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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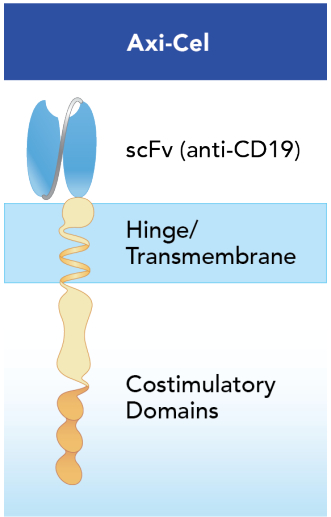
Disclosures

Sattva S Neelapu: honorarium from Kite, a Gilead Company, Merck, Bristol Myers Squibb, Novartis, Celgene, Pfizer, Allogene Therapeutics, Cell Medica/Kuur, Incyte, Precision Biosciences, Legend Biotech, Adicet Bio, Calibr, Unum Therapeutics, and Bluebird Bio; personal fees from Kite, a Gilead Company, Merck, Bristol Myers Squibb, Novartis, Celgene, Pfizer, Allogene, Kuur, Incyte, Precision BioSciences, Legend, Adicet Bio, Calibr, and Unum Therapeutics; research funding from Kite, a Gilead Company, Bristol Myers Squibb, Merck, Poseida, Cellectis, Celgene, Karus Therapeutics, Unum Therapeutics (Cogent Biosciences), Allogene, Precision BioSciences, Acerta, and Adicet Bio; and patents, royalties, or other intellectual property from Takeda Pharmaceuticals and related to cell therapy.

Background

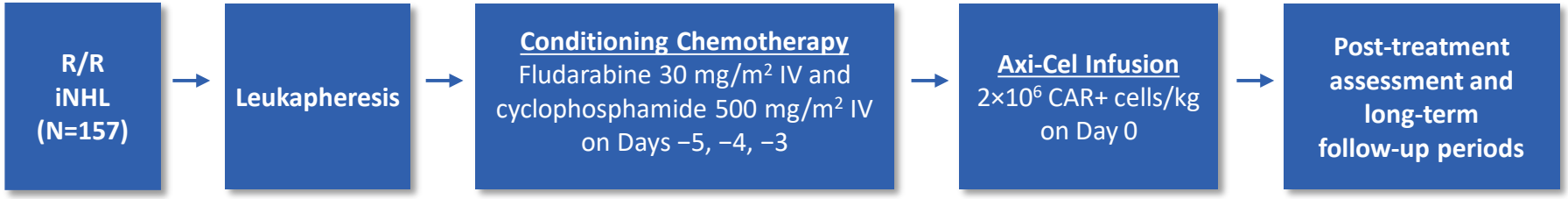
- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of adults with R/R LBCL and R/R FL, both after ≥2 lines of systemic therapy[1,2]
- ZUMA-5 is a multicenter, single-arm Phase 2 study of axi-cel in patients with R/R iNHL, including FL and MZL
  - In the primary analysis (N=104), the ORR was 92% (76% 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. ASH 2020. Abstract #700.

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[a]
- 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.

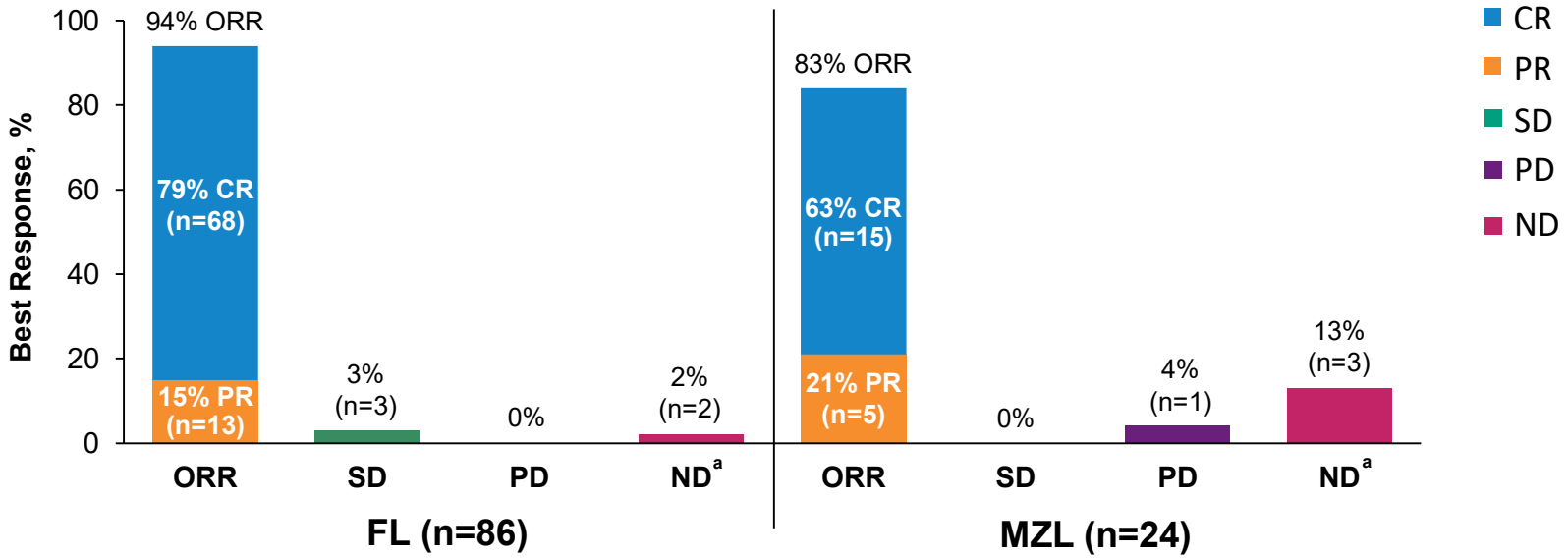
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone 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.

ORR by Central Review

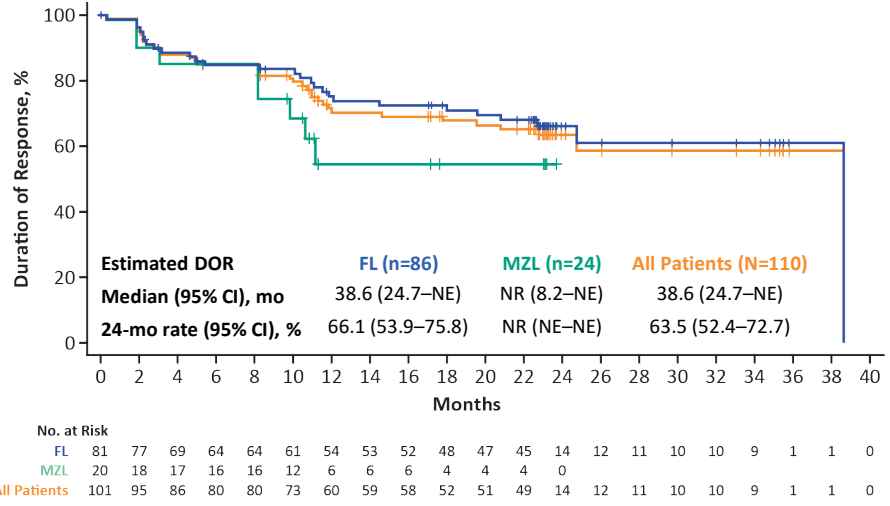


- Among efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

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.

DOR and TTNT

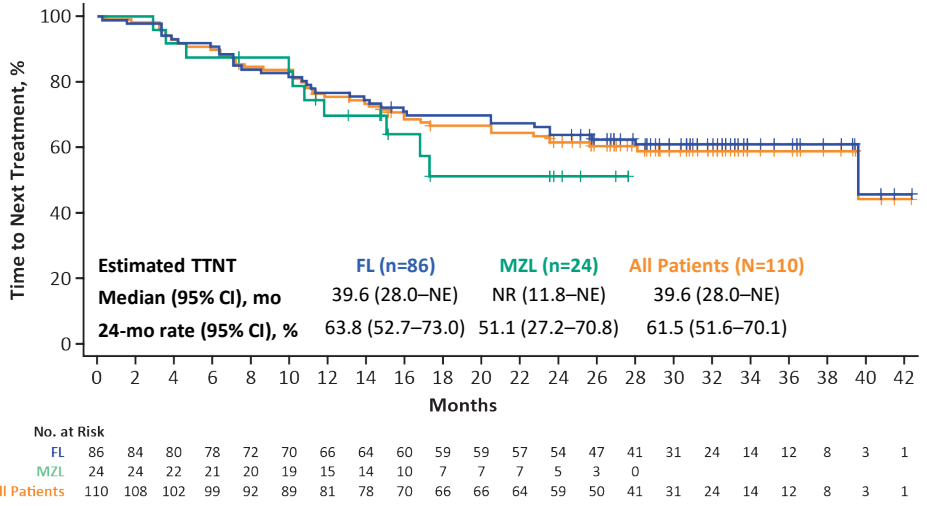
Duration of Response



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

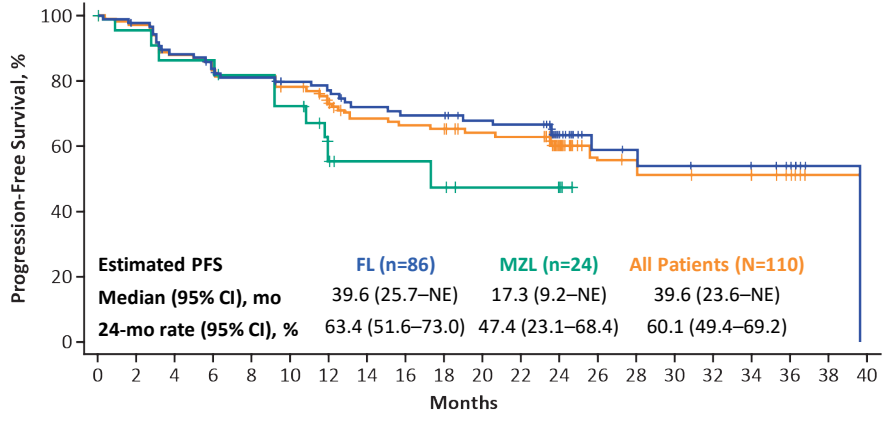
FL	86	84	80	78	72	70	66	64	60	59	59	57	54	47	41	31	24	14	12	8	3	1
MZL	24	24	22	21	20	19	15	14	10	7	7	7	5	3	0							
All Patients	110	108	102	99	92	89	81	78	70	66	66	64	59	50	41	31	24	14	12	8	3	1

- 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.

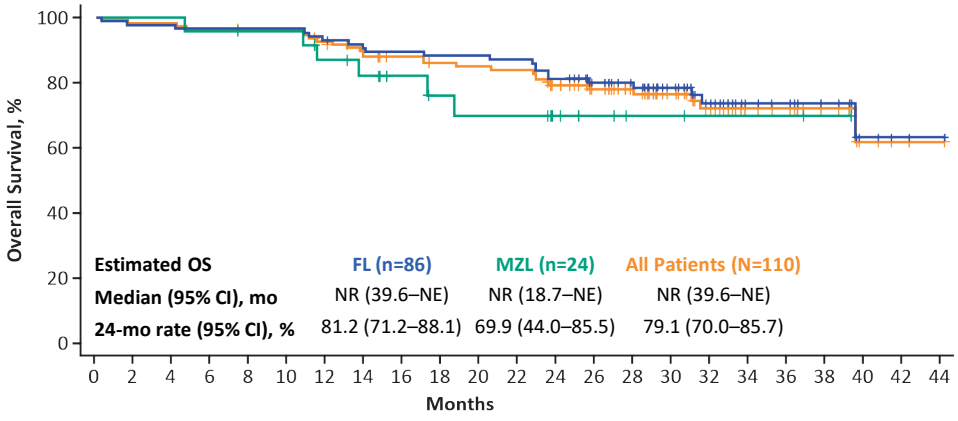
PFS and OS

Progression-Free Survival



No. at Risk																				
FL	86	83	74	69	65	62	60	55	53	53	49	48	27	13	12	11	10	9	7	1	0
MZL	24	21	19	19	17	15	10	7	7	6	4	4	3	0							
All Patients	110	104	93	88	82	77	70	62	60	59	53	52	30	13	12	11	10	9	7	1	0

Overall Survival



No. at Risk																						
FL	86	84	84	83	83	83	80	77	76	75	75	74	69	60	53	40	28	17	15	11	4	2	1
MZL	24	24	24	23	22	22	19	17	14	12	11	11	8	6	3	3	2	2	2	1	0		
All Patients	110	108	108	106	105	105	99	94	90	87	86	85	77	66	56	43	30	19	17	12	4	2	1

- 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

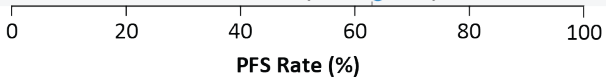
Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months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

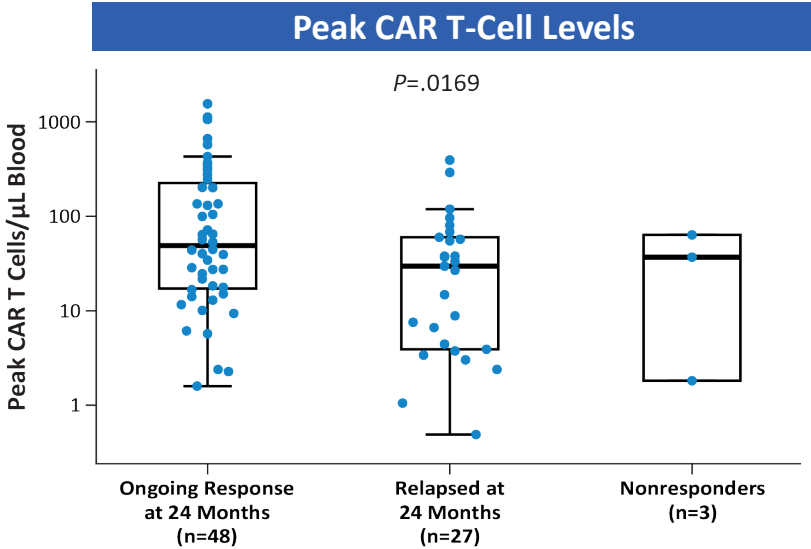
AEs With First Occurrence After the Primary Analysis DCO[a]

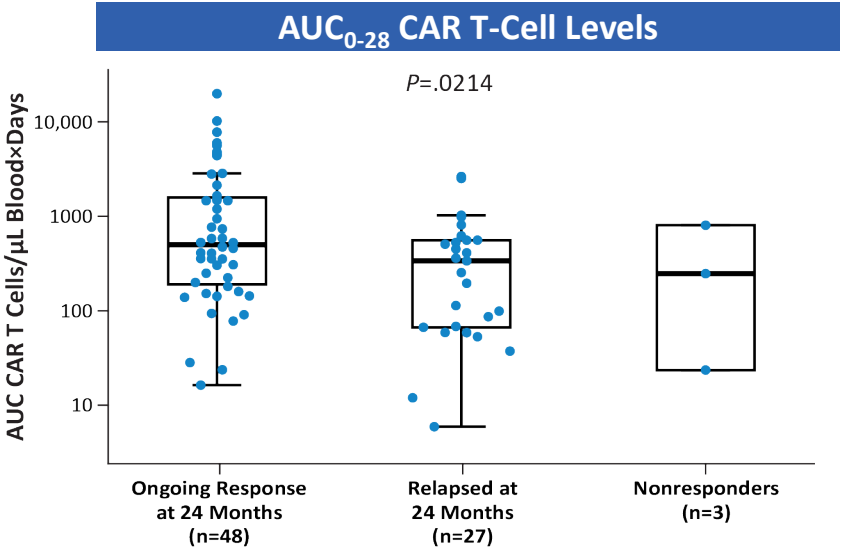
AE, n (%)	Follicular Lymphoma (N=124)		Marginal Zone Lymphoma (N=25)		All Patients (N=149)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	27 (22)	14 (11)	11 (44)	6 (24)	38 (26)	20 (13)
Serious AE	11 (9)	11 (9)	4 (16)	4 (16)	15 (10)	15 (10)
Cytopenia	8 (6)	4 (3)	3 (12)	3 (12)	11 (7)	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

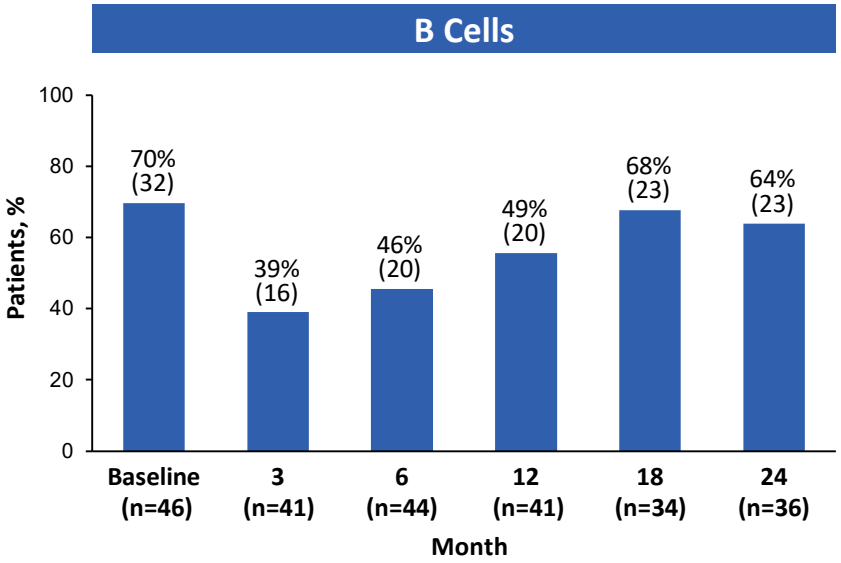


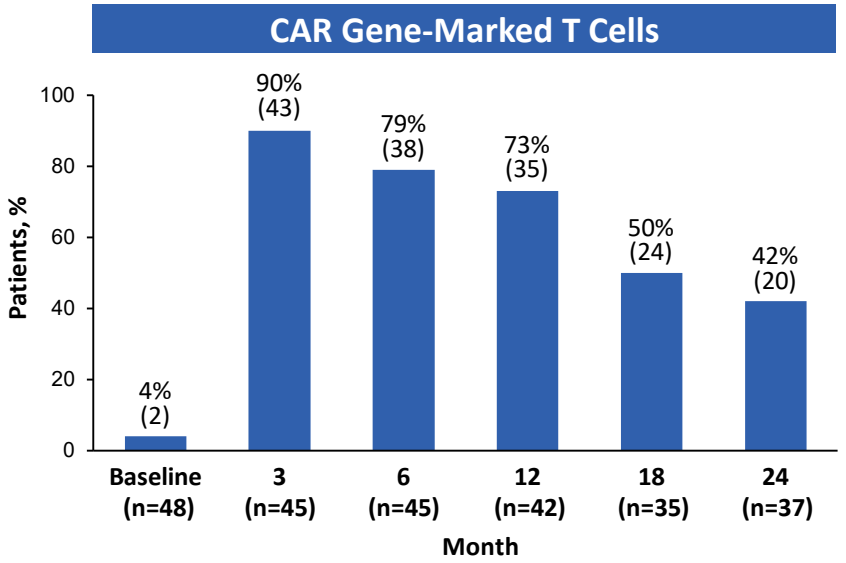


- CAR T-cell expansion by peak and AUC was significantly higher in patients with FL who had an ongoing response at 24 months post-infusion than in those who were relapsed
  - Peak CAR T-cell levels were generally comparable among patients with FL who had tumor bulk by SPD above or below the median (31.6 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 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[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.

Acknowledgments

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and healthcare staff at each study site
- The authors thank Lisa Johnson, PhD; Justin Chou, PhD; Madison Davis; and Emily Marsh, currently or formerly of Kite, a Gilead Company, for their contributions to this analysis
- Medical writing support was provided by Danielle Luebke, PhD, of Nexus Global Group Science, funded by Kite, a Gilead Company
- This study was funded by Kite, a Gilead Company