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Curative Potential of Axicabtagene Ciloleucel (Axi-Cel): an Exploratory Long-Term Survival Assessment in Patients With Refractory Large B-Cell Lymphoma From ZUMA-1

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BACKGROUND

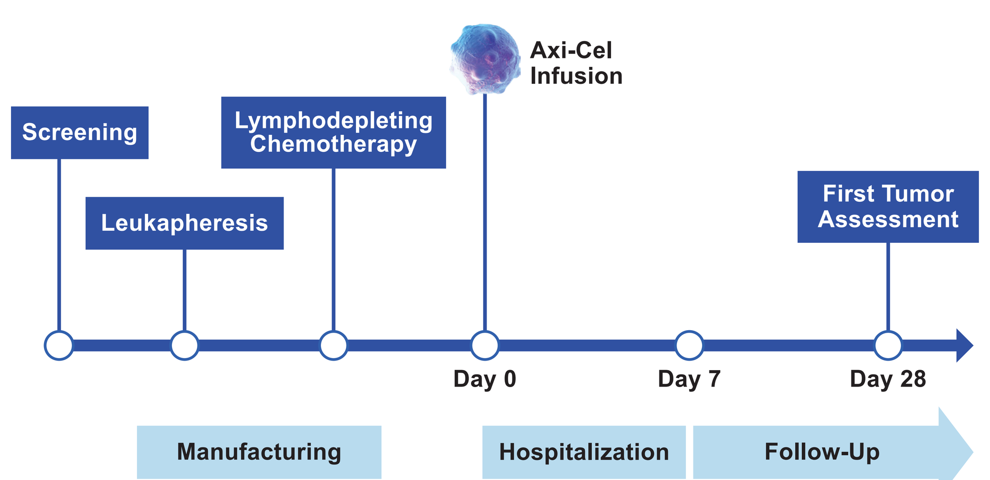
- Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of patients with relapsed/refractory large B-cell lymphoma (LBCL)[1,2]
- ZUMA-1 (NCT02348216) is the multicenter, single-arm, registrational Phase 1/2 study of axi-cel in patients with refractory LBCL after ≥2 lines of therapy[3]
- Long-term results from ZUMA-1 (N=101) demonstrated sustained overall survival (OS), with a median of 25.8 months and a 5-year estimate of 43%[4]
- Initial assessments of disease-specific survival (DSS) in ZUMA-1 suggested axi-cel may be curative for a subset of patients[4]
  - However, endpoints defining curative potential in patients with LBCL are not yet clearly established

OBJECTIVE

- To report exploratory analyses from the Phase 2 portion of ZUMA-1 (Cohorts 1 and 2) using proposed endpoints to measure cure rate of axi-cel in patients with refractory LBCL with up to 6 years of follow-up

METHODS

Figure 1. ZUMA-1 Study Design and Treatment Schema



Key Eligibility Criteria for ZUMA-1
- Refractory LBCL (DLBCL, PMBCL, TFL)
- No response to last chemotherapy or relapse ≤12 months post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

Lymphodepleting Regimen
- Cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 for 3 days

Axi-Cel
- Target of 2×10^6 CAR+ cells/kg

Primary Endpoint
- ORR, with first response assessment 4 weeks post-infusion

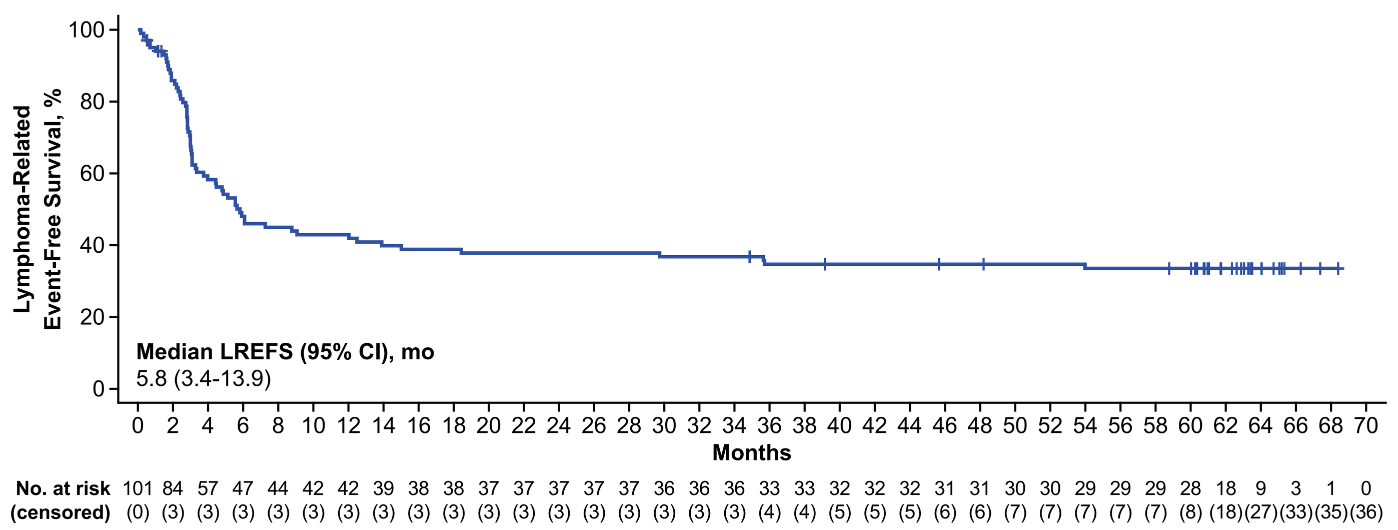
Key Additional Endpoints
- OS, safety, and translational evaluations

ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; ORR, objective response rate; OS, overall survival; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma.

- Exploratory efficacy analyses to assess curative potential were performed in treated patients from Cohorts 1 and 2 of Phase 2 (N=101)
  - Lymphoma-related event-free survival (LREFS): time from axi-cel infusion until disease progression (PD), initiation of new lymphoma therapy, autologous stem cell transplantation (ASCT), or death due to PD, whichever was earliest
  - Duration of complete response (DOCR): time from first complete response (CR) to PD, initiation of new lymphoma therapy, ASCT, or death due to PD
  - DSS: time from axi-cel infusion to death due to PD or axi-cel–related adverse events (AEs)
- Outcomes that included disease assessment (LREFS and DOCR) were analyzed via Kaplan-Meier (KM) estimates using data from the 5-year data cutoff date (August 11, 2021)
- Competing risk analyses were used to assess survival endpoints from the 6-year data cutoff date (August 11, 2022)
  - DSS was analyzed with KM estimates at this data cutoff
- Landmark analyses were used to explore prognostic potential of disease status at Week 4 and Months 3, 6, 12, and 24

RESULTS

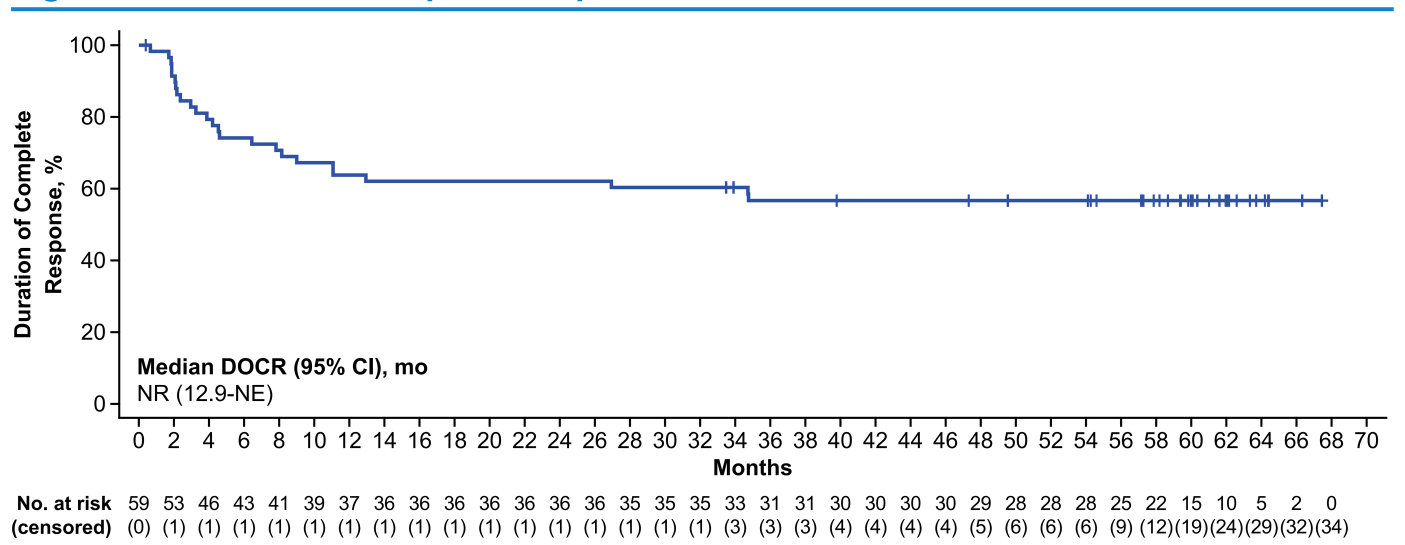
Figure 2. Lymphoma-Related Event-Free Survival



LREFS, lymphoma-related event-free survival, mo, month.

- With ≥5 years of follow-up (median 63.1 months), the 5-year LREFS rate was 33.5% (95% CI, 24.4-42.9; **Figure 2**)
  - 60 patients (59%) had PD
  - 2 patients (2%) died due to PD before a documented PD event
  - 3 patients (3%) received subsequent therapy/ASCT before documented PD
  - 7 patients (7%) had non–lymphoma-related deaths and were censored

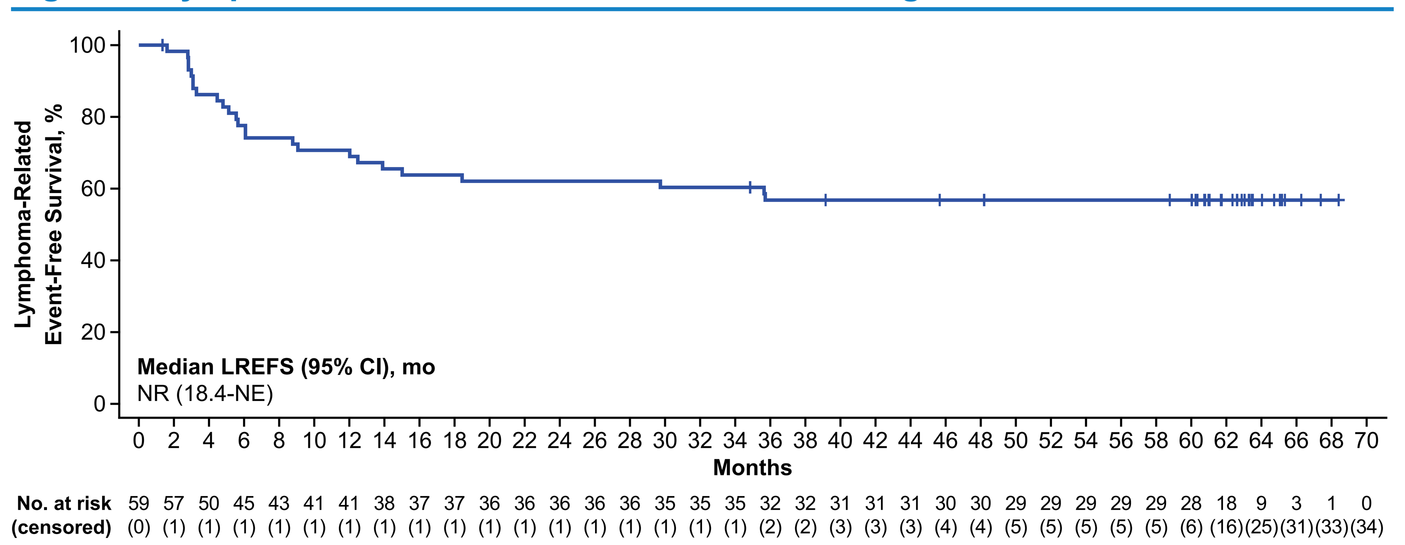
Figure 3. Duration of Complete Response



DOCR, duration of complete response; mo, month; NE, not estimable; NR, not reached.

- The 5-year estimate of DOCR among patients who achieved a CR as best response (n=59) was 56.7% (95% CI, 43.0-68.3; **Figure 3**)
  - 24 patients (41%) had PD
  - 1 patient (2%) initiated new anti-cancer therapy
  - 5 patients (8%) died due to reasons other than PD and were censored
- Among those with a CR at Months 12 and 24 post-infusion, 5-year estimates of DOCR were 84.3% and 91.3%, respectively

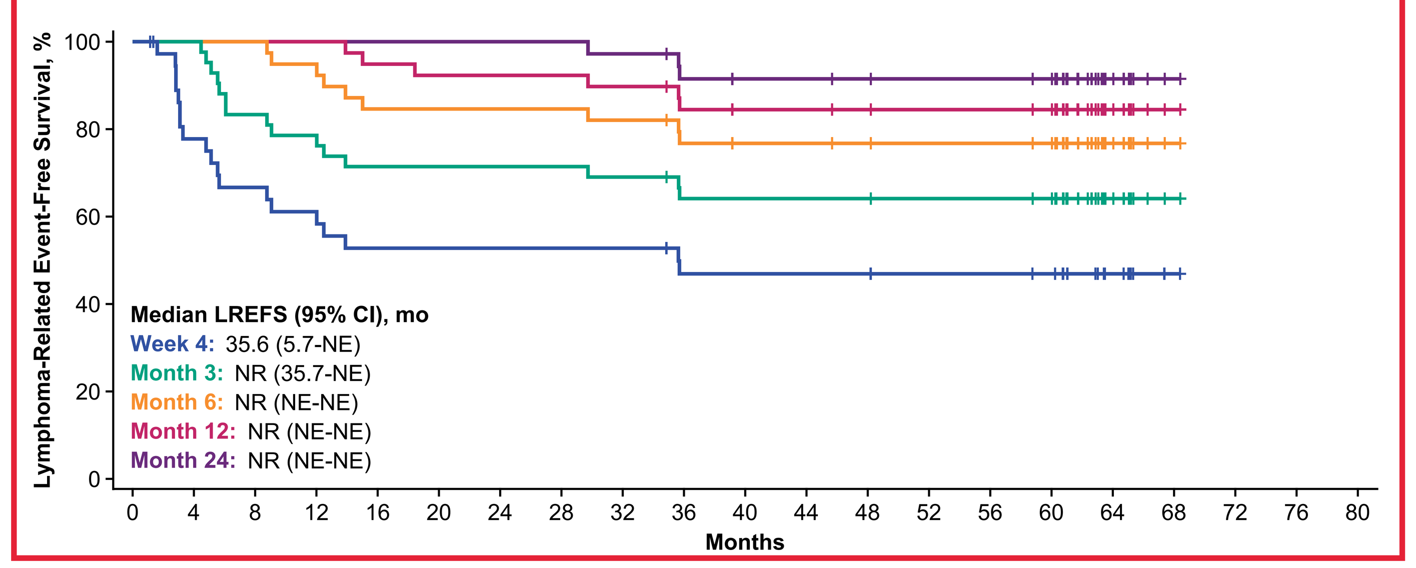
Figure 4. Lymphoma-Related Event-Free Survival Among Patients Who Achieved CR



CR, complete response; LREFS, lymphoma-related event-free survival, mo, month; NE, not estimable; NR, not reached.

- Among patients with a CR, the 5-year LREFS rate was 56.8% (95% CI, 43.1-68.4), with a plateau emerging in the curve by Month 36 (**Figure 4**)
  - A total of 29 patients (49%) remained in CR at data cutoff

Figure 5. Lymphoma-Related Event-Free Survival by CR Landmarks



CR, complete response; LREFS, lymphoma-related event-free survival, mo, month; NE, not estimable; NR, not reached.

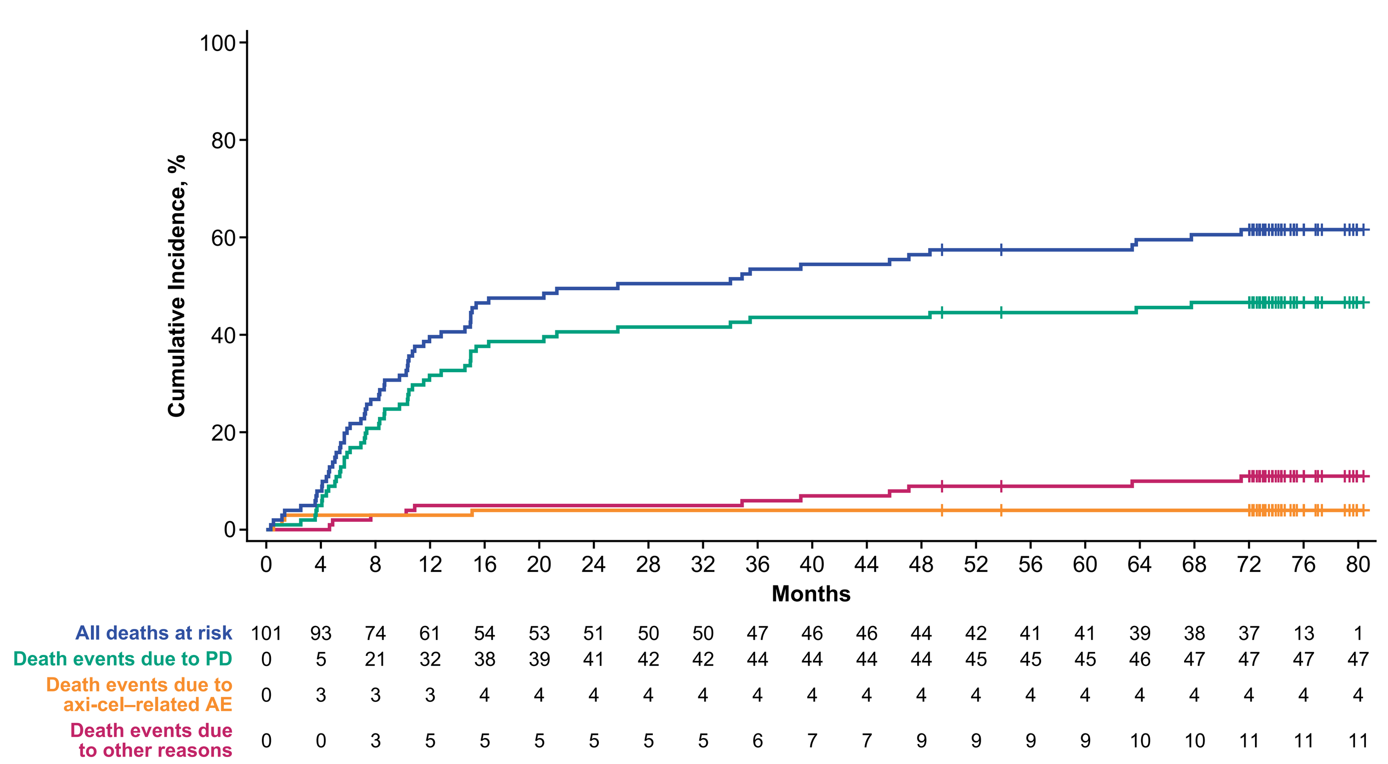
Table 1. Lymphoma-Related Event-Free Survival by CR Landmarks

	Patients With a CR				
KM Estimates (95% CI)	Week 4 (n=37)	Month 3 (n=42)	Month 6 (n=39)	Month 12 (n=39)	Month 24 (n=36)
Median LREFS, mo	35.6 (5.7-NE)	NR (35.7-NE)	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)
60-mo LREFS rate, %	46.9 (30.1-62.1)	64.1 (47.7-76.6)	76.8 (60.1-87.2)	84.5 (68.6-92.7)	91.5 (75.9-97.2)

CR, complete response; KM, Kaplan-Meier; LREFS, lymphoma-related event-free survival, mo, month; NE, not estimable; NR, not reached.

- Among patients with a CR at Months 12 and 24, 60-month estimated rates of LREFS and ongoing CR were >80% (84.5% and 91.5%, respectively; **Figure 5**; **Table 1**)
  - Those with a CR at Week 4 and Month 3 had 60-month LREFS estimates of 46.9% and 64.1%, respectively
- Among those with a partial response (PR) at Week 4 (n=33) and Month 3 (n=10), estimates of 60-month LREFS were 27.3% and 45.0%, respectively
  - Beyond Month 3, ≤4 patients had a PR, limiting further assessment

Figure 6. Cumulative Incidence of Death



AE, adverse event; axi-cel, axicabtagene ciloleucel; PD, disease progression.

- As of data cutoff for the 6-year analysis, median OS was 25.8 months, with 39 patients (39%) still alive at data cutoff
- The cumulative incidence of death at 72 months was 61.6% (**Figure 6**)
  - Between Months 24 and 72, there appeared to be an increase in cumulative incidences of death due to PD (40.6% and 46.6%, respectively) and other reasons (5.0% and 11.0%, respectively); deaths due to axi-cel–related AEs remained at 4.0% (both timepoints)
- Among patients with a CR, the cumulative incidences of death at Month 24 and Month 72 were 20.3% and 27.2% for progression, 0% and 10.4% for other reasons, and remained at 3.4% (both timepoints) for axi-cel–related AEs, respectively

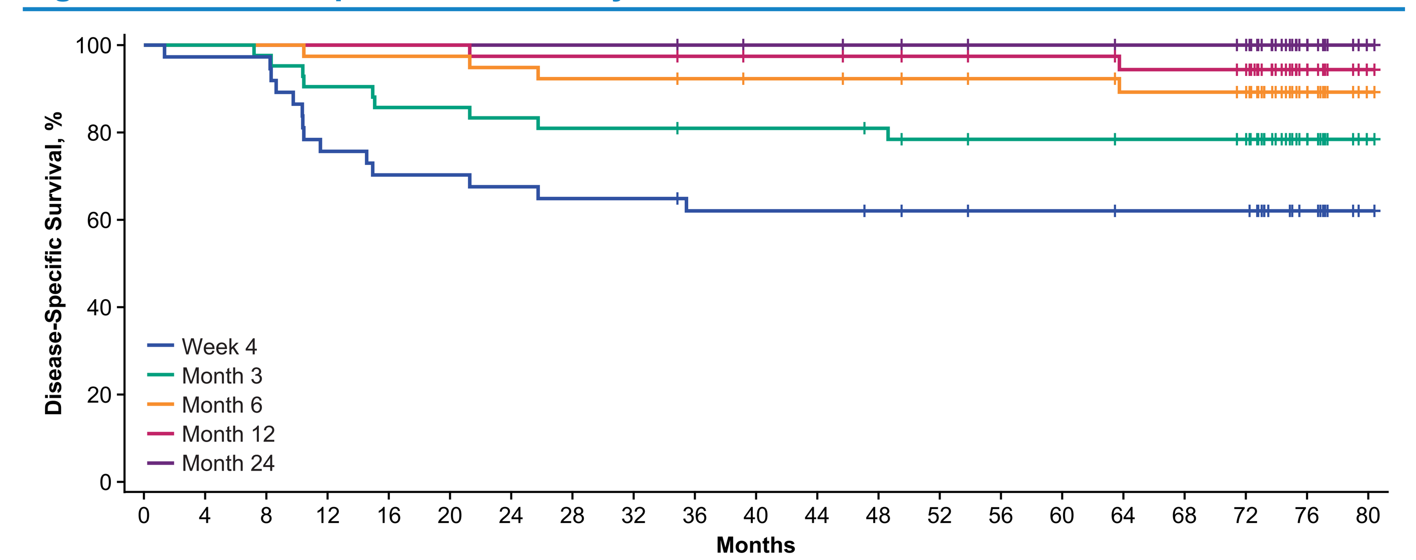
Table 2. Cumulative Incidence of Death at Month 72 by CR Landmarks

	Patients With a CR				
Cumulative Incidences	Week 4 (n=37)	Month 3 (n=42)	Month 6 (n=39)	Month 12 (n=39)	Month 24 (n=36)
Cumulative incidence of death, % (95% CI)	46.2 (29.4-61.5)	31.3 (17.8-45.7)	23.6 (11.5-38.0)	18.4 (8.0-32.2)	14.2 (5.1-27.9)
Due to PD	35.1 (20.2-50.5)	19.0 (8.8-32.2)	10.4 (3.2-22.5)	5.3 (0.9-15.8)	0
Due to axi-cel–related AEs	2.7 (0.2-12.3)	2.4 (0.2-11.0)	0	0	0
Due to other reasons	8.4 (2.1-20.5)	9.9 (3.1-21.4)	13.2 (4.7-26.0)	13.1 (4.7-26.0)	14.2 (5.1-27.9)

This table reports cumulative incidence of death based on competing risk assessment as of the data cutoff of the 6-year analysis among those with a disease assessment of a CR at each timepoint.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CR, complete response; PD, disease progression.

- Patients who had a CR at Months 12 and 24 had a 72-month cumulative incidence of death under 20% (**Table 2**)
  - The risk of death due to PD decreased among patients who remained in CR at each landmark
  - Death due to axi-cel–related AEs was uncommon and occurred mainly within 3 months of infusion
- Among patients with a PR at Week 4 and Month 3, 72-month cumulative incidences of death were 72.7% and 50.0%, respectively (representing a 26.5% and 18.7% higher risk of death than those with a CR, respectively)

Figure 7. Disease-Specific Survival by CR Landmarks



CR, complete response.

- Among patients who had a CR at landmarks between Week 4 and Month 24, medians of DSS were not reached (**Figure 7**)
- Patients who had a CR at Months 12 and 24 had 6-year KM-estimated DSS of 94.4% and 100%, respectively

CONCLUSIONS

- In this post hoc analysis of ZUMA-1, the 5-year LREFS rate was demonstrated as a potential measure of cure with axi-cel in patients with refractory LBCL
- The competing risk analyses showed that among patients who achieved a CR, the leading risks of death were reasons other than progression or axi-cel–related AEs after Month 24 post-infusion
- A CR at 12 and 24 months post-infusion may be predictive of extended survival, especially of DSS
- Overall, axi-cel may be curative for a substantial proportion of patients with refractory LBCL

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DISCLOSURES

Full author disclosures are available through the virtual meeting platform

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