Yescarta® (axicabtagene ciloleucel)
Long-Term Follow-up of the ZUMA-1 Study

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Background

ZUMA-1 was a phase 1/2 multicenter, single-arm, open-label study which evaluated the safety and efficacy of axicabtagene ciloleucel (axi-cel) in patients with chemorefractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL).[1,2,3] This study enrolled 111 patients from 22 institutions in the US and Israel.[2] Manufacturing was successful for 110 patients and 101 of these patients were eventually treated (DLBCL, n=77; PMBCL/TFL, n=24).[2] The primary endpoint for Phase 1 was the incidence of dose-limiting toxicities.[3] The primary endpoint for Phase 2 was objective response rate (ORR) per investigator assessment. Secondary endpoints included overall response as assessed by independent review committee, duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and biomarker assessments.[3]

This response describes the results from the three-year, four-year and five-year follow-up of the pivotal ZUMA-1 study.[4,5,6] Only select data, summarized below, continued to be captured as part of this longer follow-up.

Results

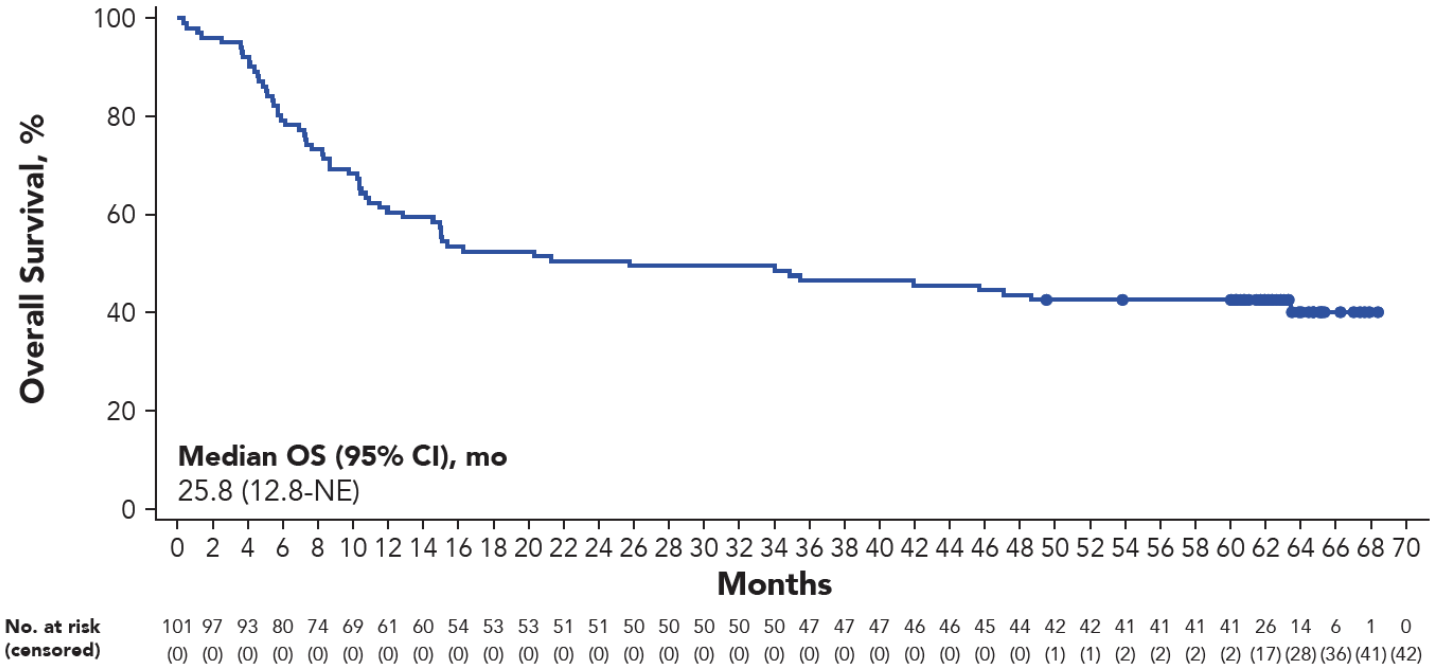
Efficacy

As reported previously, with a median follow-up of 39.1 months, the 3-year OS rate was 47%.[4] For the 101 patients with ≥4 years of follow-up (median, 51.1 months), the 4-year OS rate of 44% and a median OS of 25.8 months (95% confidence interval [CI]: 12.8–not evaluable [NE]) was seen in the modified intent-to-treat (mITT) population.[5] In the ITT population, median OS was 17.4 months with the 4-year OS rate of 41% in the ITT (n=111) population. Updated survival findings for the 101 patients with ≥5 years of follow-up (median, 63.1 months) were presented at the 2021 American Society of Hematology Annual Meeting. As shown in Figure 1, the 5-year OS rate of 42.6% (95% CI, 32.8–51.9) was

observed among the 101 patients with ≥5 years of follow-up in the mITT population.[6] Among complete responders, the 5-year OS rate was 64.4% (95% CI, 50.8–75.1), and the median OS was not reached (95% CI, 63.4 months–NE).[6] Since the 4-year data cutoff, 1 death at Month 63 (complete response [CR]) and 1 progressive disease (PD) at month 54 (partial response [PR]) were observed.[6] Table 1 further provides a summary of these findings across the 3-, 4-, and 5-year follow-up.

In the 5-year analysis, median time to next anticancer therapy (defined as time from axi-cel infusion to initiation of new anticancer therapy [including chimeric antigen receptor (CAR) T-cell retreatment and excluding stem cell transplantation] or death from any cause) was 8.7 months (range, 0.3–63.4 months).[6] A total of 34 patients (34%) were still alive with no subsequent therapy or axi-cel retreatment at the 5-year data cutoff. The 12-month event-free survival (EFS) rate was 42.8% (95% CI, 33.0–52.3) and the 24-month EFS rate was 37.7% (95% CI, 28.3–47.2).

Figure 1. ZUMA-1 Overall Survival with 5 Years of Follow-up (mITT, n=101)[6†]



†OS data should be interpreted with caution as single arm trials do not adequately characterize time-to-event endpoints. The statistical significance of OS is unknown.

Table 1. ZUMA-1 Overall Survival at Three-, Four-, and Five-Year Follow-up (mITT, n=101)[4,5,6]

	Years of Follow-up		
	Three	Four	Five
Median follow-up (months)	39.1	51.1	63.1
OS rate (%)	47	44	42.6

An exploratory analysis was conducted to evaluate the potential role of 12- and 24-month EFS as a surrogate endpoint for OS.[5] Results of the exploratory analysis showed that 5-year OS rates were 5.3% (95% CI, 1.4–13.2%) and 90.9% (95% CI, 77.6–96.5%) among patients with (n=57) and without (n=44) EFS at month 12.[5] Additionally, 5-year OS rates were 11.3% (95% CI, 5–20.5%) and 92.3% (95% CI, 78–97.5%) among patients with (n=62) and without (n=39) EFS at month 24.[6]

Safety

Since initiation of ZUMA-1, 58% of patients in the ITT population have died.[6] One death has occurred since the 5-year follow up.[6] No patients received intravenous (IV) immunoglobulin after the 5-year data cut-off date.[6] As of the 5-year data cut-off, no axi-cel-related serious adverse events (SAEs) or secondary malignancies have been reported.[6]

Table 2. ZUMA-1 Total Number and Primary Causes of Death Since Study Initiation[6]

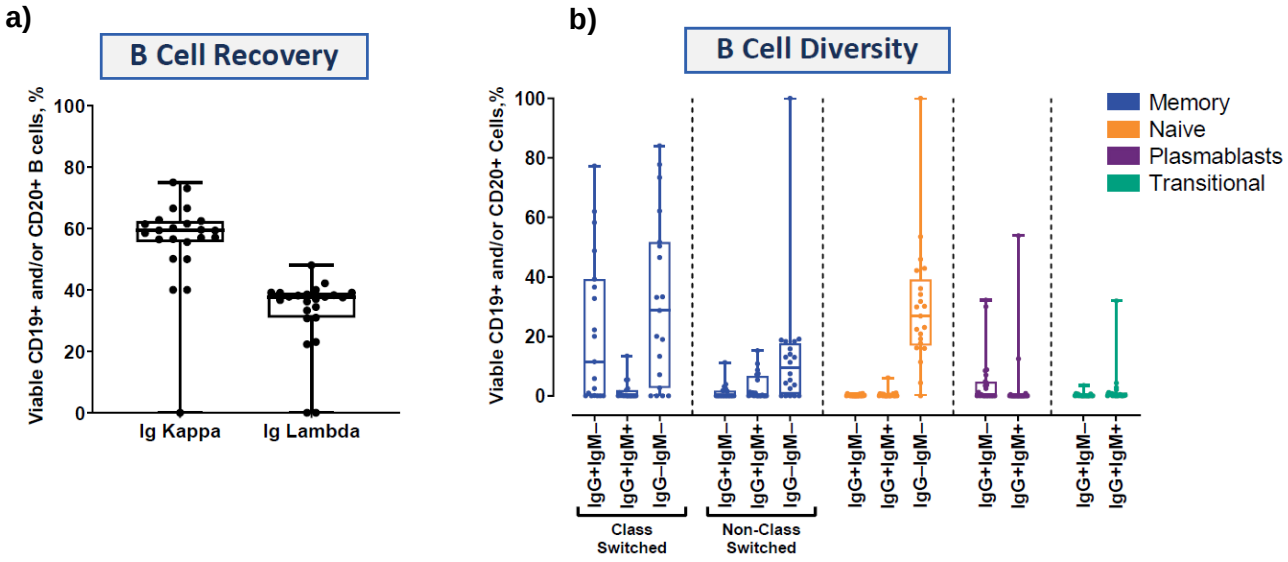
n (%)	mITT, n=101
Patients who died	59[d] (58)
Primary cause of death	
Progressive disease[a]	45 (45)
Other[b]	9 (9)
Adverse event[c]	4 (4)
Secondary malignancy	1 (1)

[a] During ongoing safety monitoring after the data cutoff, one event of central nervous system (CNS) lesion which was not amenable to biopsy was reported. Treatment for presumed progressive disease for diffuse large B-cell lymphoma was initiated by the investigator.
[b] Events included infection (n=3), cardiac arrest (n=2), pulmonary nocardiosis (n=1), sepsis (n=1), complications of allogeneic transplant for previous treatment-related myelodysplastic syndrome (MDS) not related to axi-cel (n=1), and unknown (n=1).
[c] Two events had no causal relationship (sepsis, pulmonary embolism) and 2 events were related to axi-cel (brain injury due to cardiac arrest and hemophagocytic lymphohistiocytosis).
[d] prior therapy- and/or conditioning chemotherapy-related myelodysplastic syndrome while in CR for LBCL.

B-Cell Detection, Recovery and Diversity

Blood samples from all evaluable patients (n=22) had detectable B-cells in blood at ≥ 3 years after axi-cel infusion.[4] At 3 years, 68% (n=15/22) of patients had detectable CAR gene-marked cells and polyclonal B-cells in blood. Figure 2a illustrates the 91% (n=21/23) of patients that demonstrated polyclonal B-cell recovery with a median immunoglobulin (Ig) kappa-lambda ratio of 1.6. At 3-year follow-up, there were two patients with a lambda value equal to zero. Figure 2b shows the relative levels of key B-cell immunophenotypes, indicative of the B-cell diversity.

Figure 2. ZUMA-1 Polyclonal B-Cell Recovery and Diversity at 3-Year Follow-up

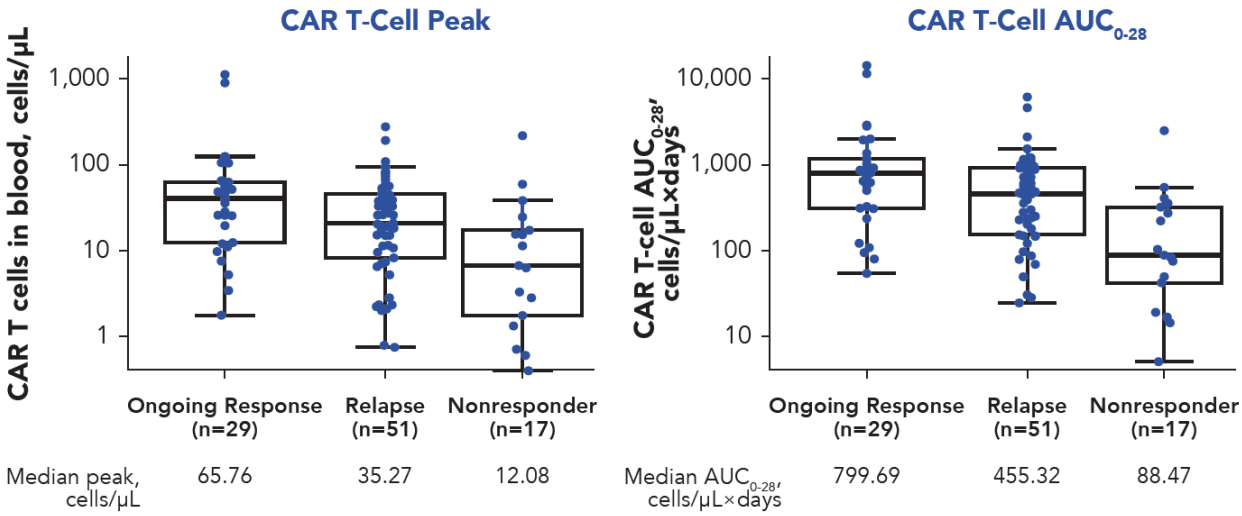


B-cells were characterized in cryopreserved peripheral blood mononuclear cells using multicolor flow cytometry. Viable cells were calculated as a percentage of the total number of viable CD45+ leukocytes. B-cell subsets were defined as CD45+CD3−CD14−CD16−CD56−CD19+ and/or CD20+ and further phenotyped as follows: Ig kappa, Ig lambda, class-switched memory (CD20+CD27+IgD−), non–class-switched memory (CD20+CD27+IgD+), naïve (CD20+CD27−IgD+CD24lowCD38low), plasmablasts (CD38highCD20−), and transitional (CD20+CD27−IgD+CD24+CD38mid).

CAR T-Cell Expansion and Association with Durable Response

In the 5-year analysis, patients with ongoing response at Month 60 had numerically higher median peak CAR T-cell levels; non-responders and patients who relapsed had notably lower median peak CAR T-cell levels (Figure 3).[6] The trend was similar for CAR T-cell expansion by area under the curve from Day 0 to Day 28 ($AUC_{0\text{-}28}$).

Figure 3. Early CAR T-Cell Expansion Associated with Ongoing Response at Month 60[6]



Ongoing response is defined as responders (complete or partial response) who did not have progressive disease or had died before the data cutoff. Four patients did not have evaluable post-infusion samples to allow for determination of CAR T-cell peak levels and AUC.

References

1. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc. 2024.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma.*New Engl J Med.* 2017;377(26):2531-2544. DOI: 10.1056/NEJMoa1707447.
3. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol*. 2019 Jan;20(1):31-42. DOI: 10.1016/S1470-2045(18)30864-7.
4. Jacobson CA, Locke FL, Ghobadi A, et al. Long-term survival and gradual recovery of B cells in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel. *Blood* 2020; 136 (Supplement 1): 40–42. DOI: 10.1182/blood-2020-134362.
5. Jacobson CA., Locke FL., Ghobadi A., et al. Long-Term (≥4 Year and ≥5 Year) Overall Survival (OS) By 12- and 24-Month Event-Free Survival (EFS): An Updated Analysis of ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Refractory Large B-Cell Lymphoma (LBCL). *Blood* 2021; 138 (Supplement 1): 1764. DOI: 10.1182/blood-2021-148078.
6. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood*. 2023 May 11;141(19):2307-2315. DOI: 10.1182/blood.2022018893.

Abbreviations

AE=adverse event
AUC=area under the curve
CAR=chimeric antigen receptor
CI=confidence interval
CR=complete response
DLBCL=diffuse large B-cell lymphoma
EFS=event-free survival
FL=follicular lymphoma
ITT=intent-to-treat
IV=intravenous
LBCL=large B-cell lymphoma
mITT=modified intent-to-treat
NE=not evaluable
ORR=objective response rate
OS=overall survival
PMBCL= primary mediastinal B-cell lymphoma
PD=progressive disease
PR=partial response
SAE-serious adverse event
TFL=transformed follicular lymphoma

Product Label

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