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Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma: 4-Year Follow-Up From the Phase 2 ZUMA-5 Trial

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BACKGROUND

- 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) follicular lymphoma (FL)[1,2]
- Approval was based on the ZUMA-5 multicenter, single-arm, Phase 2 study of axi-cel in patients with R/R indolent non-Hodgkin lymphoma (iNHL), including FL and marginal zone lymphoma (MZL)[3]
  - After a median follow-up of ≥3 years, median progression-free survival (PFS) was 40.2 months in patients with FL and not reached in those with MZL[4]
  - Late progression or death due to lymphoma or axi-cel were uncommon[4]
  - Multivariate assessment of pre- and post-treatment characteristics found that elevated serum levels of immune counter-regulatory biomarkers and high Follicular Lymphoma International Prognostic Index (FLIPI) score associated with relapse in patients with FL[4]

OBJECTIVE

- To evaluate updated clinical outcomes from ZUMA-5 after a median follow-up of ≥4 years

METHODS

Figure 1. ZUMA-5 Study Design[4]

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 (centrally assessed per Lugano[c])

Key Secondary Endpoints
- CR rate
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

[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.
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; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

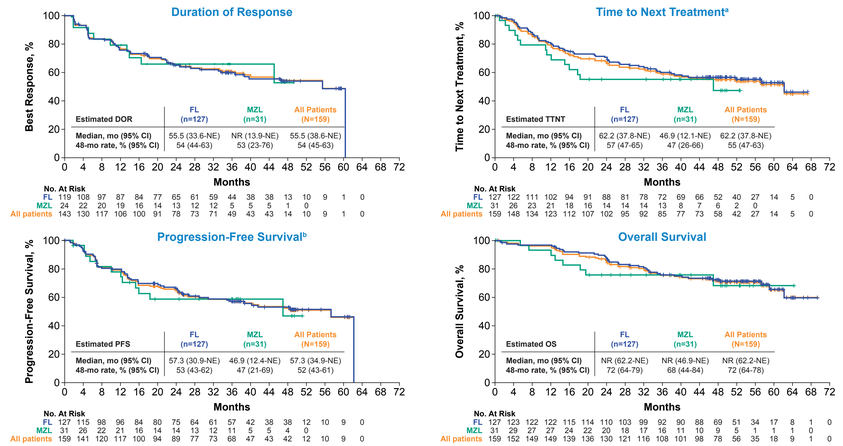
4-Year Analysis

- The updated efficacy and safety analysis occurred when the median follow-up of all enrolled patients was ≥48 months after infusion
  - Data cutoff date: March 31, 2023
  - Protocol-specified central review of response only occurred up to 24 months
- Efficacy outcomes were investigator assessed in all 159 enrolled patients (127 with FL; 31 with MZL)
  - One patient was found to have diffuse large B-cell lymphoma after enrollment via pretreatment biopsy. This patient did not receive axi-cel and discontinued the study
- Exploratory analyses of lymphoma-specific survival were performed per investigator assessment
  - For lymphoma-specific PFS, events of interest included disease progression, death due to lymphoma (including disease progression), or study treatment complications (axi-cel or lymphodepleting chemotherapy)
  - For lymphoma-specific survival, events of interest included death due to lymphoma or study treatment complications
  - Competing risks were deaths due to reasons other than lymphoma or study treatment complications
- Safety data were reported for the 152 patients treated with axi-cel (124 with FL; 28 with MZL)
  - Three months after axi-cel infusion, adverse events of special interest, serious events, and new malignancies related to axi-cel were reported (up to 15 years until disease progression or initiation of new treatment, whichever came first)

RESULTS

- Median follow-up from leukapheresis for all enrolled patients with iNHL (N=159) was 52.5 months (range, 20.3-69.4)
  - Median follow-up in patients with FL and MZL was 53.7 months (44.7-69.4) and 43.8 months (20.3-64.3)
- The overall response rate in all patients remained consistent with prior reports (90%; 95% CI, 84-94), with a 75% complete response (CR) rate[4]

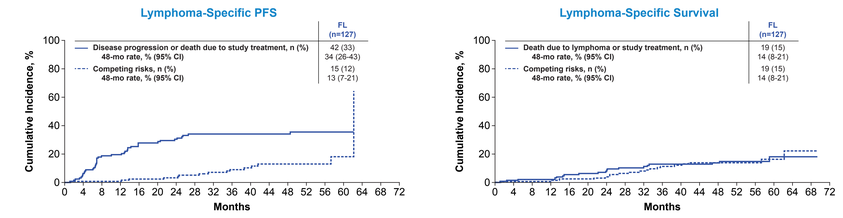
Figure 2. DOR, TTNT, PFS, and OS



[a] Time to next treatment is defined as the time from the leukapheresis date to the start of subsequent anticancer therapy or death from any cause. [b] Progression events were determined by the investigator.
DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached, OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment.

- The rate of ongoing response at data cutoff in all enrolled patients was 48% (consistent by disease type)
- Among patients who achieved a CR as best response, median duration of response (DOR) was 60.4 months (95% CI, 55.5-not estimable [NE]); those who had a partial response had a median DOR of 4.9 months (95% CI, 2.1-6.2)
- Median PFS was 57.3 months in patients with FL and 46.9 months in patients with MZL (**Figure 2**), increasing from previous reports[4]
  - Median PFS among patients with FL who had progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy (POD24) was 57.3 months (15.9-NE); those who did not have POD24 had a median PFS of 48.6 months (95% CI, 26.6-NE)
  - Most progression events occurred within 24 months post axi-cel infusion
  - After the data cutoff of the previous analysis, 1 patient with FL experienced disease progression
- Median overall survival remained not yet reached in either disease type (**Figure 2**)[4]

Figure 3. Lymphoma-Specific PFS and Lymphoma-Specific Survival in Patients With FL[a]



[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.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; PFS, progression-free survival.

- The 48-month cumulative incidence of lymphoma-specific progression or death in patients with FL was 34% (**Figure 3**)
  - The cumulative incidence of death due to reasons other than disease progression or study treatment (competing risks) was 13%
- The cumulative incidence of lymphoma-specific death at 48 months was 14% (**Figure 3**)
  - The cumulative incidence of death due to competing risks was 14%

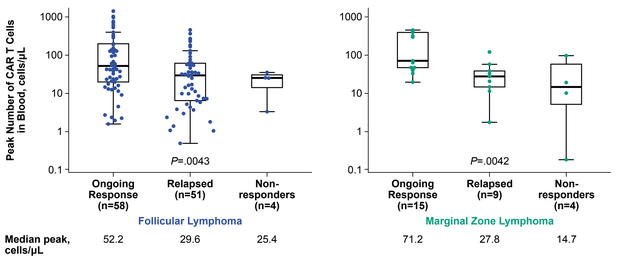
Table 1. Deaths After Axi-Cel Infusion by Year

n (%)	All Patients N=152	Year 1	Year 2	Year 3	Year 4	Year >4
Patients who died	**45 (30)**	**10 (7)**	**15 (10)**	**11 (7)**	**6 (4)**	**3 (2)**
Primary cause of death						
Progressive disease[a]	14 (9)	5 (3)	5 (3)	2 (1)	1 (1)	1 (1)
Adverse event	8 (5)	3 (2)	3 (2)	1 (1)	1 (1)	0
New malignancy	6 (4)	1 (1)	2 (1)	1 (1)	2 (1)	0
Other[b]	17 (11)	1 (1)	5 (3)	7 (5)	2 (1)	2 (1)

[a] One patient died due to progressive disease on Day 47 post-infusion, Grade 5 FL was reported due to AE reporting window. [b] One patient died after partial withdraw of consent.
AE, adverse event; axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; MZL, marginal zone lymphoma.

- After the 3-year data cutoff date, 1 patient with FL had a serious event of Grade 3 myelodysplastic syndrome, considered related to axi-cel per investigator[4]
- In total, 30% of treated patients with iNHL have died as of the data cutoff date (**Table 1**)
- Deaths occurring after the 3-year data cutoff date included[4]
  - Progressive disease in 2 patients with FL (progressive disease reported on Days 479 and 610 post-leukapheresis)
  - New malignancy in 1 patient with MZL (acute myeloid leukemia)
  - Other in 4 patients with FL (2 cardiac events, 1 acute respiratory distress syndrome/methicillin-resistant *Staphylococcus aureus*, 1 unknown)

Figure 4. CAR T-cell Expansion by Ongoing Response in Patients With FL and MZL

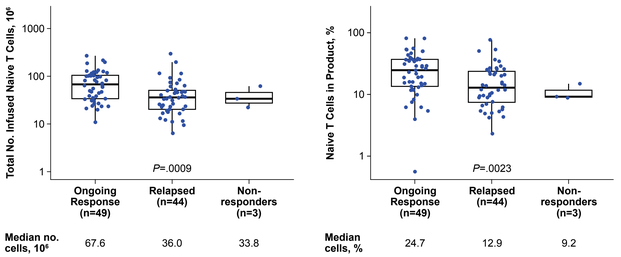


Median peak, cells/µL	52.2	29.6	25.4	71.2	27.8	14.7

P values were calculated using Wilcoxon rank sum tests comparing the ongoing response and relapsed subgroups.
AUC_{0-28}, area under the curve from Day 0 to 28; CAR, chimeric antigen receptor; FL, follicular lymphoma; MZL, marginal zone lymphoma.

- Among treated patients with both FL and MZL, those with ongoing response at 48 months continued to have higher CAR T-cell expansion by peak and area under the curve (AUC) than those who relapsed or had no response, consistent with prior reports (**Figure 4**)[4]

Figure 5. Number and Percent Naive T Cells in CAR Product by Ongoing Response in Patients With FL



Median no. cells, 10^6	67.6	36.0	33.8
Median cells, %	24.7	12.9	9.2

P values were calculated using Wilcoxon rank sum tests comparing the ongoing response and relapsed patients.
CAR, chimeric antigen receptor; FL, follicular lymphoma.

- Patients with FL and ongoing response at 48 months had a higher proportion of naive (CCR7+CD45RA+) T cells in axi-cel product (25%) than relapsed (13%) or nonresponding patients (9%, **Figure 5**)
  - Similar trends were observed in patients with MZL

CONCLUSIONS

- After ≥4 years median follow-up in ZUMA-5, axi-cel demonstrated continued durable responses and long-term survival in patients with R/R iNHL
  - In FL, median PFS was extended with longer follow-up (57.3 mo)[4]
  - In MZL, survival outcomes continued to improve with longer follow-up[4]
  - Low rate of progression or death due to lymphoma in patients with FL (33%) suggesting curative potential in those patients
- Safety outcomes were similar to those in previous data cutoffs[3,4], with no new safety signals observed
- In patients with FL, CAR T-cell expansion and preservation of a naive T-cell phenotype were more significantly pronounced in ongoing responders relative to relapsed patients, consistent with prior reports[3]
- These data continue to support axi-cel as a highly effective therapeutic approach for patients with R/R iNHL

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ACKNOWLEDGMENTS

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and healthcare staff at each study site
- Medical writing support was provided by Hameda Khandaker, PhD, of Nexus Global Group Science, funded by Kite, a Gilead Company
- This study was funded by Kite, a Gilead Company

DISCLOSURES

Full author disclosures are available through the virtual meeting platform