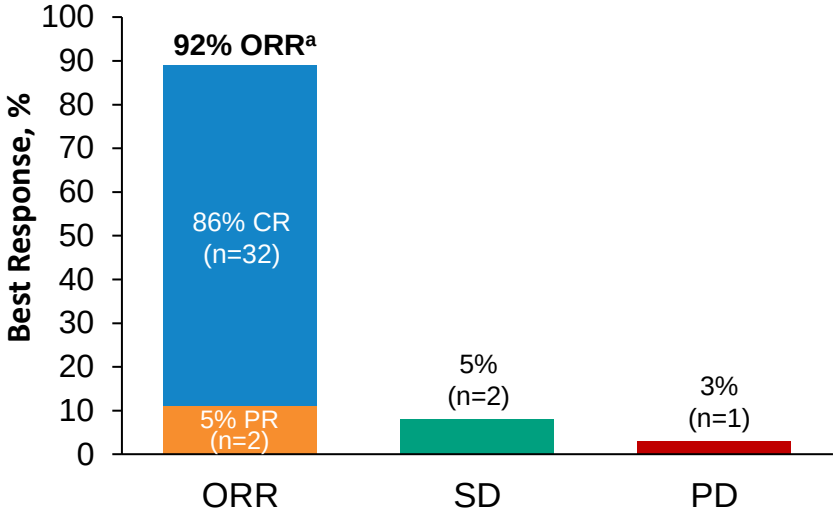
Safety and PK

- Reported in all patients treated with axi-cel (safety analysis set; n=40)

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DHL/THL, double-hit/triple-hit lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; PK, pharmacokinetics.

Objective Response Rate



	Efficacy Evaluable n=37[b]
Overall CR rate, % (95% CI)	86 (71-95)
DHL/THL and IPI score ≥3 (n/N)	4/4 100 (40-100)
DHL/THL only (n/N)	5/6 83 (36-100)
IPI score ≥3 only (n/N)	23/27 85 (66-96)
Patients converted from PR/SD to CR, n (%)	9 (24)
PR to CR	8 (22)
SD to CR	1 (3)

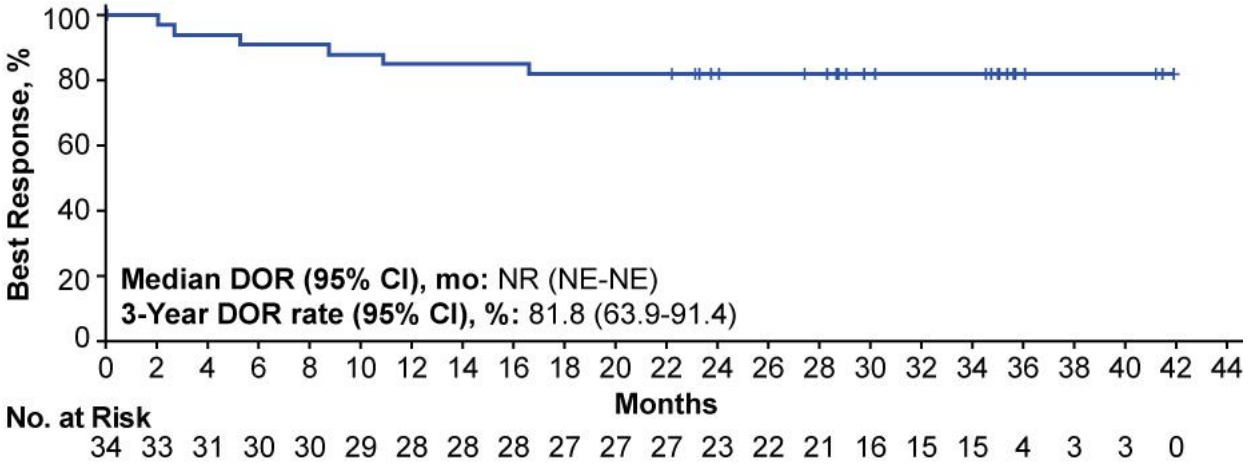
- In the efficacy-evaluable population, the CR rate was slightly higher than in the primary analysis[1] due to an additional number of patients converting from PR to CR
- Responses were ongoing in 73% of response-evaluable patients at data cutoff

[a] Response assessments are based on best overall response. [b] Includes all treated patients with centrally confirmed disease type (DHL/THL) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.

1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742.

CAR, chimeric antigen receptor; CR, complete response; DHL/THL, double-hit/triple-hit lymphoma; IPI, International Prognostic Index; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response[a]



	Efficacy Evaluable (n=37)
DOR rate, % (95% CI)	
3 months	93.9 (77.9-98.4)
9 months	87.9 (70.9-95.3)
15 months	84.8 (67.4-93.4)
18 months	81.8 (63.9-91.4)
24 months	81.8 (63.9-91.4)
36 months	81.8 (63.9-91.4)

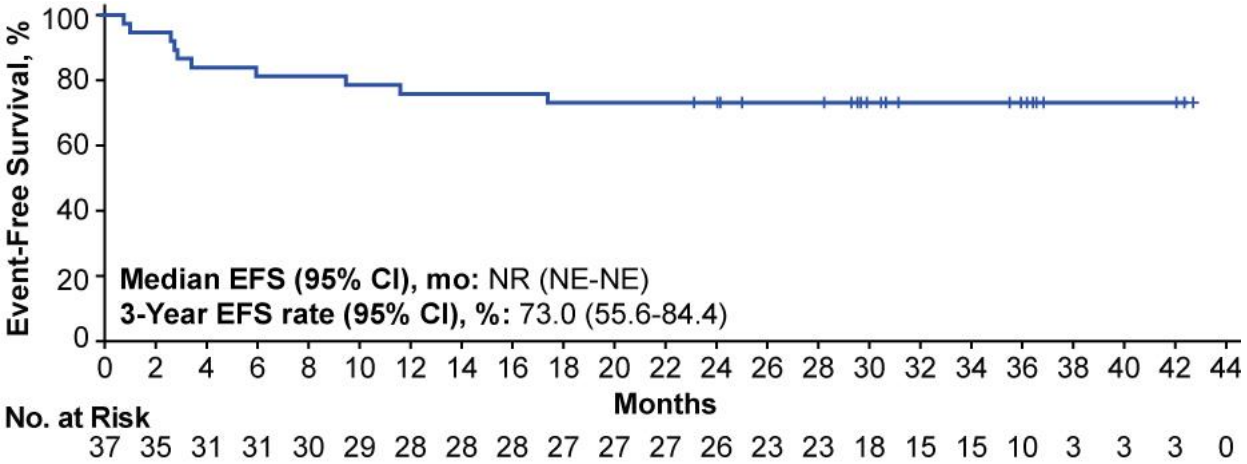
- With extended follow-up since the primary analysis,[1] median DOR was not reached in efficacy-evaluable patients
  - Among patients who achieved a CR as best response, the 3-year DOR rate was 84.4% (95% CI, 66.5-93.2)

[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.

1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742.

CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response, IPI, International Prognostic Index; NE, not evaluable; NR, not reached.

Event-Free Survival[a]



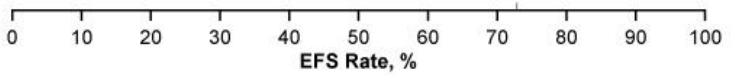
	Efficacy Evaluable (n=37)
EFS rate, % (95% CI)	
3 months	89.2 (73.7-95.8)
9 months	81.1 (64.4-90.5)
15 months	75.7 (58.5-86.5)
18 months	73.0 (55.6-84.4)
24 months	73.0 (55.6-84.4)
36 months	73.0 (55.6-84.4)

- Median EFS was not reached in efficacy-evaluable patients; the 3-year EFS rate was 73% (95% CI, 55.6-84.4) and a plateau in the curve emerged by Month 18
  - Among patients who achieved a CR as best response, the 3-year EFS rate was 84.4% (95% CI, 66.5-93.2)

[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.
CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; IPI, International Prognostic Index; NE, not evaluable; NR, not reached.

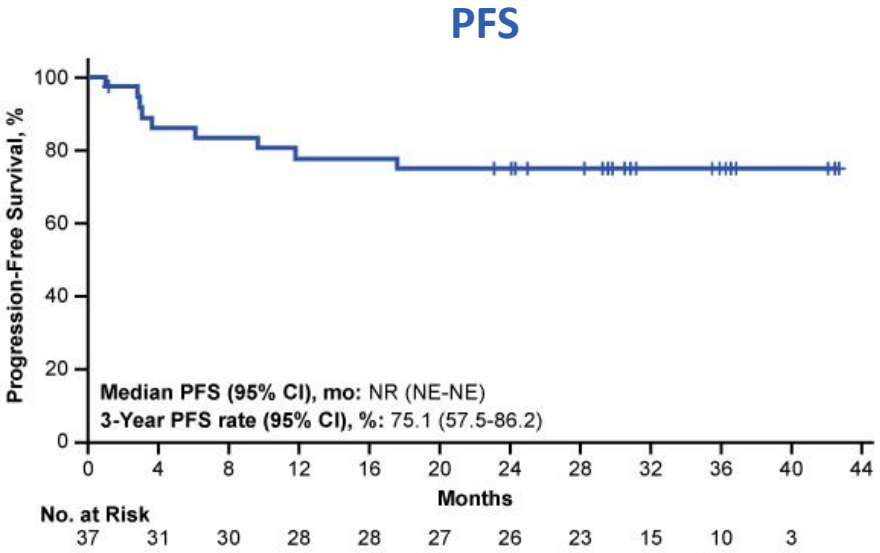
Event-Free Survival at 36 Months in Key LBCL Subgroups

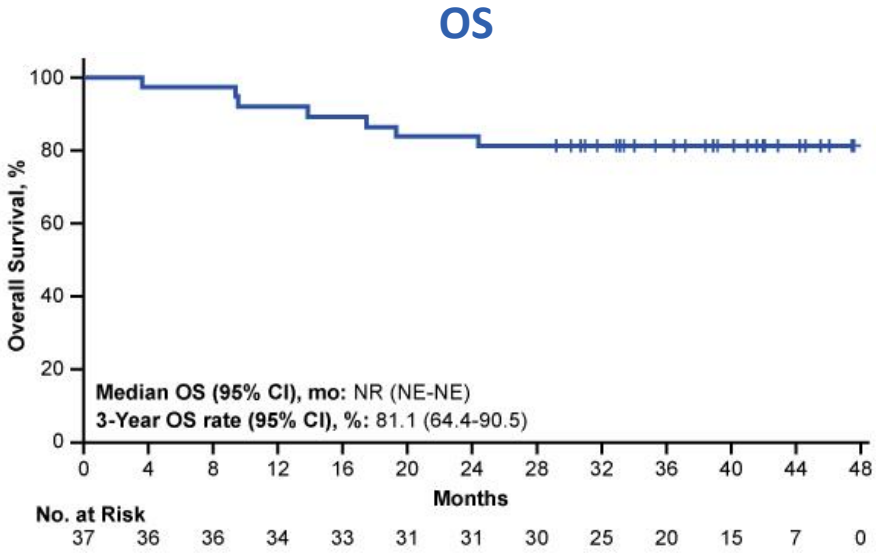
		No. of Patients	No. of Patients At Risk	EFS Rate (95% CI)
Overall		37	10	73.0 (55.6-84.4)
Age, years	<65	24	4	70.8 (48.4-84.9)
	≥65	13	6	76.9 (44.2-91.9)
Sex	Male	25	6	68.0 (46.1-82.5)
	Female	12	4	83.3 (48.2-95.6)
Double- or triple-hit status per central lab and IPI score	Double/triple-hit only	6	1	66.7 (19.5-90.4)
	IPI ≥3 only	27	7	70.4 (49.4-83.9)
	Double/triple-hit and IPI ≥3	4	2	100.0 (100.0-100.0)
Double- or triple-hit status per local lab	Double/triple-hit	13	4	84.6 (51.2-95.9)
	Neither double- nor triple-hit	20	6	70.0 (45.1-85.3)
ECOG performance status	0	15	5	80.0 (50.0-93.1)
	1	22	5	68.2 (44.6-83.4)
Deauville five-point scale	4	18	5	83.3 (56.8-94.3)
	5	19	5	63.2 (37.9-80.4)
Prior chemotherapy category	EPOCH	17	6	70.6 (43.1-86.6)
	R-CHOP	19	4	73.7 (47.9-88.1)
	Other	1	0	NE (NE-NE)
Best response to prior therapy	PR/SD	21	5	76.2 (51.9-89.3)
	PD	15	5	66.7 (37.5-84.6)



ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; NE, not evaluable; PD, progressive disease; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; SD, stable disease.

Progression-Free Survival and Overall Survival[a]





- Medians for PFS and OS were not reached in efficacy-evaluable patients
  - Among patients who achieved a CR as best response, the 3-year PFS and OS rates were 84.4% (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.
CAR, chimeric antigen receptor; CR, complete response; IPI, International Prognostic Index; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Adverse Events and Deaths

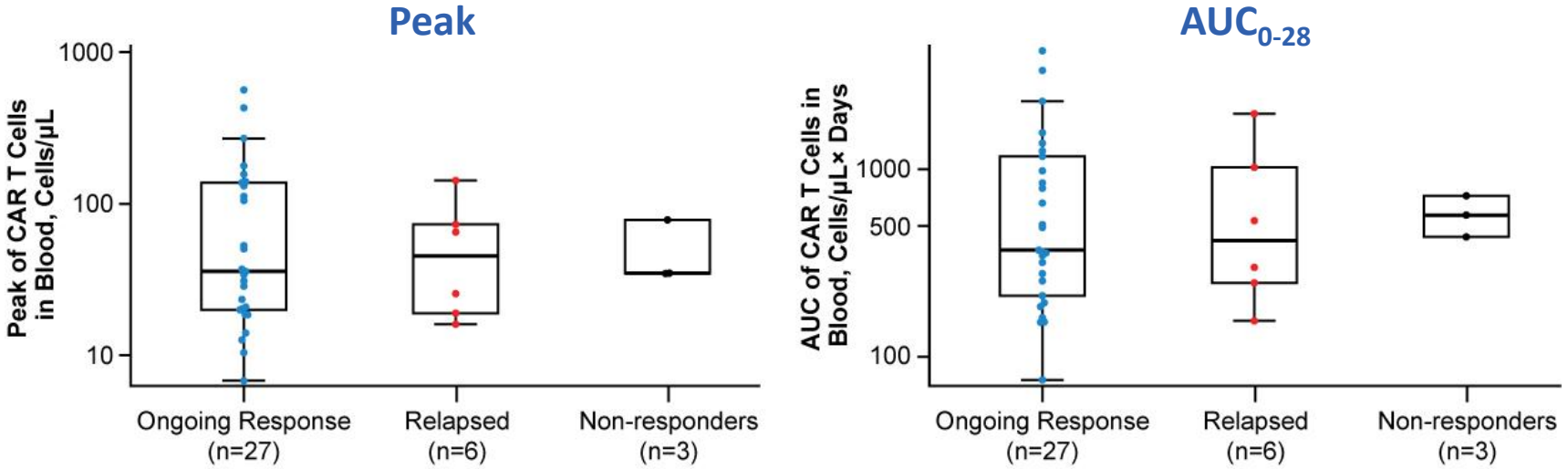
New TEAEs After Primary Analysis, n (%)	All Treated (N=40)
Any TEAE[a]	5 (13)
Grade ≥3	3 (8)
Serious TEAEs	3 (8)
Any infection/infestation	4 (10)
Grade ≥3	2 (5)
COVID-related infections	3 (8)
Device related infection	1 (3)
Sinusitis	1 (3)

- In total, there were 8 deaths in ZUMA-12
  - 5 were due to PD (1 occurring after the primary analysis data cutoff)[1]
  - 1 COVID-19 (Day 350; Grade 5 and unrelated to axi-cel)
  - 1 esophageal adenocarcinoma (Day 535, occurring after the primary analysis data cutoff; Grade 5 and unrelated to axi-cel)[1]
  - 1 septic shock (Day 287; unrelated to axi-cel)

- No new cases of CRS or neurologic events of any grade occurred since the prior data cut and all cases previously reported[1] were resolved by data cutoff
- Since the primary analysis,[1] prolonged cytopenia[b] of any grade occurred in only 1 patient and was resolved by data cutoff

[a] AEs were graded per CTCAE version 5.0. Neurologic events were identified based on modified Topp et al 2015.[2] CRS events were graded according to a modification of the criteria of Lee and colleagues.[3]
[b] Present on Day ≥30 post-infusion.
1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742. 2. Topp CW, et al. *Psychother Psychosom.* 2015;84:167-176. 3. Lee DW, et al. *Blood*. 2014;124:188-195.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; PD, progressive disease; TEAE, treatment-emergent adverse event.

CAR T-Cell Expansion by Ongoing Response



- Median post-infusion CAR T-cell expansion by peak and $AUC_{0\text{-}28}$ was 35.7 cells/µL and 368.0 cells/µL×days, respectively, in those with ongoing complete or partial response at the 30-month data cutoff date (n=27)
- Median post-infusion CAR T-cell expansion by peak and $AUC_{0\text{-}28}$ was 45.1 cells/µL and 413.4 cells/µL×days, respectively, in those who relapsed (n=6), and 34.7 cells/µL and 566.8 cells/µL×days in non-responders (n=3)

$AUC_{0\text{-}28}$, area under the curve from Days 0-28; CAR, chimeric antigen receptor.

Conclusions

- In this updated analysis of ZUMA-12, axi-cel demonstrated a high rate of durable responses
  - At data cutoff, with a median follow-up of ≥40 months, responses were ongoing in 73% of response-evaluable patients
  - Medians for DOR, EFS, PFS, and OS were not reached
- Safety outcomes were similar to previous reports,[1] with no new safety signals observed
- CAR T-cell expansion by peak and $AUC_{0\text{-}28}$ was consistent with the primary analysis[1]
- Axi-cel may benefit patients exposed to fewer prior therapies and those with high-risk LBCL, a population with high unmet need and poor outcomes after standard first-line chemoimmunotherapy
- Further investigation in randomized controlled trials is warranted in this patient population to determine the benefit of axi-cel as first-line therapy versus standard chemoimmunotherapy
  - ZUMA-23 (NCT05605899) is a Phase 3, randomized controlled study that will evaluate axi-cel as a first-line regimen versus standard of care in patients with high-risk LBCL[2]

1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742. 2. Westin et al. *J Clin Oncol.* 2023;41:TPS7578.

$AUC_{0\text{-}28}$, area under the curve from Days 0-28; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DOR, duration of response; EFS, event-free survival; LBCL, large B-cell lymphoma; OS, overall survival; PFS, progression-free survival.

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