Poster 53

Long-Term Follow-Up Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

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BACKGROUND

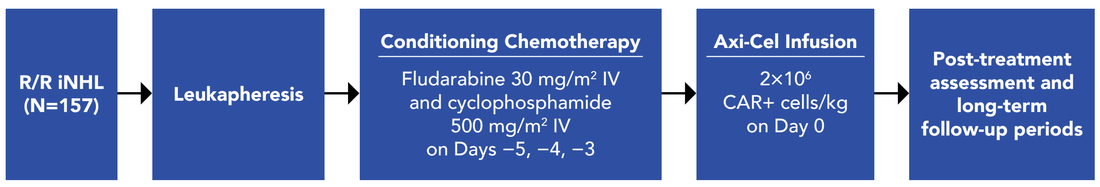
- Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of adults with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) and R/R follicular lymphoma (FL), both after ≥2 lines of systemic therapy[1,2]
- ZUMA-5 is a multicenter, single-arm Phase 2 study of axi-cel in patients with R/R indolent non-Hodgkin lymphoma (iNHL), including FL and marginal zone lymphoma (MZL)
  - In the primary analysis (N=104), the overall response rate (ORR) was 92% (74% complete response [CR] rate) after a 17.5-month median follow-up[3]
  - Median peak CAR T-cell levels were numerically greater in patients with FL who were in ongoing response at data cutoff than in those who relapsed[3]

OBJECTIVE

- To evaluate updated clinical and pharmacologic outcomes from ZUMA-5 with ≥2 years of follow-up

METHODS

Figure 1. ZUMA-5 Study Design



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 (IRRC assessed per the Lugano classification[4])

Key Secondary Endpoints

- CR rate (IRRC assessed)
- Investigator-assessed ORR[4]
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

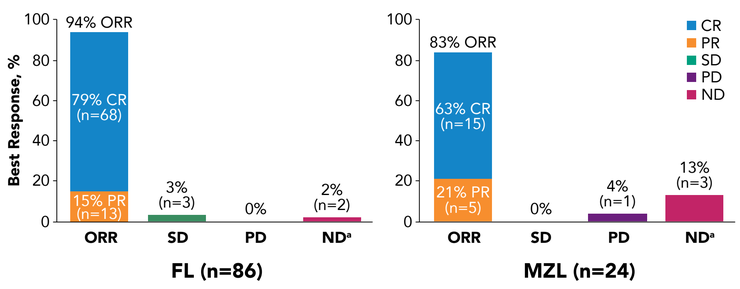
[a] Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible. [b] Single-agent anti-CD20 antibody did not count as line of therapy for eligibility.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Updated Analysis

- The updated efficacy analysis occurred when ≥80 treated patients with FL had ≥24 months of follow-up, per protocol
  - Efficacy-eligible patients (inferential analysis set) included ≥80 treated patients with FL who had ≥24 months of follow-up after axi-cel infusion and treated patients with MZL who had ≥4 weeks of follow-up after axi-cel infusion as of the data cutoff date
- Efficacy analyses are reported in the 110 efficacy-eligible patients (86 with FL; 24 with MZL)
  - The median follow-up for patients with FL was 30.9 months (range, 24.7–44.3)
  - The median follow-up for patients with MZL was 23.8 months (range, 7.4–39.4)
- Safety data are reported for all 149 patients treated with axi-cel (124 with FL; 25 with MZL)
- Data cutoff date: March 31, 2021

RESULTS

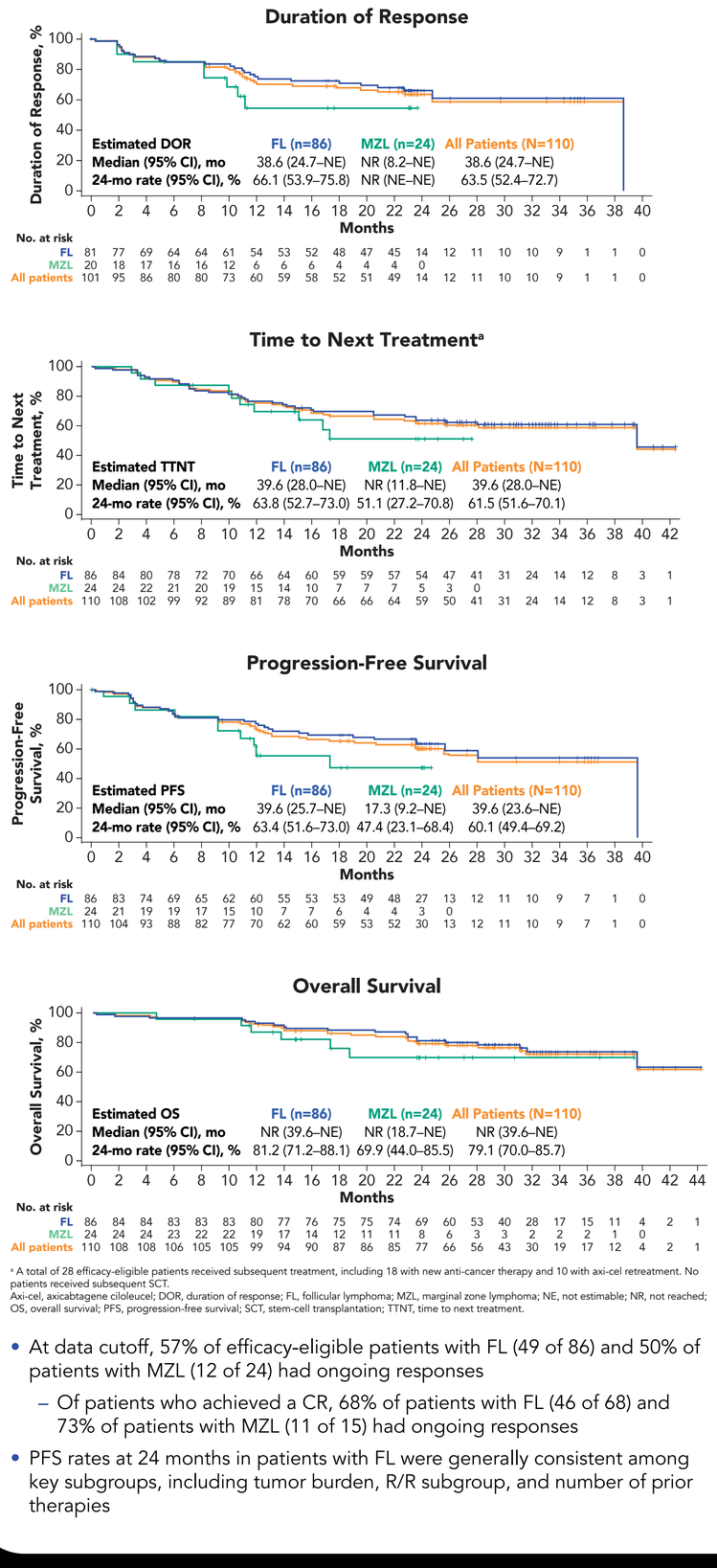
Figure 2. ORR by Central Review



Assessed in efficacy-eligible patients (n=110) by an IRRC according to the Lugano Classification.[4]
[a] Among the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and post-baseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment.
CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, not done/undefined; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- Among efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

Figure 3. DOR, TTNT, PFS, and OS



[a] A total of 28 efficacy-eligible patients received subsequent treatment, including 18 with new anti-cancer therapy and 10 with axi-cel retreatment. No patients received subsequent SCT.
Axi-cel, axicabtagene ciloleucel; DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; SCT, stem-cell transplantation; TTNT, time to next treatment.

- At data cutoff, 57% of efficacy-eligible patients with FL (49 of 86) and 50% of patients with MZL (12 of 24) had ongoing responses
  - Of patients who achieved a CR, 68% of patients with FL (46 of 68) and 73% of patients with MZL (11 of 15) had ongoing responses
- PFS rates at 24 months in patients with FL were generally consistent among key subgroups, including tumor burden, R/R subgroup, and number of prior therapies
- Despite limited sample size (n=24), the progression-free survival (PFS) rate at 12 months appeared to be consistent among key subgroups, including prior treatment with a Bruton tyrosine kinase inhibitor
- Median overall survival (OS) was not yet reached in efficacy-eligible patients with FL or MZL (**Figure 3**)
- Among patients with FL, 3 deaths occurred after Month 24; no disease progression events occurred after Month 24 (**Figure 3**)
  - Of the 3 deaths, 2 were from COVID-19 and 1 was from sepsis

Table 1. Efficacy Outcomes in Patients With FL by POD24 Status

Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

[a] Axi-cel–treated patients with FL and available efficacy data on progression after an anti-CD20 mAb + alkylating agent were included in the POD24 analysis.
Axi-cel, axicabtagene ciloleucel; DOR, duration of response; FL, follicular lymphoma; mAb, monoclonal antibody; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; POD24, progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy.

- Patients with FL who had progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy (POD24) benefitted from axi-cel, with estimated medians and 24-month rates of duration of response (DOR) and PFS consistent with all efficacy-eligible patients (**Table 1**)
  - Medians of DOR and PFS among patients without POD24 were not yet reached at data cutoff
- Consistent with prior reports, the most common Grade ≥3 adverse events (AEs) were neutropenia (33%), decreased neutrophil count (28%), and anemia (25%)
- Grade ≥3 cytokine release syndrome (CRS) and neurologic events (NEs) occurred in 7% of patients (6% FL; 8% MZL) and 19% of patients (15% FL; 36% MZL), respectively
  - Most CRS cases (120 of 121) and NEs (82 of 87) of any grade resolved by data cutoff
  - Nearly half of NEs (49%) resolved ≤2 weeks after onset; most NEs (76%) resolved ≤8 weeks after onset
- Grade ≥3 cytopenias present ≥30 days postinfusion were reported in 34% of patients (33% FL; 36% MZL), most commonly neutropenia in 29% of patients (27% FL; 36% MZL)

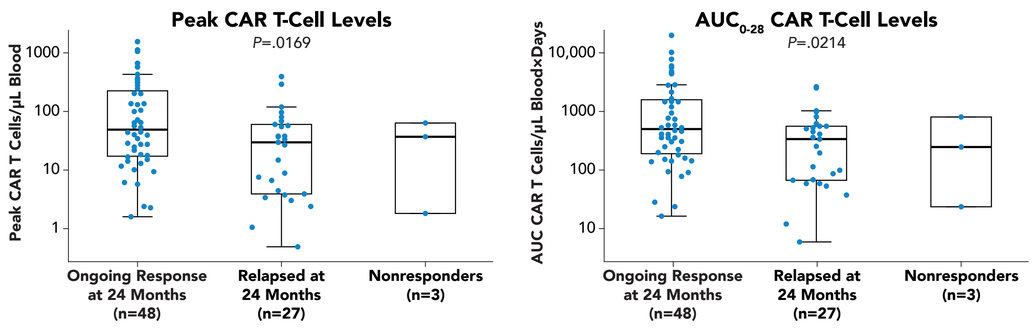
Table 2. AEs With First Occurrence After the Primary Analysis DCO[a]

AE, n (%)	All Patients (N=149)	
	Any Grade	Grade ≥3
Any AE	38 (26)	20 (13)
Serious AE	15 (10)	15 (10)
Cytopenia	11 (7)	7 (5)
Infection	25 (17)	11 (7)
CRS[b]	2 (1)	0 (0)
Neurologic event[b]	2 (1)	0 (0)
Hypogammaglobulinemia	4 (3)	0 (0)
Tumor lysis syndrome	0 (0)	0 (0)

CRS was graded according to Lee et al.[5] NEs were identified using the modified blinatumomab registrational study.[6] The severity of all AEs, including NEs and symptoms of CRS, was graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
[a] Includes all AEs that occurred after the primary analysis data cutoff date (March 12, 2020) and by the data cutoff date of the current analysis (March 31, 2021). [b] One patient with FL died of multisystem organ failure in the context of CRS (Day 7) prior to the resolution of CRS. Ongoing NEs in FL included Grade 1 attention disturbance, Grade 1 memory impairment, and Grade 1 paresthesia. Ongoing NEs in patients with MZL included Grade 2 facial paresthesia, and Grade 1 memory impairment.
AE, adverse event; CRS, cytokine release syndrome; DCO, data cutoff; NE, neurologic event.

- Grade 5 AEs occurred in 6 patients after the data cutoff of the primary analysis
  - Grade 5 infectious AEs occurred in 5 patients: 1 COVID-19 (FL, Day 717, unrelated), 1 COVID-19 pneumonia (FL, Day 780, related to axi-cel), 1 progressive multifocal leukoencephalopathy (FL, Day 697, related to axi-cel and conditioning chemotherapy, occurring after axi-cel retreatment) and 2 sepsis (FL, Day 1204; MZL, Day 139; both unrelated)
  - Acute bilineal leukemia occurred in 1 patient (FL, Day 623, conditioning chemotherapy related)
  - No Grade 5 AEs were due to progressive disease

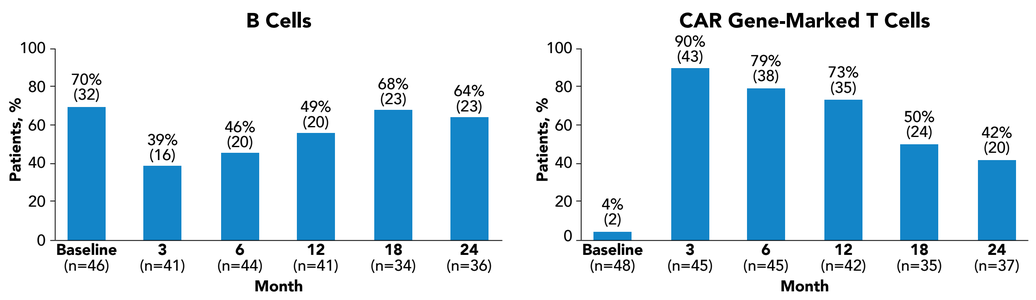
Figure 4. Robust CAR T-Cell Expansion in Patients With FL and Ongoing Responses at 24 Months



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

- CAR T-cell expansion by peak and area under the curve was significantly higher in patients with FL who had an ongoing response at 24 months postinfusion than in those who were relapsed (**Figure 4**)
  - Peak CAR T-cell levels were generally comparable among patients with FL who had tumor bulk by the sum of product diameters above or below the median (31.6 vs 42.5 cells/µL)
  - Pharmacokinetic findings were similar in patients with MZL

Figure 5. Detectable B Cells and CAR T Cells Over Time in Patients With FL and Ongoing Responses at 24 Months



CAR, chimeric antigen receptor; FL, follicular lymphoma.

- The majority of patients with FL and an ongoing response had detectable B cells by Month 18; by Month 24, less than half had low levels of detectable CAR gene-marked cells (**Figure 5**)
  - The levels of CAR gene-marked T cells were inversely correlated with that of B cells at each time point postinfusion

CONCLUSIONS

- With long-term follow-up in ZUMA-5, axi-cel demonstrated substantial and continued benefit in patients with R/R iNHL
  - In FL, high response rates translated to durability after 31 months median follow-up
    - Median DOR was 38.6 months, and 57% of efficacy-eligible patients were in ongoing response at data cutoff
    - Median PFS was nearly 40 months, and median OS was not yet reached
  - In MZL, efficacy outcomes appeared to improve with longer follow-up (median, 24 months)
    - Median DOR and OS not yet reached; median PFS was 17.3 months
    - 50% of patients were in ongoing response at data cutoff
- Axi-cel maintained a manageable safety profile in iNHL, with no new safety signals
- Results of the long-term pharmacokinetic analysis suggest that functional CAR T-cell persistence may not be required for long-term remissions in patients with FL, consistent with prior findings in aggressive lymphomas[7]
- Axi-cel is a highly effective therapeutic approach for patients with R/R iNHL

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