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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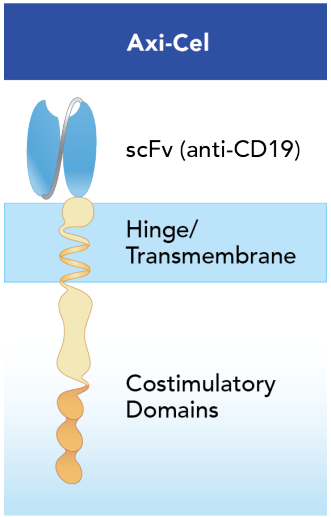
Background

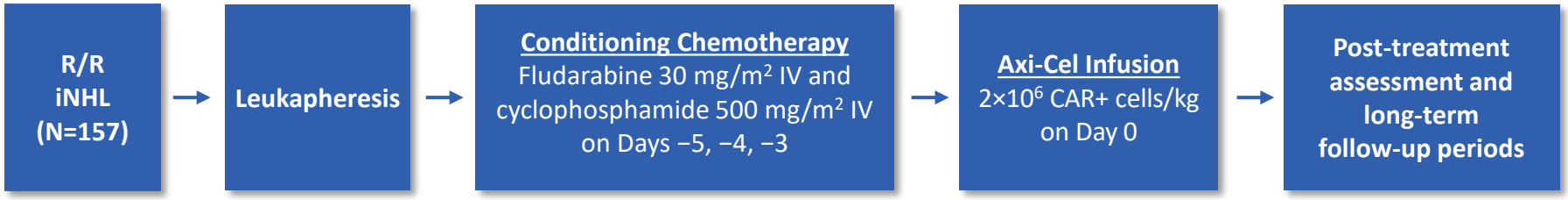
- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of adults with R/R LBCL and R/R FL, both after ≥2 lines of systemic therapy[1,2]
- ZUMA-5 is a multicenter, single-arm Phase 2 study of axi-cel in patients with R/R iNHL, including FL and MZL
  - In the primary analysis (N=104), the ORR was 92% (74% 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]
- Here, we report updated clinical and pharmacologic outcomes from ZUMA-5 with ≥2 years of follow-up



1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2021. 2. YESCARTA® (axicabtagene ciloleucel) [Summary of Product Characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2021. 3. Jacobson CA, et al. *Lancet Oncol.* 2022 Jan;23(1):91-103.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; LBCL, large B-cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; R/R, relapsed/refractory; scFv, single-chain variable fragment.

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[1])

Key Secondary Endpoints

- CR rate (IRRC assessed)
- Investigator-assessed ORR[1]
- 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.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

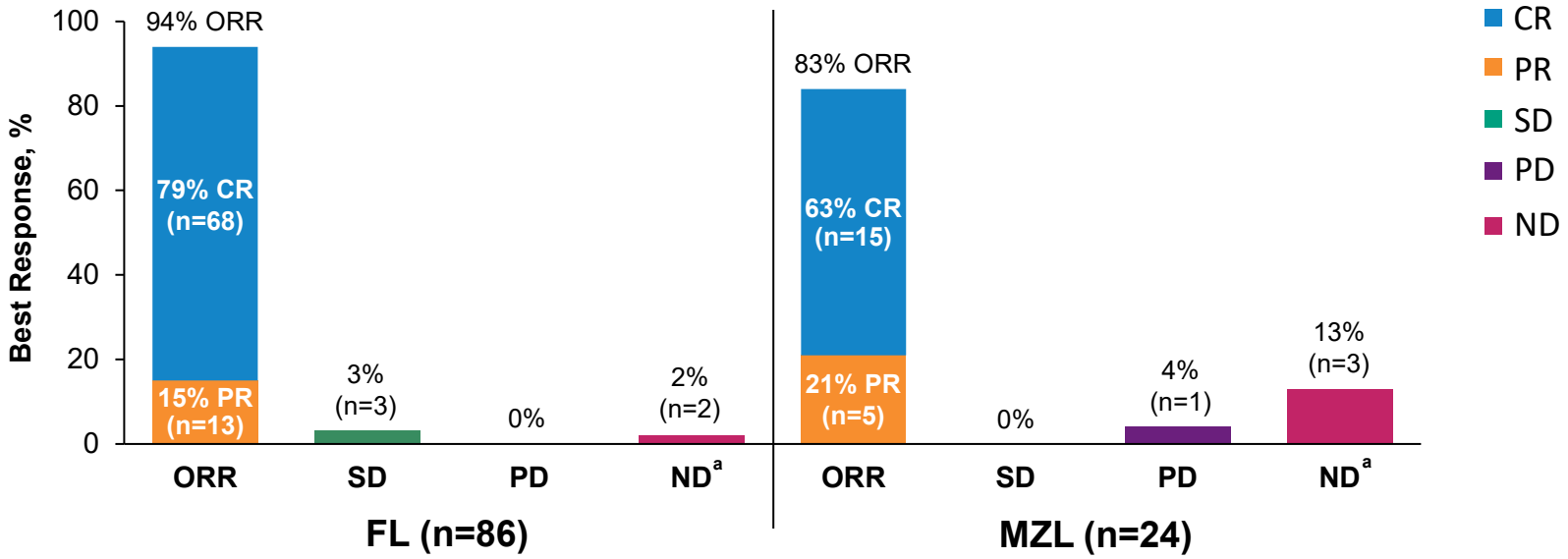
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone 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[a]
- Efficacy analyses are reported in the 110 efficacy-eligible patients (86 with FL; 24 with MZL)[a]
  - 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

[a] 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.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; MZL, marginal zone lymphoma.

Overall Response Rate by Central Review

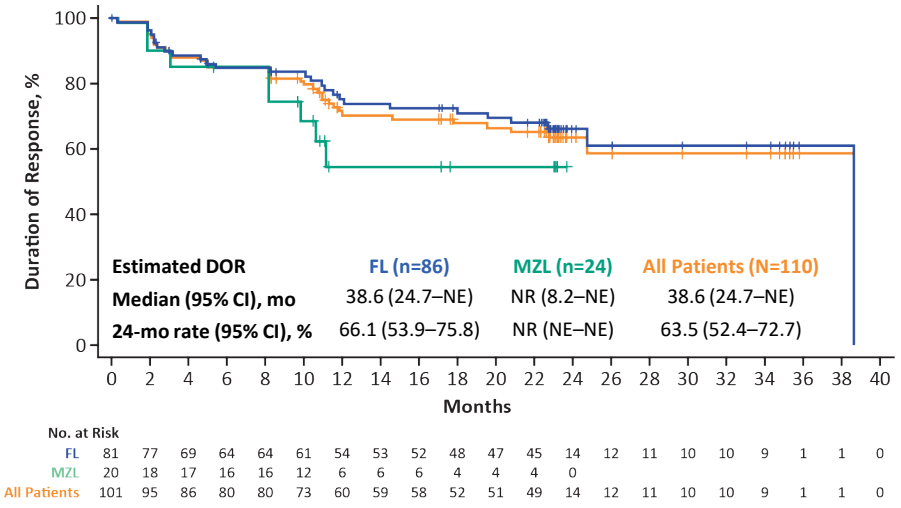


- Among all efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

Assessed in efficacy-eligible patients (n=110) by an IRRC according to the Lugano Classification (Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068).
[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; iNHL, indolent non-Hodgkin 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.

Duration of Response and Time to Next Treatment

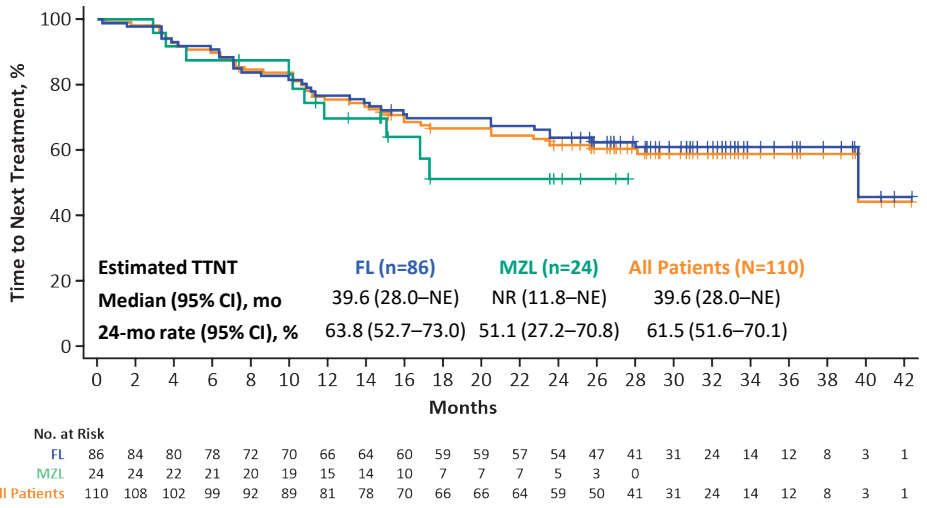
Duration of Response



No. at Risk

FL	81	77	69	64	64	61	54	53	52	48	47	45	14	12	11	10	10	9	1	1	0
MZL	20	18	17	16	16	12	6	6	6	4	4	4	0								
All Patients	101	95	86	80	80	73	60	59	58	52	51	49	14	12	11	10	10	9	1	1	0

Time to Next Treatment[a]



No. at Risk

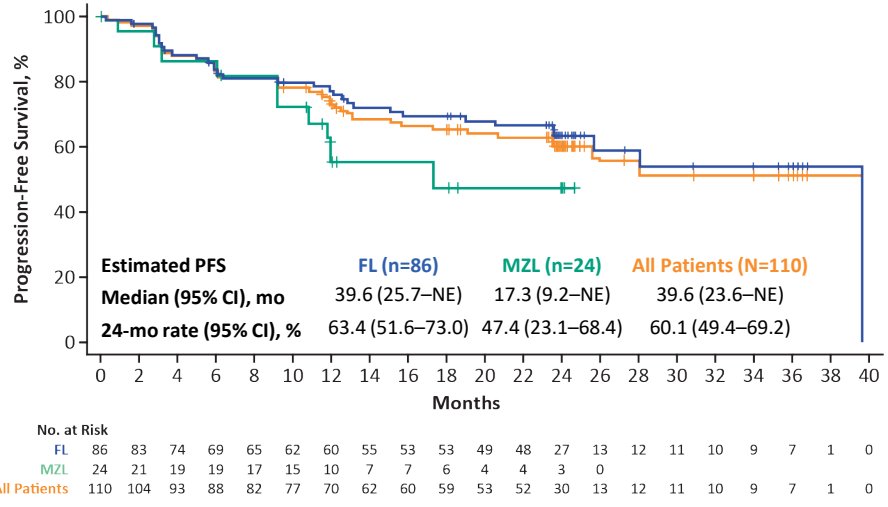
FL	86	84	80	78	72	70	66	64	60	59	59	57	54	47	41	31	24	14	12	8	3	1
MZL	24	24	22	21	20	19	15	14	10	7	7	7	5	3	0							
All Patients	110	108	102	99	92	89	81	78	70	66	66	64	59	50	41	31	24	14	12	8	3	1

- 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

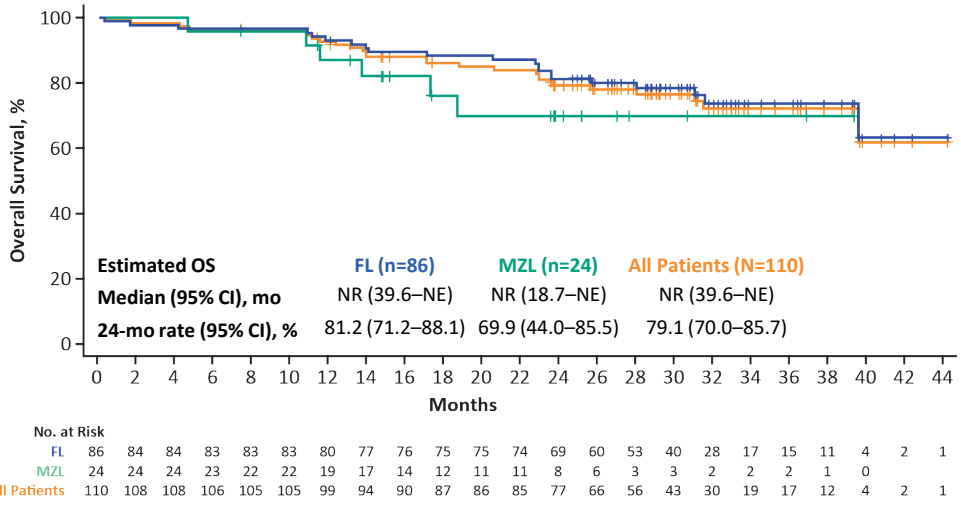
[a] A total of 28 efficacy-eligible patients received subsequent treatment, including 18 with new anti-cancer therapy and 10 with axi-cel retreatment. No patients received subsequent SCT.
Axi-cel, axicabtagene ciloleucel; CR, complete response; DOR, duration of response; FL, follicular lymphoma; MZL,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

Progression-Free Survival and Overall Survival

Progression-Free Survival



Overall Survival



- Median OS was not yet reached in efficacy-eligible patients with FL or MZL
- Among patients with FL, 3 deaths occurred after Month 24[a]; no disease-progression events occurred after Month 24

[a] Of the 3 deaths, 2 were from COVID-19 and 1 was from sepsis.

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Efficacy Outcomes in Patients With FL by POD24 Status

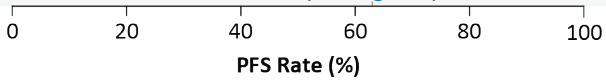
Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months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

- Patients with FL who had POD24 benefitted from axi-cel, with estimated medians and 24-month rates of DOR and PFS consistent with all efficacy-eligible patients
  - Medians of DOR and PFS among patients without POD24 were not yet reached at data cutoff

[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.

PFS Rate at 24 Months in Key FL Subgroups

		No. of Patients	No. of Patients At Risk	PFS Rate (95% CI)
Overall		**86**	**27**	**63 (52–73)**
Age, years	<65	55	17	65 (50–76)
	≥65	31	10	61 (41–77)
Sex	Male	48	13	59 (43–72)
	Female	38	14	69 (51–82)
ECOG performance status	0	51	17	67 (52–79)
	1	35	10	56 (36–72)
High tumor burden (GELF criteria)	Yes	42	10	55 (37–69)
	No	44	17	71 (55–83)
Relapse/refractory subgroup	Relapsed	23	8	73 (49–87)
	Refractory	63	19	60 (46–72)
Number of prior lines of therapy	2	26	11	73 (51–86)
	3	20	3	45 (22–66)
	≥4	40	13	66 (48–79)
Prior stem cell transplantation	Yes	21	7	85 (61–95)
	No	65	20	56 (42–68)
Prior lenalidomide	Yes	27	6	58 (36–75)
	No	59	21	66 (51–77)
Prior PI3K inhibitor	Yes	28	9	56 (35–73)
	No	58	18	67 (53–78)
Prior BTK inhibitor	Yes	6	2	50 (11–80)
	No	80	25	64 (52–74)



- Long-term PFS rates in patients with FL were generally consistent among key subgroups

BTK, Bruton tyrosine kinase; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival.

PFS Rate at 12 Months in Key MZL Subgroups

		No. of Patients	No. of Patients At Risk	PFS Rate (95% CI)
Overall		**24**	**10**	**61 (37–79)**
Age, years	<65	11	3	63 (22–87)
	≥65	13	7	58 (27–80)
Sex	Male	11	3	49 (17–75)
	Female	13	7	73 (37–90)
ECOG performance status	0	14	7	74 (39–91)
	1	10	3	47 (15–74)
High tumor burden (GELF criteria)	Yes	10	4	53 (17–79)
	No	14	6	67 (34–86)
Relapse/refractory subgroup	Relapsed	6	2	50 (6–85)
	Refractory	18	8	66 (39–83)
Number of prior lines of therapy	2	8	3	71 (26–92)
	3	7	5	83 (27–98)
	≥4	9	2	38 (9–67)
Prior stem cell transplantation	Yes	3	1	50 (1–91)
	No	21	9	64 (38–81)
Prior lenalidomide	Yes	8	4	75 (32–93)
	No	16	6	55 (26–77)
Prior PI3K inhibitor	Yes	9	4	63 (23–86)
	No	15	6	61 (29–82)
Prior BTK inhibitor	Yes	12	4	61 (27–84)
	No	12	6	64 (30–85)

- Despite limited sample size, the PFS rate at 12 months appeared to be consistent among key subgroups, including prior treatment with a BTK inhibitor

BTK, Bruton tyrosine kinase; ECOG, Eastern Cooperative Oncology Group; GELF, Groupe d'Etude des Lymphomes Folliculaires; MZL, marginal zone lymphoma; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival.

Safety Results

- Consistent with prior reports, the most common Grade ≥3 AEs were neutropenia (33%), decreased neutrophil count (28%), and anemia (25%)

- Grade ≥3 CRS and 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[a]
  - Nearly half of NEs (49%) resolved ≤2 weeks after onset; most NEs (76%) resolved ≤8 weeks after onset

- Grade ≥3 cytopenias present ≥30 days post-infusion were reported in 34% of patients (33% FL; 36% MZL), most commonly neutropenia in 29% of patients (27% FL; 36% MZL)

CRS was graded according to Lee DW, et al. *Blood*. 2014;124:188-195. NEs were identified using the modified blinatumomab registrational study (Topp MS, et al. *Lancet Oncol.* 2015;16;57-66). 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] 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; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, neurologic event.

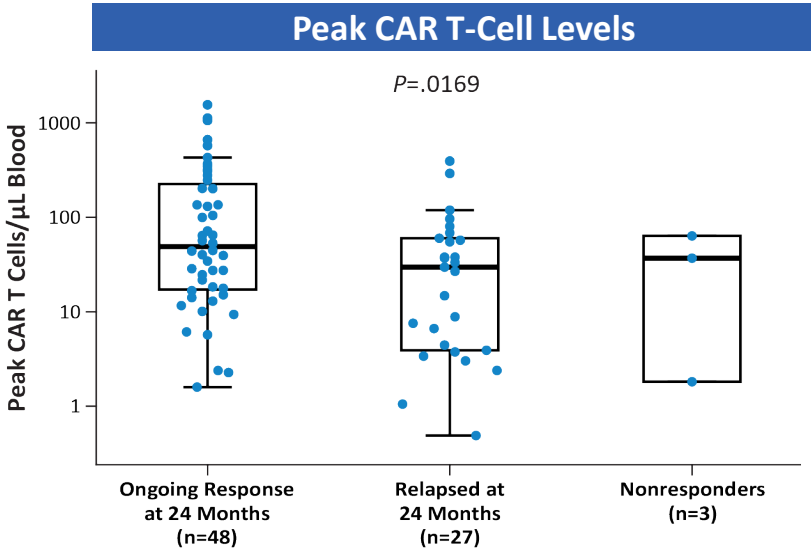
AEs With First Occurrence After the Primary Analysis DCO[a]

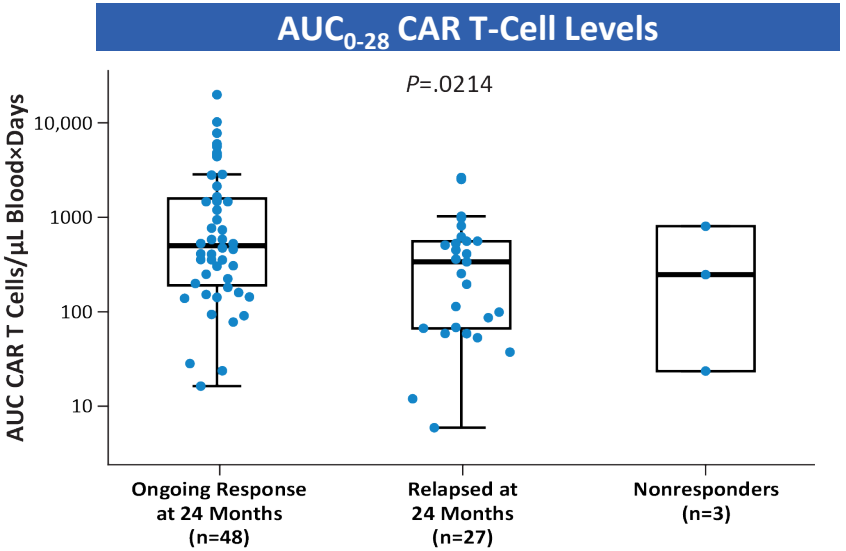
AE, n (%)	Follicular Lymphoma (N=124)		Marginal Zone Lymphoma (N=25)		All Patients (N=149)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	27 (22)	14 (11)	11 (44)	6 (24)	38 (26)	20 (13)
Serious AE	11 (9)	11 (9)	4 (16)	4 (16)	15 (10)	15 (10)
Cytopenia	8 (6)	4 (3)	3 (12)	3 (12)	11 (7)	7 (5)
Infection	18 (15)	7 (6)	7 (28)	4 (16)	25 (17)	11 (7)
CRS	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Neurologic event	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Hypogammaglobulinemia	2 (2)	0 (0)	2 (8)	0 (0)	4 (3)	0 (0)
Tumor lysis syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- Grade 5 AEs occurred in 6 patients after the data cutoff of the primary analysis[b]
  - 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 PML[c] (FL, Day 697, related to axi-cel and CC), and 2 sepsis (FL, Day 1204; MZL, Day 139; both unrelated)
  - Acute bilineal leukemia occurred in 1 patient (FL, Day 623, CC related)

[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] No Grade 5 AEs were due to progressive disease.
[c] The Grade 5 PML event occurred after axi-cel retreatment.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CC, conditioning chemotherapy; CRS, cytokine release syndrome; DCO, data cutoff; FL, follicular lymphoma; MZL, marginal zone lymphoma; PML, progressive multifocal leukoencephalopathy.

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

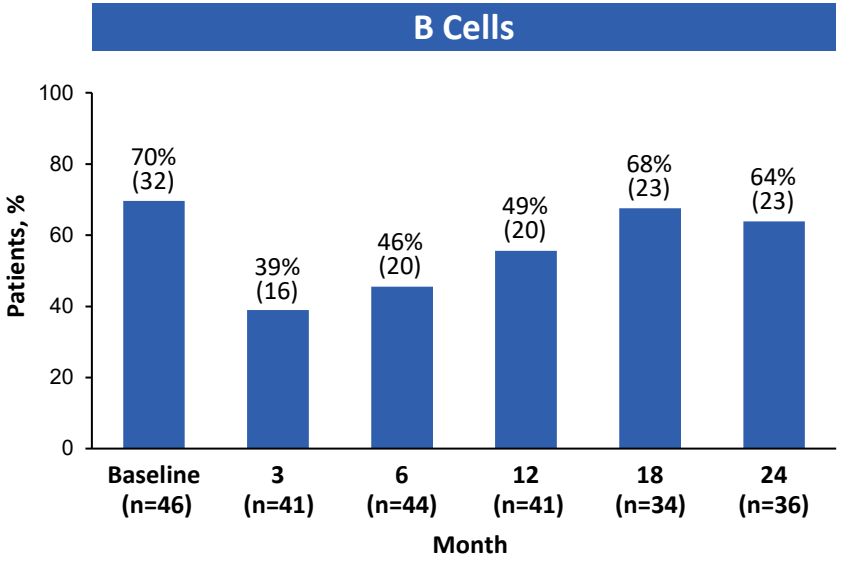


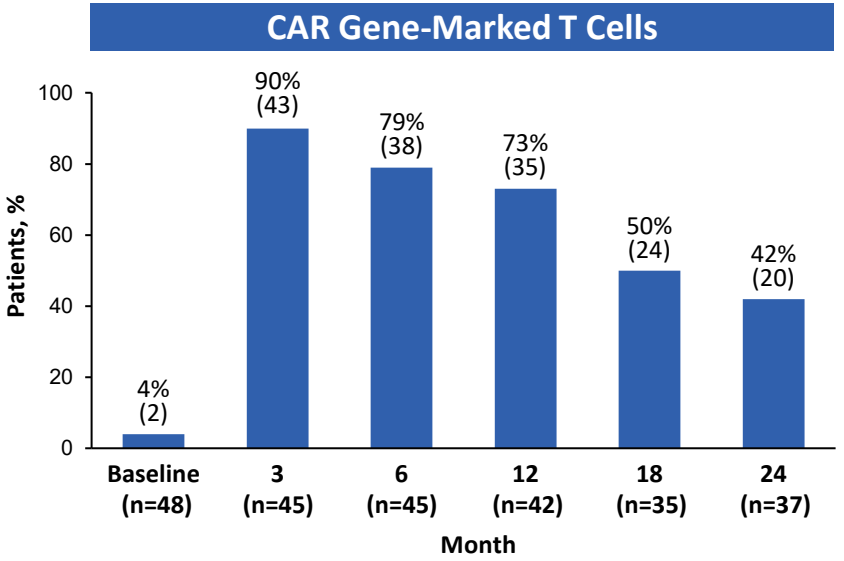


- CAR T-cell expansion by peak and AUC was significantly higher in patients with FL who had an ongoing response at 24 months post-infusion than in those who were relapsed
  - Peak CAR T-cell levels were generally comparable among patients with FL who had tumor bulk by SPD above or below the median (31.6 vs 42.5 cells/µL)
  - Pharmacokinetic findings were similar in patients with MZL

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 0-28; CAR, chimeric antigen receptor; FL, follicular lymphoma, MZL, marginal zone lymphoma; SPD, sum of product diameters.

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





- 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
  - The levels of CAR gene-marked T cells were inversely correlated with that of B cells at each timepoint post-infusion

CAR, chimeric antigen receptor; FL, follicular lymphoma.

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-month 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[1]
- Axi-cel is a highly effective therapeutic approach for patients with R/R iNHL

1. Neelapu SS, et al. ASH 2018. Abstract 2967.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

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- These data were previously presented at the 2021 Annual Meeting of the American Society of Hematology[1]

1. Neelapu SS, et al. ASH 2021. Abstract 93.