5-Year Follow-Up Analysis From ZUMA-5: A Phase 2 Trial of Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

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Background

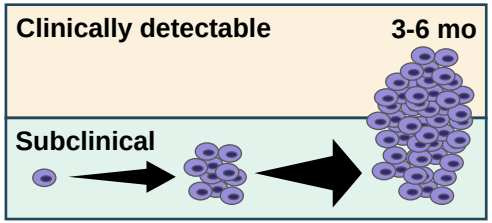
- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of patients with R/R FL based on the Phase 2 ZUMA-5 trial in patients with R/R iNHL[1-5]

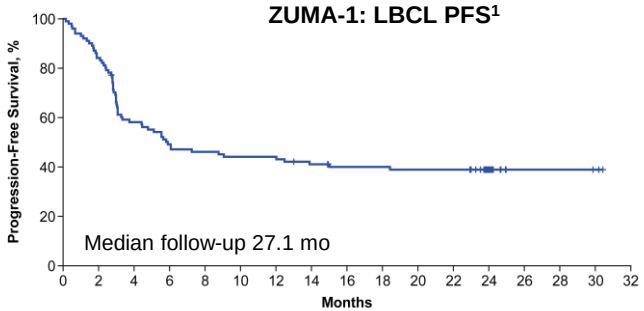
- Previously, after a median follow-up of 52.5 months in ZUMA-5 (N=159)[4]
  - Median DOR was 55.5 months, median PFS was 57.3 months, and median OS was not reached among all patients with iNHL
  - Late progression or death due to lymphoma or study treatment was rare among treated patients, and no new safety signals emerged
  - Patients with FL who had an ongoing response were found to have a higher proportion of naive (CCR7+CD45RA+) T cells in their axi-cel product (25%) than those who relapsed (13%) or those who did not respond to axi-cel (9%)

1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2024. 2. YESCARTA® (axicabtagene ciloleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2024. 3. Jacobson CA, et al. *Lancet Oncol*. 2022;23:91-103. 4. Neelapu S, et al. *Blood.* 2023;142(Suppl 1):4868.
5. Neelapu S, et al. *Blood*. 2024;143(6):496-506.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Background (cont'd)

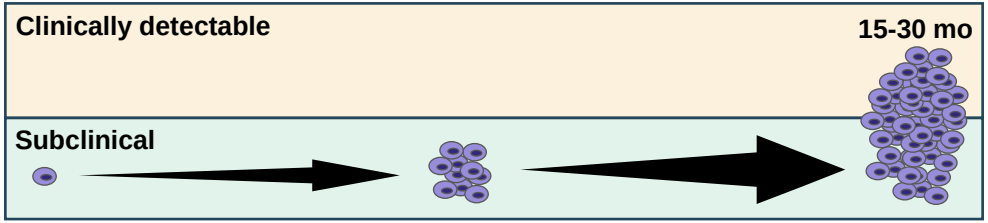
LBCL

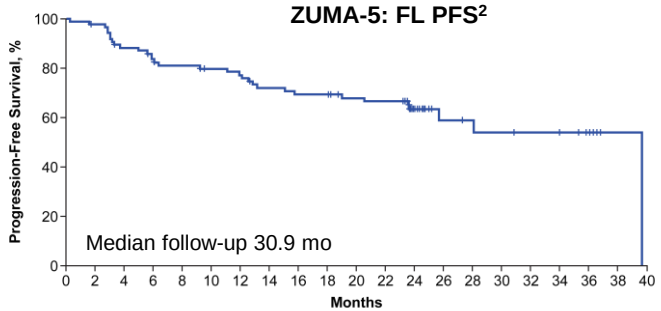




- With curative therapies in LBCL, most PFS events are PD-related, occurring early and resulting in a plateau within 2 years

FL



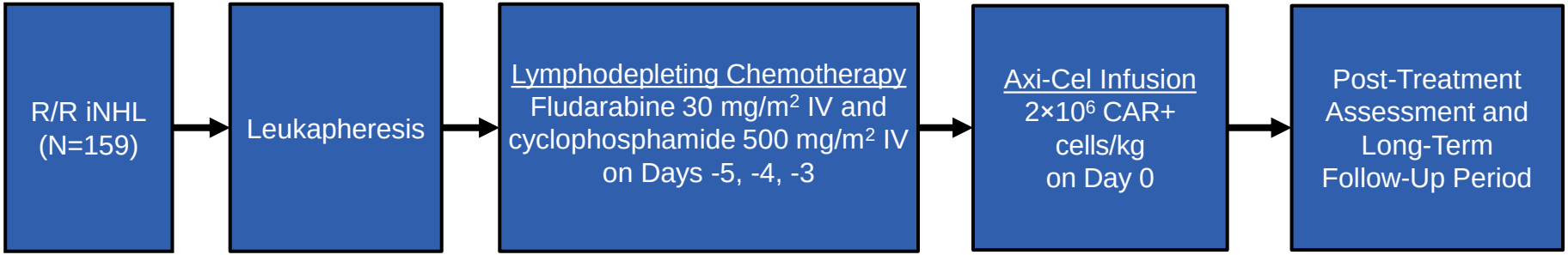


- In FL, PFS events are likely to occur over a longer period, including PD- and non–PD-related events, with no obvious plateau within 2 years

- Lymphoma-specific assessment of survival may be necessary to determine curative potential in FL
- Here we evaluate updated outcomes from ZUMA-5 after a median follow-up of ≥5 years, including lymphoma-specific survival analyses

1. Locke F, et al. *Lancet Oncol.* 2019;20:31-42. 2. Neelapu S, et al. *Blood.* 2021;138(Suppl 1):93.
FL, follicular lymphoma; LBCL, large B-cell lymphoma; PD, progressive disease; PFS, progression-free survival.

ZUMA-5 Study Design[1]



Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1-3a) or MZL (nodal or extranodal)[a]
- ≥2 prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint

- ORR (per Lugano[2])

Key Secondary Endpoints

- CR rate
- DOR, PFS, OS, TTNT
- AEs
- CAR T-cell and cytokine levels

Key Exploratory Efficacy Endpoints

- LSS
- LSPFS

[a] Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible. [b] Single-agent anti-CD20 antibody did not count as line of therapy for eligibility.

1. Jacobson CA, et al. *Lancet Oncol*. 2022;23:91-103. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; LSPFS, lymphoma-specific progression-free survival; LSS, lymphoma-specific survival; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TTNT, time to next therapy.

5-Year Analysis Methods

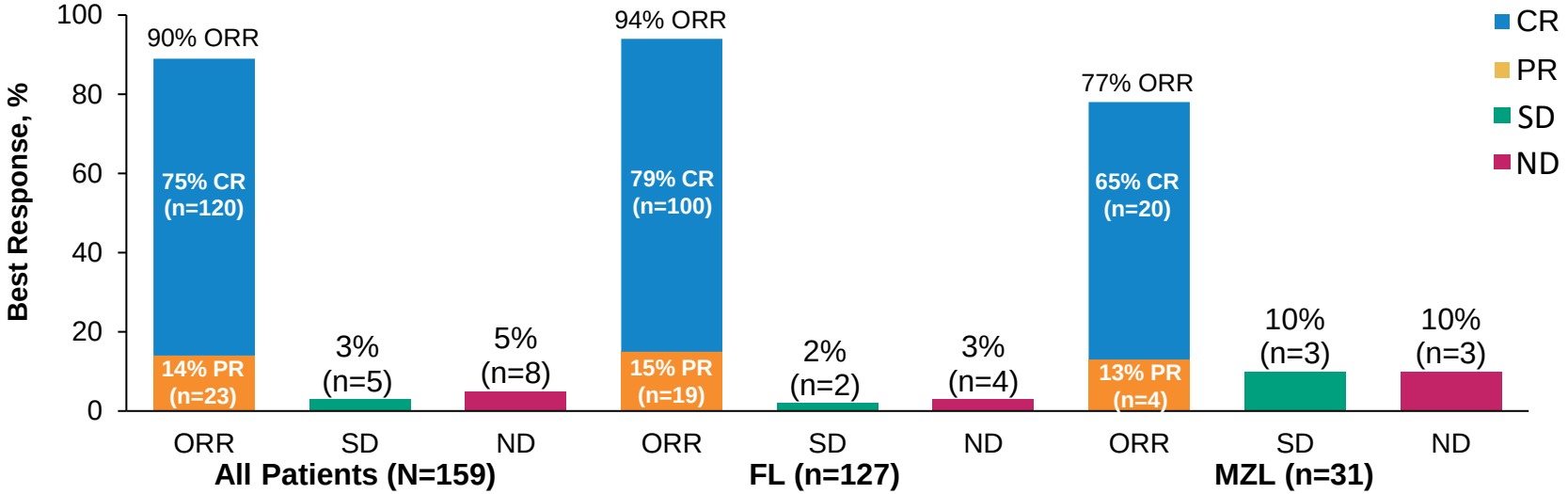
- The 5-year analysis occurred after the median follow-up of all enrolled patients reached ≥60 months post-infusion
  - Data cutoff date: March 31, 2024

- Efficacy assessments were performed per investigator in all enrolled patients (N=159[a]; FL, n=127; MZL, n=31)
  - Exploratory analyses of lymphoma-specific survival were performed
    - Events of interest in lymphoma-specific PFS were PD and death due to lymphoma or complications from study treatment (axi-cel or lymphodepleting chemotherapy)
    - Events of interest in lymphoma-specific survival were death due to lymphoma or study treatment
    - Competing risks were deaths due to reasons other than lymphoma or study treatment

- Safety was reported in all patients treated with axi-cel (N=152; FL, n=124; MZL, n=28)
  - Beginning at 3 months after infusion, data on AEs of interest, serious AEs related to axi-cel, and secondary malignancies were collected until 15 years post-infusion, PD, or initiation of new treatment

[a] One patient was found to have DLBCL after enrollment, did not receive axi-cel infusion, and discontinued the study.
AE, adverse event; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; PFS, progression-free survival.

Overall Response and Complete Response Rates



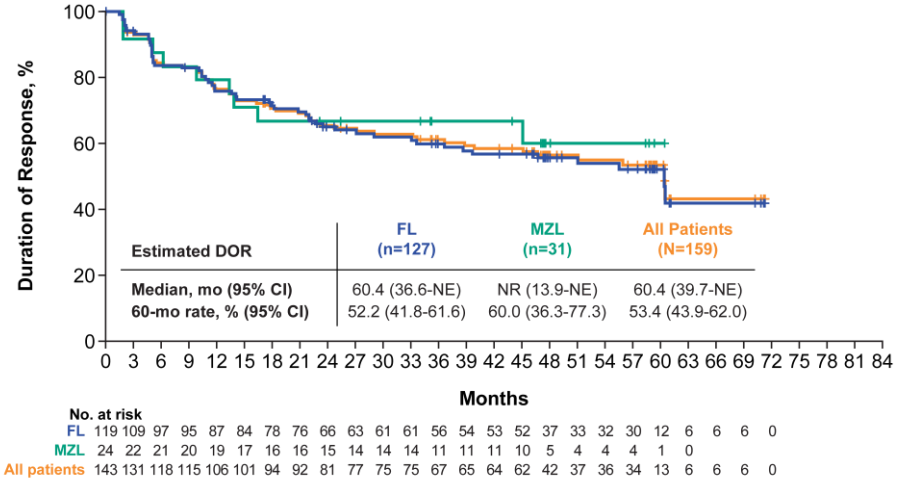
- Median follow-up from leukapheresis in enrolled patients with iNHL (N=159) was 64.6 months (range, 32.3-81.4)
  - In FL (n=127), median follow-up was 65.7 months (range, 56.7-81.4)
  - In MZL (n=31), median follow-up was 55.8 months (range, 32.3-76.4)
- Response remained consistent with prior analyses[1]

1. Neelapu S, et al. *Blood.* 2023;142(Suppl 1):4868.

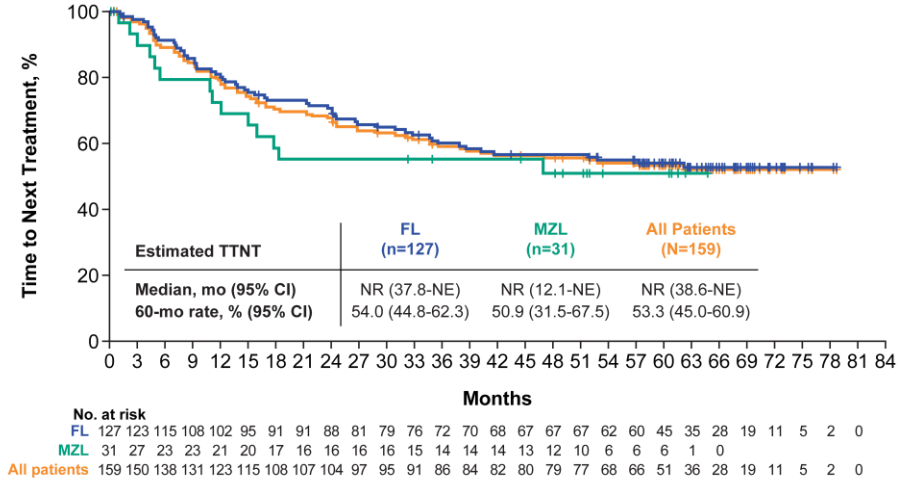
CR, complete response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; ND, not done; ORR, overall response rate; PR, partial response; SD, stable disease.

Duration of Response and Time to Next Treatment

Duration of Response



Time to Next Treatment



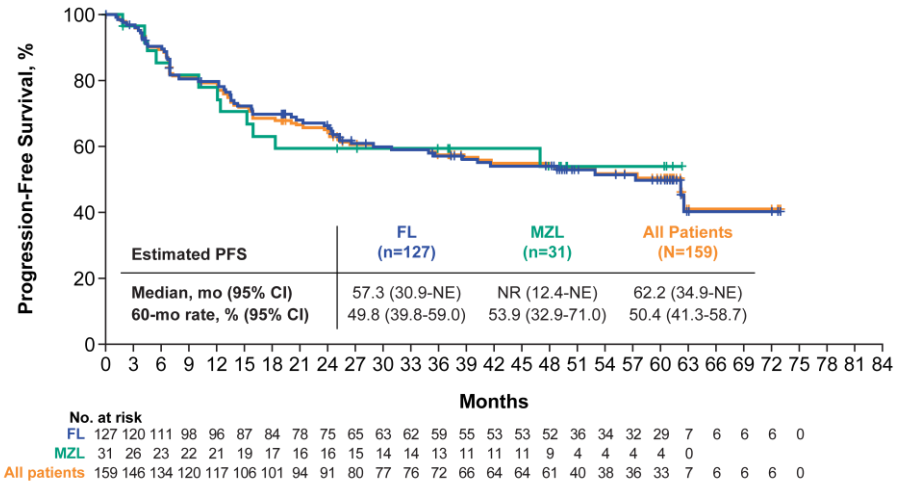
- At cutoff, 55% of patients (n=87) were alive without requiring any new anticancer therapy
- Median DOR was 60.4 months, with an estimated 60-month DOR rate of 53.4%
  - Ongoing response rate was 44% (FL: 43%, MZL: 48%)
  - Among patients who achieved a CR, 58% remained in CR at data cutoff; median DOR was 60.5 months (95% CI, 60.4-NE)
- Median TTNT remained not reached[1]

1. Neelapu S, et al. *Blood.* 2023;142(Suppl 1):4868.

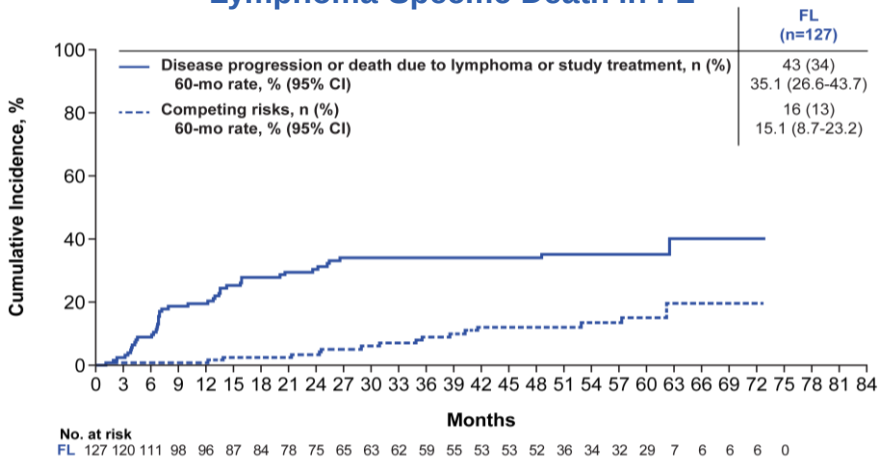
DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; TTNT, time to next treatment.

PFS and Cumulative Incidence of Progression and Lymphoma-Specific Death

Progression-Free Survival[a]



Cumulative Incidence of Progression and Lymphoma-Specific Death in FL[a,b]

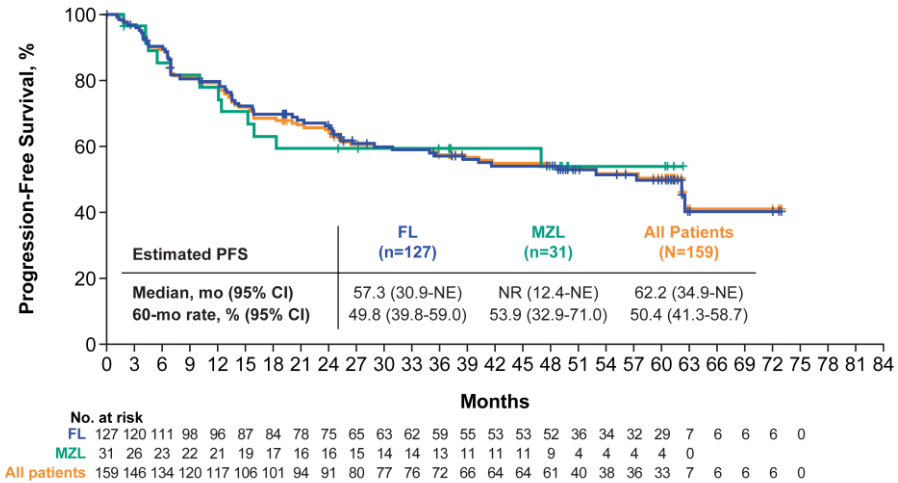


- Median PFS was 62.2 months; the 60-month PFS rate was 50.4%
  - 60-month PFS rates in patients with FL were consistent regardless of high-risk factors, including POD24
  - In those with a CR, the 60-month PFS rate was 61.9%; in those with PR, the rate was 9.1%
- Among patients with FL, the 60-month rate of progression or lymphoma-specific death was 35.1%

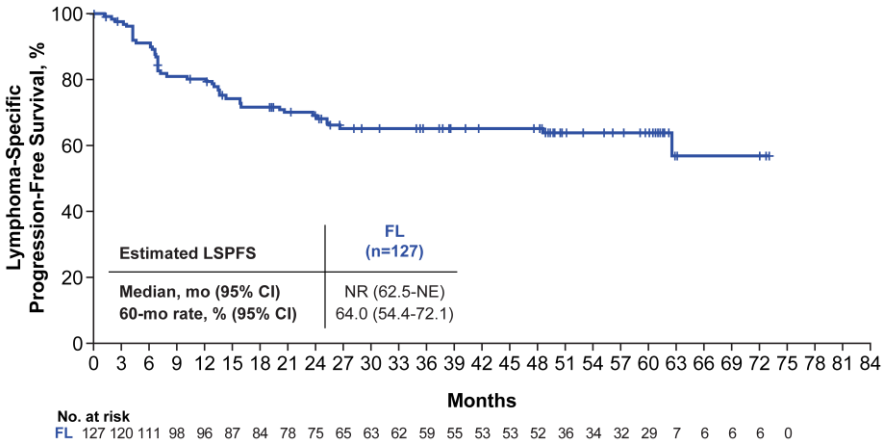
[a] Progression events were determined by the investigator. [b] Death due to lymphoma included death due to disease progression or determined to be disease related. Death due to study treatment complications included death determined to be related to axi-cel or lymphodepleting chemotherapy. These were analyzed per investigator assessment.
Axi-cel, axicabtagene ciloleucel; CR, complete response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; PFS, progression-free survival; POD24, progression <2 years from initiating first anti-CD20–containing chemoimmunotherapy; PR, partial response.

PFS and Lymphoma-Specific PFS

Progression-Free Survival[a]



Lymphoma-Specific Progression-Free Survival[a,b]

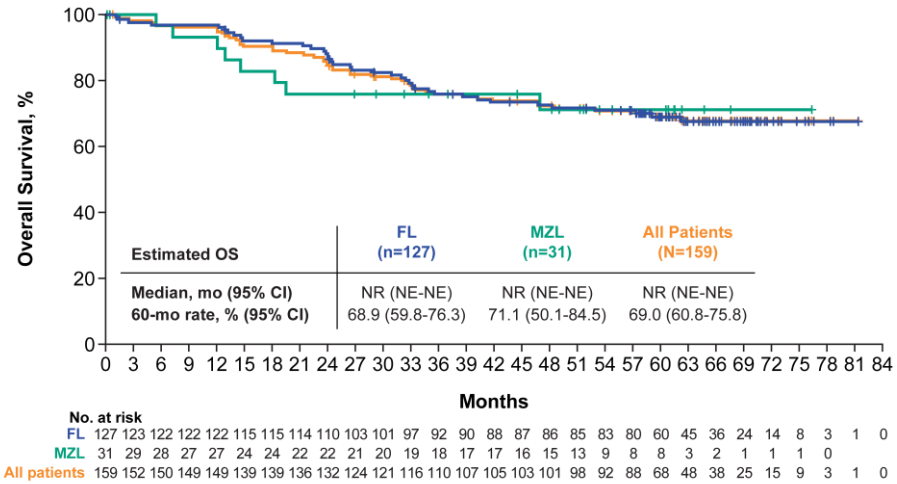


- Median lymphoma-specific PFS in FL was not reached (95% CI, 62.5-NE), with 64.0% of patients achieving the 60-month landmark
  - Only 4 patients progressed >24 months post-leukapheresis; 2 patients progressed >30 months post-leukapheresis

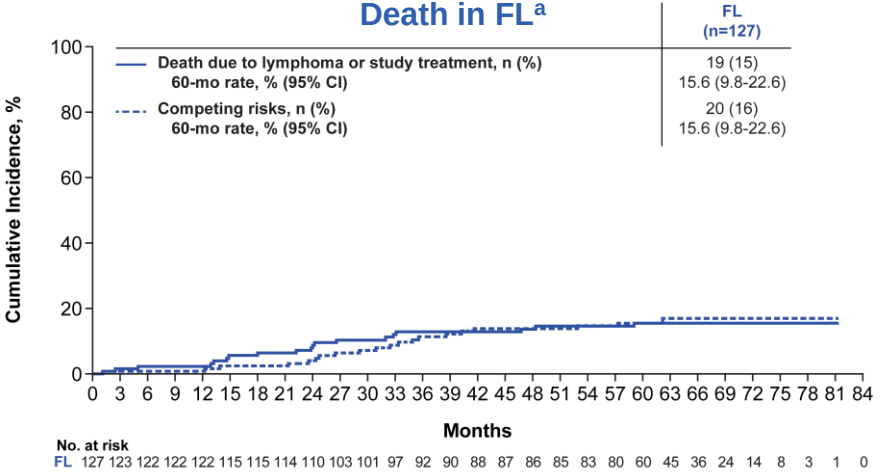
[a] Progression events were determined by the investigator. [b] Death due to lymphoma included death due to disease progression or determined to be disease related. Death due to study treatment complications included death determined to be related to axi-cel or lymphodepleting chemotherapy. These were analyzed per investigator assessment. Deaths not related to lymphoma or study treatment were censored.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; LSPFS, lymphoma-specific progression-free survival; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; PFS, progression-free survival.

OS and Cumulative Incidence of Lymphoma-Specific Death

Overall Survival



Cumulative Incidence of Lymphoma-Specific Death in FL[a]



- Median OS remained not reached[1]
- The rate of lymphoma-specific death at 60 months in FL was 15.6%
  - A total of 19 patients died due to lymphoma or study treatment (lymphoma, n=15; study treatment, n=4)

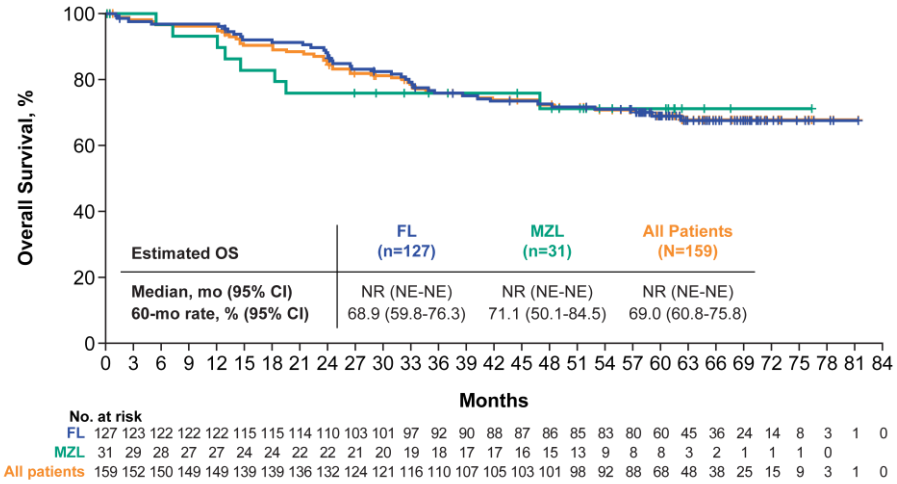
[a] Death due to lymphoma included death due to disease progression or determined to be disease related. Death due to study treatment complications included death determined to be related to axi-cel or lymphodepleting chemotherapy. These were analyzed per investigator assessment.

1. Neelapu S, et al. *Blood.* 2023;142(Suppl 1):4868.

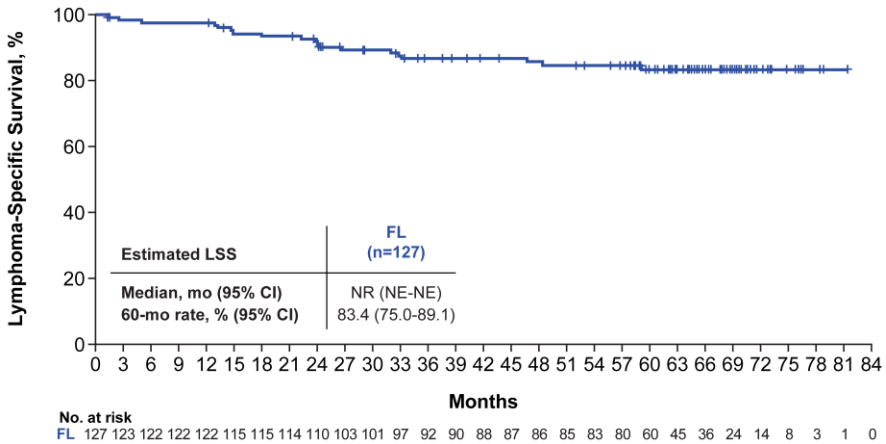
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR not reached; OS, overall survival.

OS and Lymphoma-Specific Survival

Overall Survival



Lymphoma-Specific Survival[a]



- Median lymphoma-specific survival in FL was not reached (95% CI, NE-NE), with 83.4% of patients achieving the 60-month landmark

[a] Death due to lymphoma included death due to disease progression or determined to be disease related. Death due to study treatment complications included death determined to be related to axi-cel or lymphodepleting chemotherapy. These were analyzed per investigator assessment. Deaths not related to lymphoma or study treatment were censored.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; LSS, lymphoma-specific survival; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; OS, overall survival.

Long-Term Safety and Deaths by Year

Following the 4-year analysis[1]:

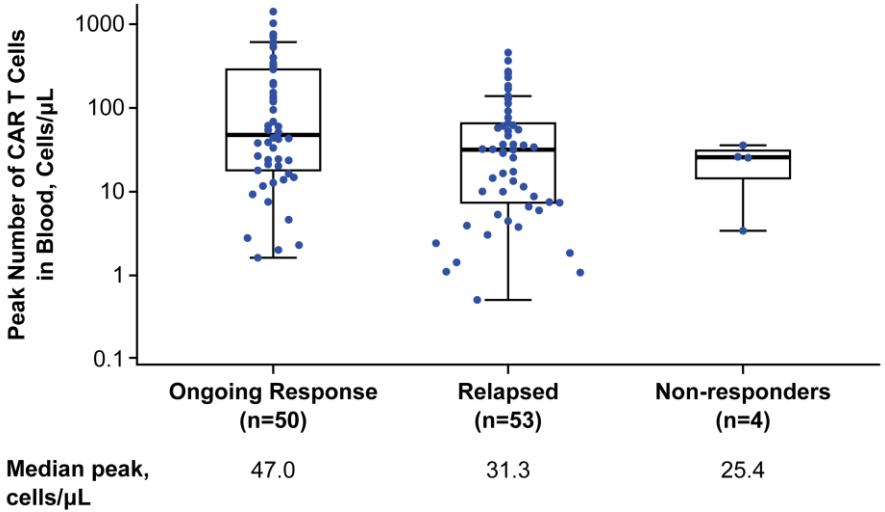
- 3 new events not related to axi-cel were reported, including Grade 3 prostate cancer, Grade 1 bladder cancer, and Grade 4 myelodysplastic syndrome
- 1 patient died due to pneumonia (not related to axi-cel)
  - No patients died of disease progression following the previous analysis

n, (%)	All Patients N=152	Years Post–Axi-Cel Infusion					
		0-1	1-2	2-3	3-4	4-5	>5
Patients who died	46 (30)	10 (7)	15 (10)	11 (7)	6 (4)	3 (2)	1 (1)
Relapse mortalities							
Progressive disease	14 (9)	5 (3)	5 (3)	2 (1)	1 (1)	1 (1)	0
Non-PD after PD	9 (6)	1 (1)	3 (2)	4 (3)	1 (1)	0	0
Non-relapse mortalities							
Secondary malignancy[a]	6 (4)	1 (1)	2 (1)	1 (1)	2 (1)	0	0
Cardiac-related	3 (2)	0	1 (1)	0	1 (1)	0	1 (1)
Infection-related[b]	11 (7)	2 (1)	2 (1)	4 (3)	1 (1)	2 (1)	0
Other[c]	3 (2)	1 (1)	2 (1)	0	0	0	0

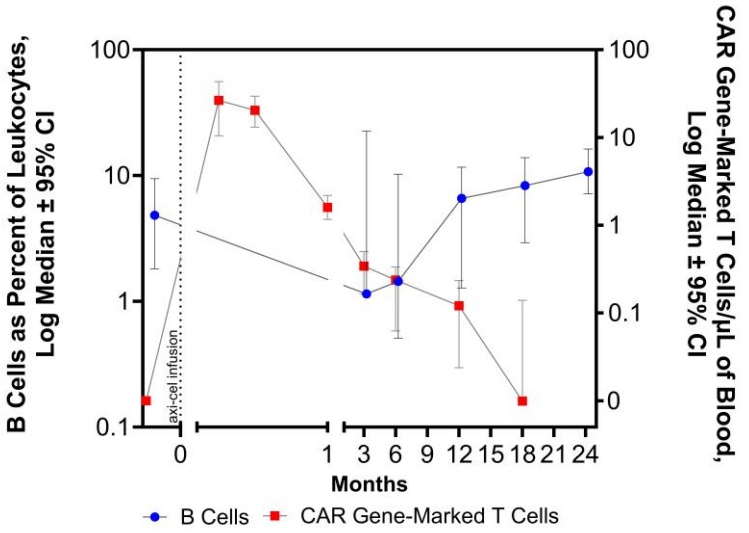
[a] No secondary malignancy was of T-cell origin. [b] Three of the infection-related deaths were related to COVID-19.
[c] Two deaths were due to unknown causes and 1 was due to CRS and multi-organ failure.
Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; PD, progressive disease.

CAR T-Cell Expansion and B-Cell Recovery in FL

Peak CAR T-Cell Expansion



B Cells and CAR Gene-Marked T Cells Over Time



- Treated patients with FL in ongoing response at data cutoff had greater CAR T-cell expansion than relapsed or non-responding patients
- Consistent with the prior analysis,[1] levels of CAR gene–marked T cells were inversely correlated with that of B cells at each timepoint post-infusion

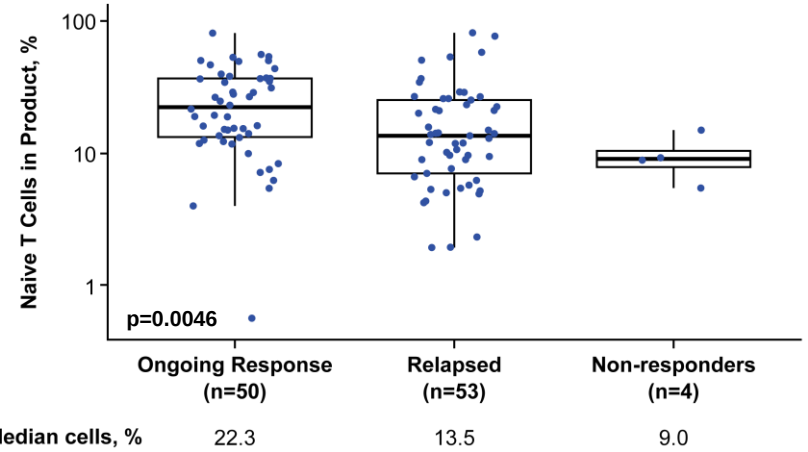
For additional correlative analyses, please refer to Poddar S, et al. ASH 2024. Abstract 4368.

1. Neelapu S, et al. *Blood.* 2023;142(Suppl 1):4868.

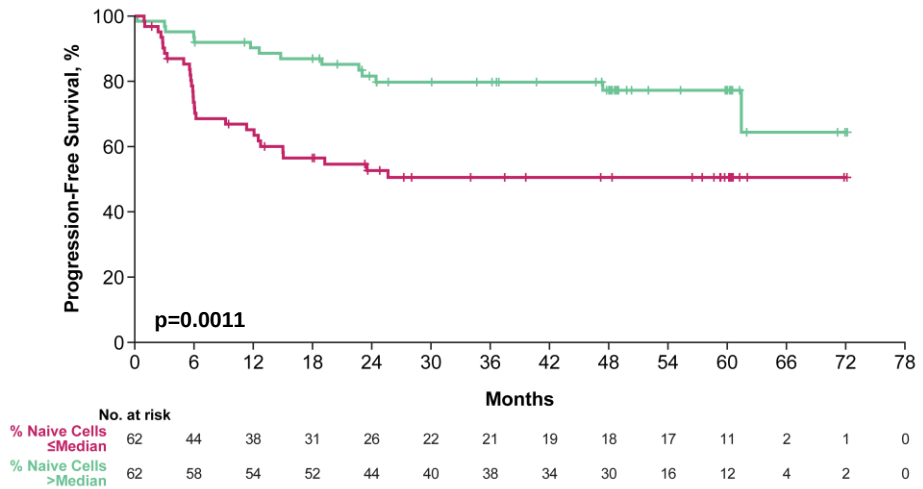
CAR, chimeric antigen receptor; FL, follicular lymphoma.

Naive Phenotype by Ongoing Response and PFS in FL

Naive T Cells in Product



PFS by Median Naive T Cells in Product



- Among patients with FL, a higher percentage of naive T cells (CCR7+CD45RA+) in axi-cel product, indicative of naive phenotype, was associated with ongoing response at 60 months and longer PFS

For additional correlative analyses, please refer to Poddar S, et al. ASH 2024. Abstract 4368.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; PFS, progression-free survival.

Conclusions

- After a median follow-up of >5 years in ZUMA-5, axi-cel continued to demonstrate durable responses and long-term survival in patients with R/R iNHL
  - Over half of patients were alive at data cutoff without the need for a subsequent therapy
  - Following the 4-year analysis, there was one PD event in FL and no lymphoma-specific deaths occurred
  - The plateau in lymphoma-specific PFS, with only two progression events after month 30, indicates the curative potential of axi-cel in FL[1]
- Safety outcomes with axi-cel remained consistent with previous analyses, and no new safety signals were observed[1]
- Elevated early CAR T-cell expansion and a naive product phenotype continued to be associated with durable response
- Collectively, these long-term data support axi-cel as a highly effective therapeutic approach for patients with R/R iNHL, with curative potential in patients with FL

1. Neelapu S, et al. *Blood.* 2023;142(Suppl 1):4868.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory.

Acknowledgments

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and healthcare staff at each study site
- Medical writing support was provided by Jordan Kesner, PhD, of Nexus Global Group Science LLC, funded by Kite
- This study was funded by Kite

Additional Resources

- Full author disclosures are available through the virtual meeting platform
- A plain language summary of the key results from this presentation is available through the Quick Response (QR) code