Poster
P089

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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BACKGROUND

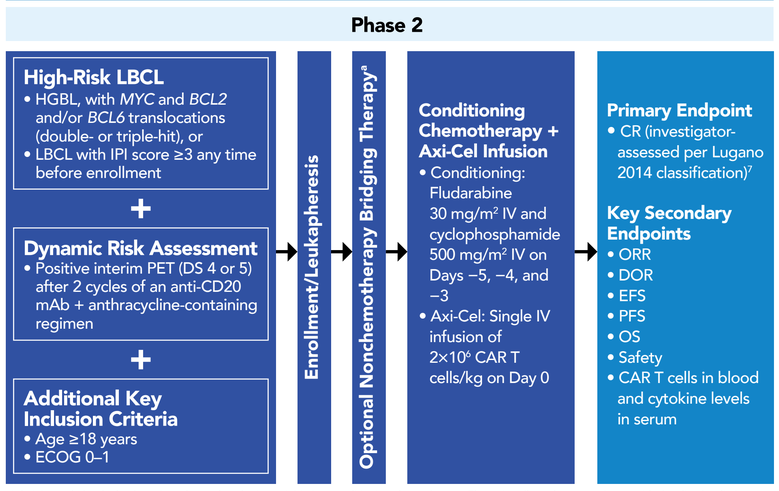
- Patients with high-risk large B-cell lymphoma (LBCL) have poor outcomes, including lower response rates and poorer overall survival (OS)[1]
  - Patients with early disease resistance (assessed by dynamic positron emission tomography [PET]) after first-line rituximab-based chemoimmunotherapy have an increased risk of death[2,3]
- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of adults with relapsed/refractory (R/R) LBCL and adults with R/R follicular lymphoma, both after ≥2 lines of systemic therapy[4,5]
  - A long-term follow-up analysis of axi-cel in refractory LBCL recently presented 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

OBJECTIVE

- To evaluate efficacy, safety, and pharmacokinetic (PK)/pharmacodynamic outcomes with axi-cel as part of first-line therapy in patients with high-risk LBCL

METHODS

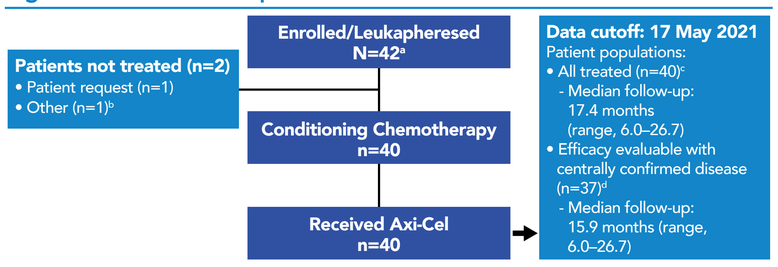
Figure 1. ZUMA-12 Study Design



[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.
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.

RESULTS

Figure 2. ZUMA-12 Disposition



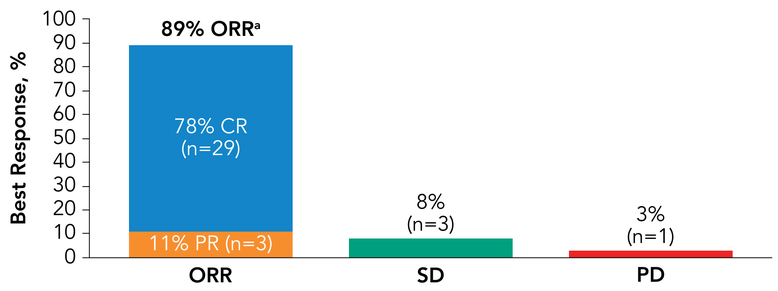
[a]Prior to conditioning chemotherapy, 7 patients received nonchemotherapy bridging therapy. [b]Patient was withdrawn from study due to additional biopsy that revealed a second primary tumor. [c]Includes all treated patients who received any dose of axi-cel. [d]Includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10⁶ 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.

Table 1. 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 per investigator, n (%)[b]	16 (40)
Double- or triple-hit 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]Double- or triple-hit status was determined by FISH. 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.

Figure 3. Objective Response and Best Response Among Efficacy-Evaluable Patients (N=37)



[a]Response assessments are based on best overall response. Analysis includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10⁶ CAR T cells/kg.
CAR, chimeric antigen receptor; CR, complete response; IPI, International Prognostic Index; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- Among all treated patients (N=40), the objective response rate (ORR) was 90% (95% CI, 76–97); the complete response (CR) rate was 80% (95% CI, 64–91)
- The CR rate was consistent among key subgroups of patient and disease characteristics

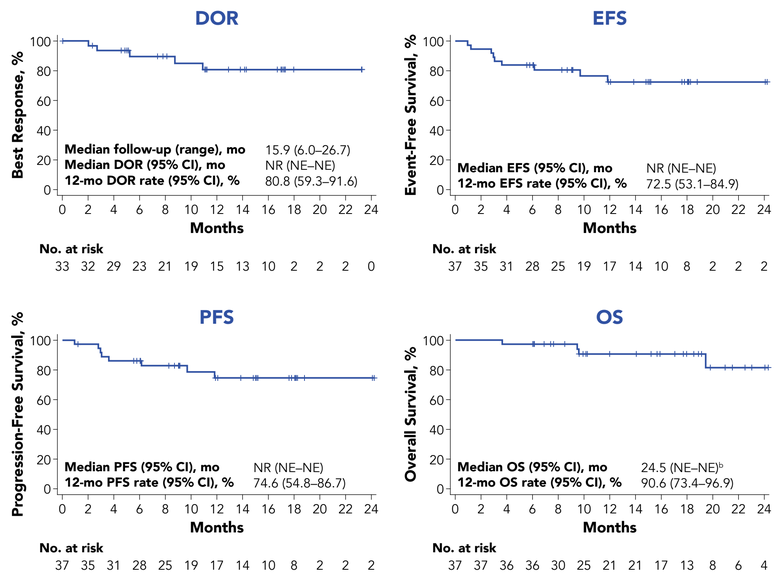
RESULTS *(Continued)*

Table 2. Follow-Up Time, Time to Response, and Conversion to CR

Characteristic	Efficacy Evaluable N=37[a]
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 (%)[b]	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

[a]Includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10⁶ CAR T cells/kg. [b]All 7 patients converted to a CR by Month 6 postinfusion.
CAR, chimeric antigen receptor; CR, complete response; IPI, International Prognostic Index; PR, partial response; SD, stable disease.

Figure 4. 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 ≥1×10⁶ CAR T cells/kg. [b]One patient died after progression after 24 months (cause of death was progression).
CAR, chimeric antigen receptor; DOR, duration of response; IPI, International Prognostic Index; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Table 3. Common Treatment-Emergent Adverse Events

AE, n (%)[a]	All Treated (N=40) Any-Grade	All Treated (N=40) 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)

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

Table 4. Additional Safety Results

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

[a]Of 8 patients with prolonged Grade ≥3 cytopenias, 7 had neutropenias. [b]The majority of deaths were due to progressive disease after proceeding to subsequent therapies (4/6; 67%). [c]Septic shock was reported after the patient had proceeded to subsequent therapy.
AE, adverse event.

- The most common axi-cel–related Grade ≥3 adverse events (AEs) were neutrophil count decrease (53%), white blood cell count decrease (43%), anemia (30%), encephalopathy (15%), and platelet count decrease (15%; **Table 3**)
- One Grade 5 AE of COVID-19 occurred (Day 350 postinfusion; not related to treatment; **Table 4**)

Table 5. Cytokine Release Syndrome and Neurologic Events

Parameter	All Treated (N=40) CRS	All Treated (N=40) NEs
Any grade, n (%)[a]	40 (100)	29 (73)
Grade ≥3	3 (8)	9 (23)
AE management, n (%)		
Tocilizumab	25 (63)	1 (3)
Steroids	14 (35)	13 (33)
Median time to onset (range), days	4 (1–10)	9 (2–44)
Median duration of events (range), days	6 (1–18)	7 (1–280)
Patients with resolved events by data cutoff, n/n (%)	40/40 (100)	28/29 (97)

[a]CRS was graded per Lee DW, et al[8]. NEs were coded using MedDRA version 23.0. NEs and 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; MedDRA, Medical Dictionary for Regulatory Activities; NE, neurologic event.

- No Grade 4 or 5 cytokine release syndrome (CRS) occurred (**Table 5**)
- Grade 4 neurologic events (NEs) occurred in 2 patients (5%, both events were encephalopathy, resolving by data cutoff); no Grade 5 NEs occurred (**Table 5**)
- One event of Grade 1 tremor was ongoing at data cutoff

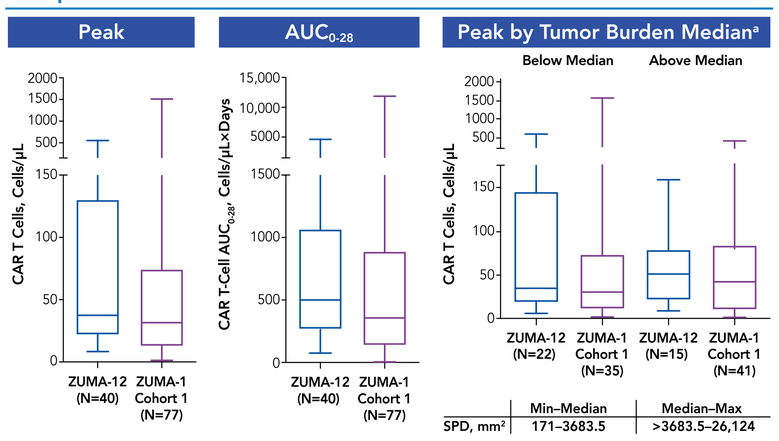
Table 6. Product Characteristics: Higher Frequency of CCR7+CD45RA+ T Cells in ZUMA-12 Compared With ZUMA-1

Parameter, Median (Range)	ZUMA-12[a] (N=40)	ZUMA-1 Cohort 1[b] (N=77)
Total no. of T cells infused×10⁶	304 (165 –603)	295 (149–760)
Total no. of CAR T cells infused×10⁶	165 (95–200)	160 (96–200)
Total no. of CCR7+CD45RA+ T cells[c] infused×10⁶	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)

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.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; IFN, interferon.

- Levels of CCR7+CD45RA+ T cells in preinfusion product have been associated with a favorable PK profile[9]
- 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

Figure 5. CAR T-Cell Expansion Appeared Greater in ZUMA-12 Compared With ZUMA-1



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

- Median tumor burden appeared lower in ZUMA-12 than in ZUMA-1 Cohort 1 (2778 mm² vs 3897 mm², respectively; **Figure 5**)
- 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 International Prognostic Index (IPI) score ≥3
- Median peak serum analytes associated with Grade ≥3 NEs or CRS in ZUMA-12 were consistent with prior findings in ZUMA-1[10]

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[10]
- 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

REFERENCES

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.
7. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.
8. Lee DW, et al. *Blood.* 2014;124:188-195.
9. Locke FL, et al. *Blood Adv.* 2020;4(19):4898-4911.
10. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544.
11. Neelapu SS, et al. ASH 2021. #739.

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