Primary 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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Disclosures

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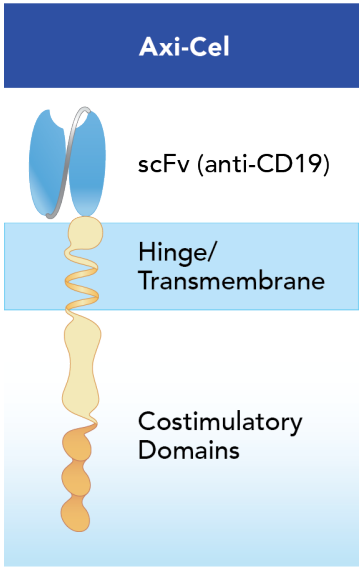
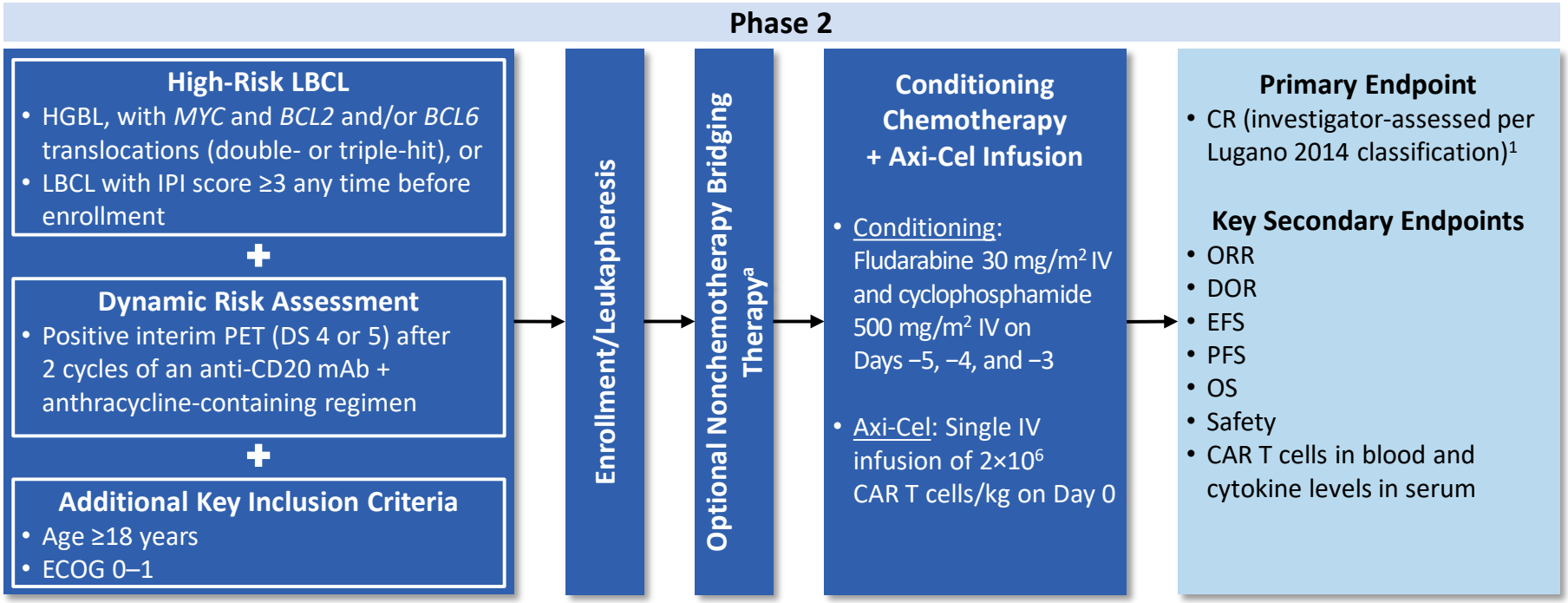
Background

- Patients with high-risk LBCL have poor outcomes, including lower response rates and poorer OS[1]
  - Patients with early disease resistance (assessed by dynamic PET) after first-line rituximab-based chemoimmunotherapy have an increased risk of death[2,3]
- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of adults with R/R LBCL and adults with R/R FL, both after ≥2 lines of systemic therapy[4,5]
  - A long-term follow-up analysis of axi-cel in refractory LBCL recently presented here at ASH 2021 demonstrated a 5-year OS rate of 43% after a median follow-up of 63 months[6]
- ZUMA-12 (NCT03761056) is a Phase 2, multicenter, open-label, single-arm study of axi-cel as part of first-line therapy in patients with high-risk LBCL
  - Presented here are efficacy, safety, and PK/PD results from the primary analysis of ZUMA-12



1. Sehn LH, et al. *New Engl J Med*. 2021;384:842-858. 2. Mamot C, et al. *J Clin Oncol*. 2015;33:2523-2529. 3. Casasnovas RO, et al. *Blood*. 2017;130:1315-1326. 4. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2021. 5. YESCARTA® (axicabtagene ciloleucel) [Summary of Product Characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2021. 6. Jacobson CA, et al. ASH 2021. #1764.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; FL, follicular lymphoma; LBCL, large B-cell lymphoma; OS, overall survival; PET, positron-emission tomography; PD, pharmacodynamic; PK, pharmacokinetic; R/R, relapsed/refractory; scFv, single-chain variable fragment.

ZUMA-12 Study Design

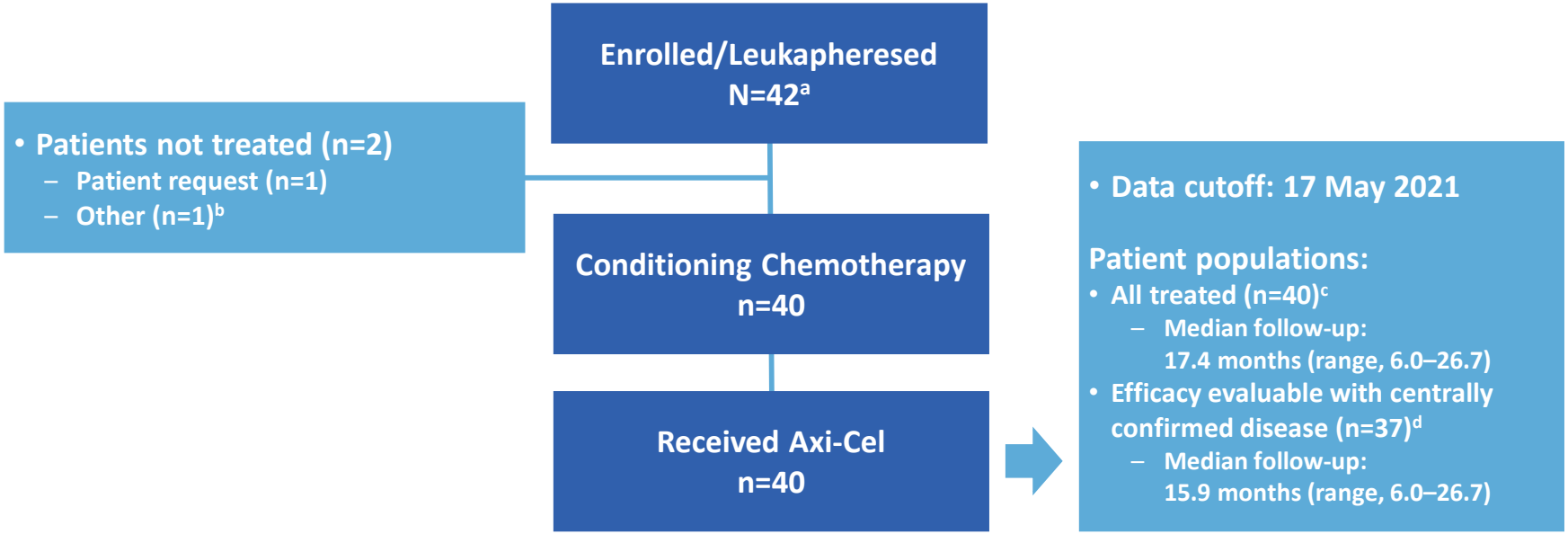


[a] Administered after leukapheresis and completed prior to initiating conditioning chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

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, 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.

ZUMA-12 Disposition



[a] Prior to conditioning chemotherapy, 7 patients received non-chemotherapy bridging therapy. [b] Patient was withdrawn from study due to additional biopsy which revealed a second primary tumor. [c] Includes all treated patients who received any dose of axi-cel. [d] Includes 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. Of all 40 treated patients, 3 were excluded from the efficacy analysis: 2 had an IPI score of 2 and neither double-/triple-hit lymphoma per central review; 1 patient had an IPI score of 2 and no central confirmation of disease type.

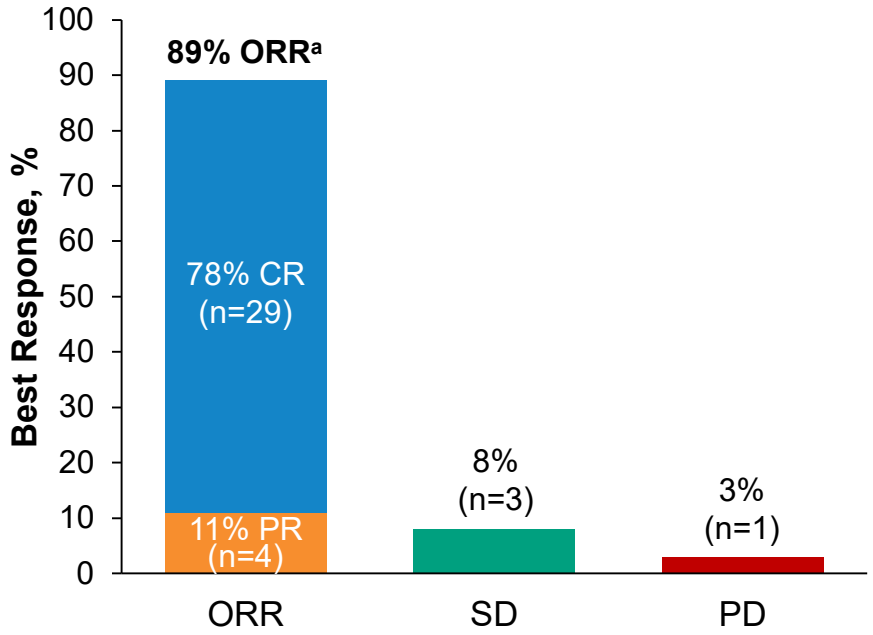
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; IPI, International Prognostic Index.

Baseline Patient Characteristics

Characteristic	All Treated (N=40)
Median age (range), years	61 (23–86)
≥65 years, n (%)	15 (38)
Male, n (%)	27 (68)
Disease stage III/IV, n (%)	38 (95)
ECOG 1, n (%)	25 (63)
1 Prior line of systemic therapy (2 cycles), n (%)	40 (100)
Best response of PR/SD to prior therapy[a]	23 (58)
Best response of PD to prior therapy[a]	16 (40)
Double- or triple-hit as determined by FISH per investigator, n (%)[b]	16 (40)
Double- or triple-hit as determined by FISH per central laboratory, n (%)[b]	10 (25)
IPI score ≥3, n (%)[c]	31 (78)
Deauville score 4, n (%)	19 (48)
Deauville score 5, n (%)	21 (53)

[a] One patient was not estimable for response to prior therapy. [b] Of 6 patients reported to be double- or triple-hit per investigator, 3 remained inconclusive, 1 was determined not to be double- or triple-hit, and 2 were not tested by the central laboratory. A total of 8 treated patients did not have central laboratory testing. [c] IPI score for eligibility was at the time of diagnosis or any time between diagnosis and enrollment.
ECOG, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IPI, International Prognostic Index; PD, progressive disease; PR, partial response; SD, stable disease.

ORR Was 89% (95% CI, 75–97) and CR Rate Was 78% (95% CI, 62–90) Among Efficacy-Evaluable Patients



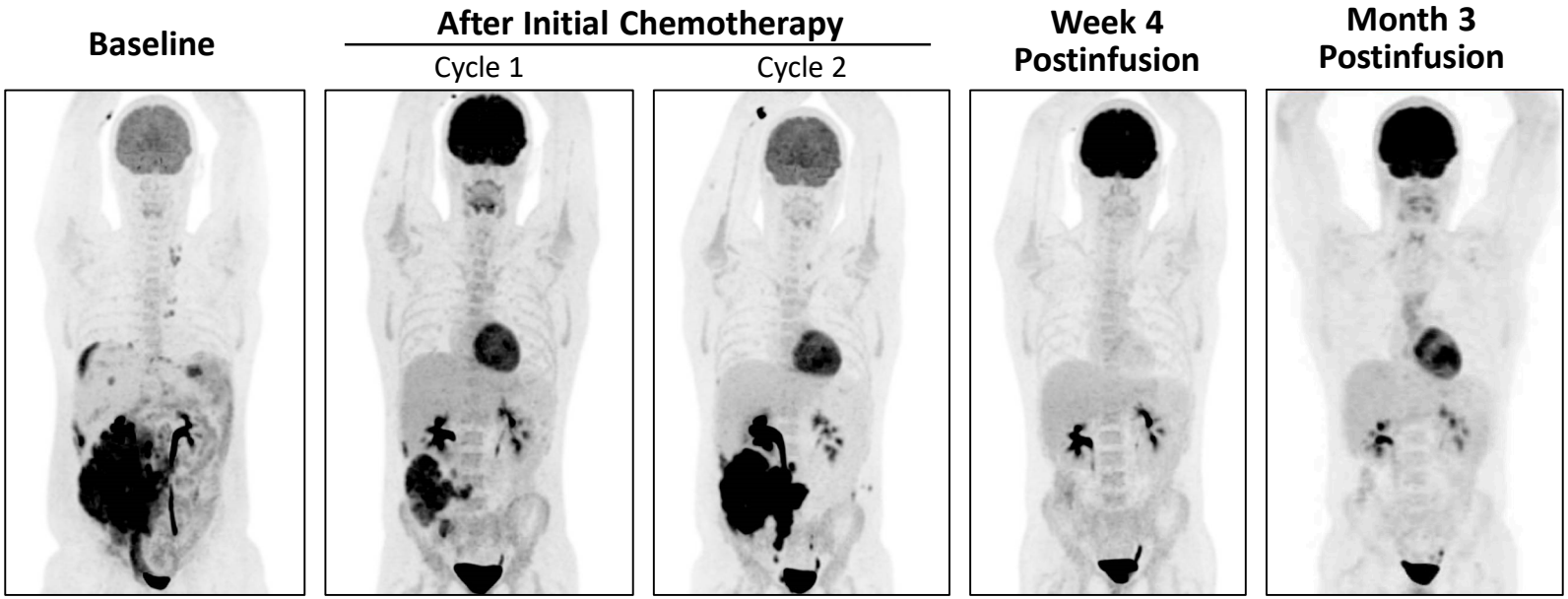
	Efficacy Evaluable N=37[b]
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)[c]	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

- Among all treated patients (N=40), ORR was 90% (95% CI, 76–97); CR rate was 80% (95% CI, 64–91)

[a] Response assessments are based on best overall response. [b] Includes 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.
[c] All 7 patients converted to a CR by Month 6 postinfusion.
CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Representative Images of a Complete Response

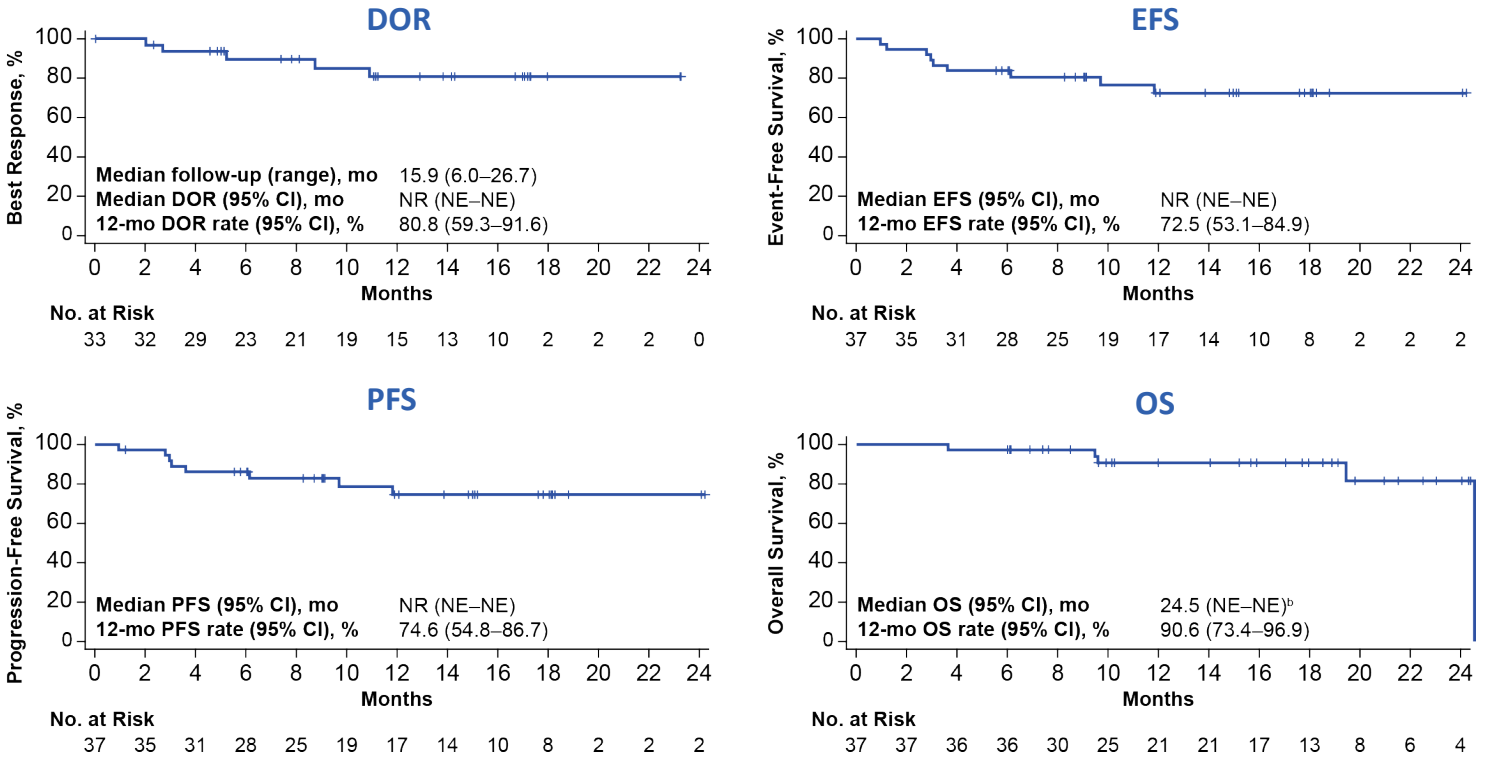
- 23-year-old male with HGBL-NOS per investigator (*MYC* rearrangement), IPI 3, and tumor burden (SPD) 7424 mm^2
- After axi-cel infusion, he achieved a CR at Month 3 and remains in response 7 months later



Patient images courtesy of Michael Dickinson.

Axi-cel, axicabtagene ciloleucel; CR, complete response; HGBL-NOS, high-grade B-cell lymphoma-not otherwise specified; IPI, International Prognostic Index; SPD, sum of product diameters.

Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival[a]

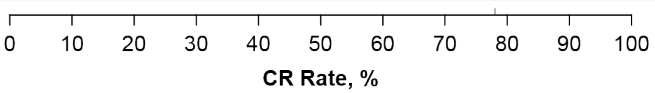


[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg. [b] One patient died after progression (cause of death was progression).

DOR, duration of response; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

CR Rate Was Consistent Among Key Subgroups[a]

		Evaluable Patients	Patients With a CR	CR Rate (95% CI)
Overall		37	29	78 (62-90)
Age, years	<65	24	17	71 (49-87)
	≥65	13	12	92 (64-100)
Sex	Male	25	18	72 (51-88)
	Female	12	11	92 (62-100)
Double- or triple-hit status per central lab and IPI score	Double- or triple-hit only	6	3	50 (12-88)
	IPI ≥3 only	27	22	81 (62-94)
	Double- or triple-hit and IPI ≥3	4	4	100 (40-100)
Double- or triple-hit status per local lab[b]	Double- or triple-hit	13	10	77 (46-95)
	Neither double- nor triple-hit	20	16	80 (56-94)
ECOG performance status	0	15	13	87 (60-98)
	1	22	16	73 (50-89)
Deauville five-point scale	4	18	15	83 (59-96)
	5	19	14	74 (49-91)
Prior therapy category	DA-EPOCH-R/EPOCH-R	17	13	76 (50-93)
	R-CHOP	19	15	79 (54-94)
	Other	1	1	100 (3-100)
Best response to prior therapy	PR/SD	21	17	81 (58-95)
	PD	15	11	73 (45-92)



[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. [b] The CR rate among patients with or without double- or triple-hit lymphoma per central laboratory was 70% (95% CI, 35-95) and 80% (95% CI, 56-94), respectively.

CR, complete response; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; PD, progressive disease; PR, partial response; SD, stable disease.

Treatment-Emergent Adverse Events

AE, n (%)[a]	All Treated (N=40)	
	Any-Grade	Grade ≥3
Any AE	40 (100)	34 (85)
Pyrexia	40 (100)	4 (10)
Headache	28 (70)	0 (0)
Neutrophil count decreased	22 (55)	21 (53)
Nausea	21 (53)	1 (3)
Diarrhea	20 (50)	0 (0)
Fatigue	20 (50)	0 (0)
White blood cell count decreased	18 (45)	17 (43)
Hypotension	14 (35)	1 (3)
Anemia	13 (33)	12 (30)

Parameter, n (%)	All Treated (N=40)
Serious AEs	18 (45)
Grade ≥3 cytopenias	27 (68)
Present on Day ≥30	8 (20)[b]
Grade ≥3 infections	6 (15)
COVID-related infections	3 (8)
Secondary malignancies	0 (0)
Deaths[c]	6 (15)
Progressive disease	4 (10)
AE (COVID-19)	1 (3)
Other (septic shock)[d]	1 (3)

- The most common axi-cel–related Grade ≥3 AEs were neutrophil count decrease (53%), white blood cell count decrease (43%), anemia (30%), encephalopathy (15%) and platelet count decrease (15%)
- One Grade 5 AE of COVID-19 occurred (Day 350 postinfusion; not related to treatment)

[a] Any-grade treatment-emergent AEs that occurred in >30% of patients. AEs were coded using MedDRA version 23.1 and graded per National Cancer Institute CTCAE version 5.0. [b] Of 8 patients with prolonged Grade ≥3 cytopenias, 7 had neutropenias. [c] The majority of deaths were due to progressive disease after proceeding to subsequent therapies (4/6; 67%). [d] Septic shock was reported after the patient had proceeded to subsequent therapy.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

Cytokine Release Syndrome

Parameter	All Treated (N=40)
Any grade CRS, n (%)[a]	40 (100)
Grade 3	3 (8)
Most common any-grade symptoms of CRS, n (%)	
Pyrexia	40 (100)
Hypotension	12 (30)
Chills	10 (25)
Hypoxia	9 (23)
AE management for CRS, n (%)	
Tocilizumab	25 (63)
Steroids	14 (35)
Vasopressors	1 (3)
Median time to onset (range), days	4 (1–10)
Median duration of events (range), days	6 (1–18)
Patients with resolved events by data cutoff, n/n (%)	40/40 (100)
Patients with resolved events by Day 14 post–axi-cel, n/n (%)	39/40 (98)

- No Grade 4 and 5 CRS occurred

[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.
AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.

Neurologic Events

Parameter	All Treated (N=40)
Any grade NE, n (%)[a]	29 (73)
Grade ≥3	9 (23)
Grade ≥2	15 (38)
Most common any-grade symptoms of NE, n (%)	
Confusional state	11 (28)
Encephalopathy	10 (25)
Tremor	10 (25)
AE management for NE, n (%)	
Steroids	13 (33)
Tocilizumab	1 (3)
Median time to onset (range), days	9 (2–44)
Median duration of events (range), days	7 (1–280)
Patients with resolved events by data cutoff, n/n (%)	28/29 (97)
Patients with resolved events by Day 21 post–axi-cel, n/n (%)	20/29 (69)

- Grade 4 NEs occurred in 2 patients (5%[b]); no Grade 5 NEs occurred
- One event of Grade 1 tremor was ongoing at data cutoff

[a] AEs were coded using MedDRA version 23.0 and graded per National Cancer Institute CTCAE version 5.0. [b] Both events were encephalopathy and both resolved by data cutoff.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NE, neurologic event.

Product Characteristics: Higher Frequency of CCR7+CD45RA+ T Cells in ZUMA-12 Compared With ZUMA-1

Parameter, Median (Range)	ZUMA-12[a] (N=40)	ZUMA-1 Cohort 1[b] (N=77)
Total no. of T cells infused×10^6	304 (165 –603)	295 (149–760)
Total no. of CAR T cells infused×10^6	165 (95–200)	160 (96–200)
Total no. of CCR7+CD45RA+ T cells[c] infused×10^6	105 (33–254)	40 (2–215)
CCR7+CD45RA+ T cells[c], %	35 (7–80)	14 (1–76)
Doubling time, days	1.6 (1.3–3.4)	1.5 (1.0–3.8)
IFN-γ, pg/mL	4013 (529–14,700)	5826 (858–17,800)

- Levels of CCR7+CD45RA+ T cells in preinfusion product have been associated with a favorable PK profile[1]
- Axi-cel was successfully manufactured for all 42 enrolled patients, with a median turnaround time of 18 days between leukapheresis and delivery to the trial site for treated patients

Median percent transduction rate, percent viability, and the CD4/CD8 ratio were consistent between ZUMA-12 and ZUMA-1 Phase 2 Cohort 1.

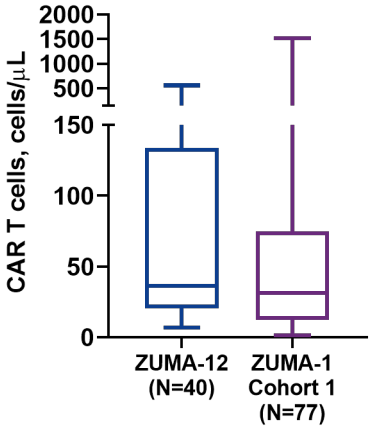
[a] ZUMA-12 includes all treated patients who received any dose of axi-cel. [b] ZUMA-1 Phase 2 Cohort 1 data are presented, as this cohort enrolled patients with DLBCL, including some with HGBL (though not an inclusion criterion). Data include all treated patients who received any dose of axi-cel and have ≥24 months of follow-up. [c] Data are reported based on the total number of T cells infused and not the CAR+ T-cell population.

1. Locke FL, et al. *Blood Adv*. 2020;4(19):4898-4911.

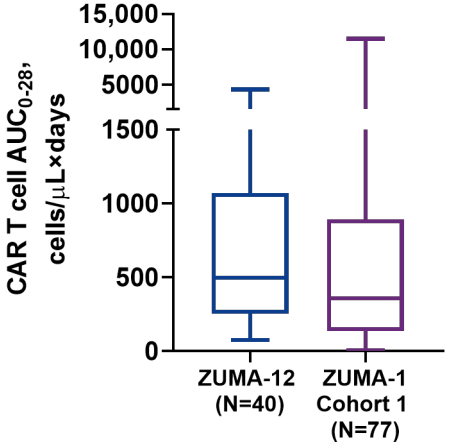
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CCR7, C-C chemokine receptor type 7; DLBCL, diffuse large B-cell lymphoma; HGBL, high grade B-cell lymphoma; IFN, interferon; PK, pharamacokinetic.

CAR T-Cell Expansion Appeared Greater in ZUMA-12 Compared With ZUMA-1

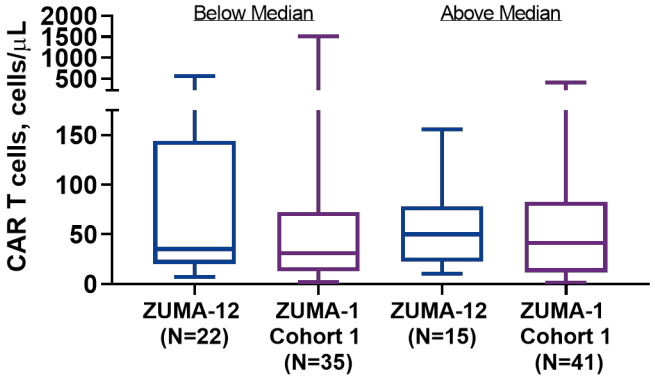
Peak



AUC_{0-28}



Peak by Tumor Burden Median[a]



	Min–Median	Median–Max
SPD, mm^2	171–3683.5	>3683.5–26,124

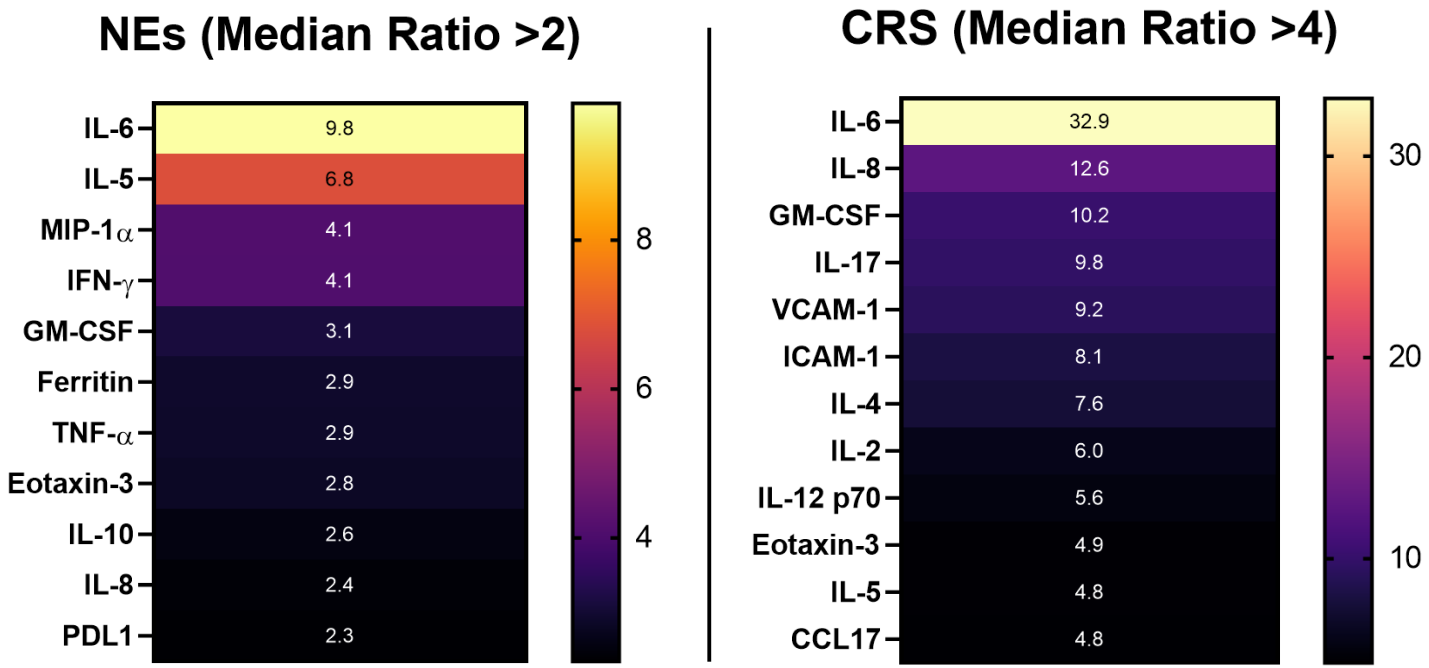
- Median tumor burden appeared lower in ZUMA-12 than in ZUMA-1 Cohort 1 (2778 mm^2 vs 3897 mm^2, respectively)
- Median time to peak levels of CAR T cells in blood was 8 days for ZUMA-12
- PK profiles were similar in patients with double- or triple-hit lymphoma and LBCL with IPI score ≥3

ZUMA-1 Phase 2 Cohort 1 includes all treated patients who received any dose of axi-cel and have ≥24 months of follow-up. Blood draws for CAR T-cell levels were collected prior to leukapheresis and on Day 7, Weeks 2 and 4, and Month 3. CAR T-cell concentrations were assessed by validated polymerase chain reaction enumerating gene-marked cells in blood.

[a] Tumor burden median was determined by the SPD of target lesions and is based on the median baseline tumor burden of pooled data from ZUMA-12 and ZUMA-1 Phase 2 Cohort 1.

AUC_{0-28}, area under the curve from Days 0-28; CAR, chimeric antigen receptor; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; PK, pharmacokinetic; SPD, sum of product diameters.

Median Peak Serum Analytes Associated With Grade ≥3 NEs or CRS in ZUMA-12 Are Consistent With Prior Findings in ZUMA-1[1]



Blood draws for cytokines were collected prior to leukapheresis, on Day 0 prior to administration of axi-cel, and on Days 1, 3, and 7 and Weeks 2 and 4. Cytokines associated with NEs and CRS were selected for having median ratio >2 after taking the ratio of median peak levels in Grade ≥3 events to Grade 2, Grade 1, or no events. The resultant values with ratio >2 for NEs and >4 for CRS are depicted.

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544.

Axi-cel, axicabtagene ciloleucel; CCL, chemokine ligand; CRS, cytokine release syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular cell adhesion molecule; IL, interleukin; IFN, interferon; NE, neurologic event; PDL1, programmed death ligand 1; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Conclusions

- ZUMA-12 is the first study evaluating CAR T-cell therapy as part of first-line therapy in high-risk LBCL, defined by both histology and/or IPI and dynamic risk assessment with PET scan
- Axi-cel demonstrated a high rate of rapid and durable responses in patients with an unmet medical need. In the primary analysis of ZUMA-12:
  - Efficacy-evaluable patients experienced a high ORR (89%) and CR rate (78%)
  - With a median follow-up of 15.9 months, 73% of patients remained in response at data cutoff
- The safety profile of axi-cel was manageable and no new safety signals were observed with axi-cel in an earlier line than previous reports[1]
- In ZUMA-12, higher frequency of CCR7+CD45RA+ T cells in axi-cel product was associated with greater CAR T-cell expansion than in ZUMA-1, suggestive of improved T-cell fitness in first-line treatment
- Overall, axi-cel may benefit patients exposed to fewer prior therapies and those with high-risk LBCL; further trials of axi-cel in first-line LBCL are warranted

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; ORR, objective response rate; PET, positron-emission tomography.

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