Three-Year Follow-Up Analysis of Axicabtagene Ciloleucel in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5)

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Supplementary Methods

Disease Assessments Among Patients With FL and ≥3 Prior Lines of Therapy.

A discrepancy was noted between central and local histological diagnoses of follicular-lymphoma (FL)-subtype iNHL in the FL population of ZUMA-5. A discrepancy was expected as diagnosis of FL relies heavily on the size of the tissue sample as well as the location of the biopsies. Due to these diagnostic challenges as well as the hypothesis that patients with non-confirmed FL may benefit from axicabtagene ciloleucel (axi-cel) treatment, as per protocol, eligibility requirement for enrollment was based on the histopathological diagnosis by local assessments. A retrospective central confirmation was completed; this analysis was not required for treatment or continued enrollment on the study per protocol. Nonetheless, cases with central lab assessment that were highly suggestive of an alternative diagnosis were excluded from the analysis, defined as "patients with FL excluding centrally confirmed non-FL diagnosis." The 5 excluded patients included 3 patients who were found to have diffuse large B-cell lymphoma (DLBCL) transformed in background of FL, 1 patient who was found to have small B-cell lymphoma, and 1 subject who was found to have marginal zone lymphoma (MZL) per central pathology. Those patients were not included in the population of FL excluding centrally confirmed non-FL. Of note, cases without available tissue for central lab assessment were included in the dataset. Patients with MZL were excluded from the analysis.

Total Metabolic Tumor Volume Assessment (TMTV)

TMTV was based on attenuation-corrected, whole-body FDG PET-CT scans at screening, consistent with previous assessments.[1] Briefly, whole-body FDG PET-CT scans were performed in ZUMA-5 patients who underwent at least a 4-hour fast before FDG administration. Patients with acceptable blood glucose values (<200 mg/dl), received an intravenous dose of FDG (recommended range: 370–740 MBq [10 – 20 mCi] with weight-based adjustments allowed) per institutional standard procedures. Following a 60 (+10) minute incubation period, low-dose CT for attenuation correction (CTAC) was obtained (70–80mA, 120–140 kvP) followed by PET emission scanning in 2D or 3D mode at 2–5 minutes/bed position. Reconstruction algorithms (iterative reconstruction, with time of flight, if available) and post-acquisition filtering were performed per manufacturer's recommendation based on local institutional practices. Images were uploaded to a centralized site to determine MTV. Whole-tumor volumes of interest (VOI) were placed on individual tumors using a predefined, semiautomated approach that included semiautomated placement of outlines around regions of abnormal FDG uptake at least moderately greater than that of normal liver (visual Lugano score >3) followed by manual adjustments of the lesion contours by a single PET radiologist per patient to ensure entire tumor lesions were included and/or nontumorous/normal tissue regions were excluded. Subsequent radiologist-defined adjustments of VOI placement included adding regions of tumor not initially captured and excluding normal tissue. MTV was calculated as the number of

voxels, or volume picture elements, with standardized uptake value (SUV) measurements between 41% and 100% of tumor SUVmax and reported as total MTV (mL) per patient.

Propensity Score Matching to Analyze Prior Bendamustine Exposure Among Patients With FL.

Covariates used for propensity score estimation and matching were baseline metabolic tumor volume (continuous), ECOG performance score (1 vs 0; binary), FLIPI score (≥3 vs <3; binary), number of prior chemotherapy lines (≥4 vs 3 vs ≤2; categorical), age (continuous), double refractory status to the prior anti-CD20 monoclonal antibody, alkylating agent (yes vs no; binary), and whether the last systemic therapy was administered <12 months from enrollment (yes vs no; binary). Progression of disease within 24 months (POD24) could not be used as a matching variable due to missing values and was used as a variable determining balancing after matching. Propensity score matching was performed after a 1:1 matching within a caliper of 1 on log2-transformed metabolic tumor volume and a caliper of 1.5 on age, while exact matching was performed on whether the last systemic therapy was administered <12 months from enrollment.

Figure S1. Baseline Metabolic Tumor Volume Correlated With SPD in Patients With FL

Association between metabolic tumor volume and tumor volume per SPD in enrolled patients with FL, as assessed by Spearman rank-sum correlation. The solid line represents the fit and the blue shading represents the 95% CI. FL, follicular lymphoma; SPD, sum of product diameters.

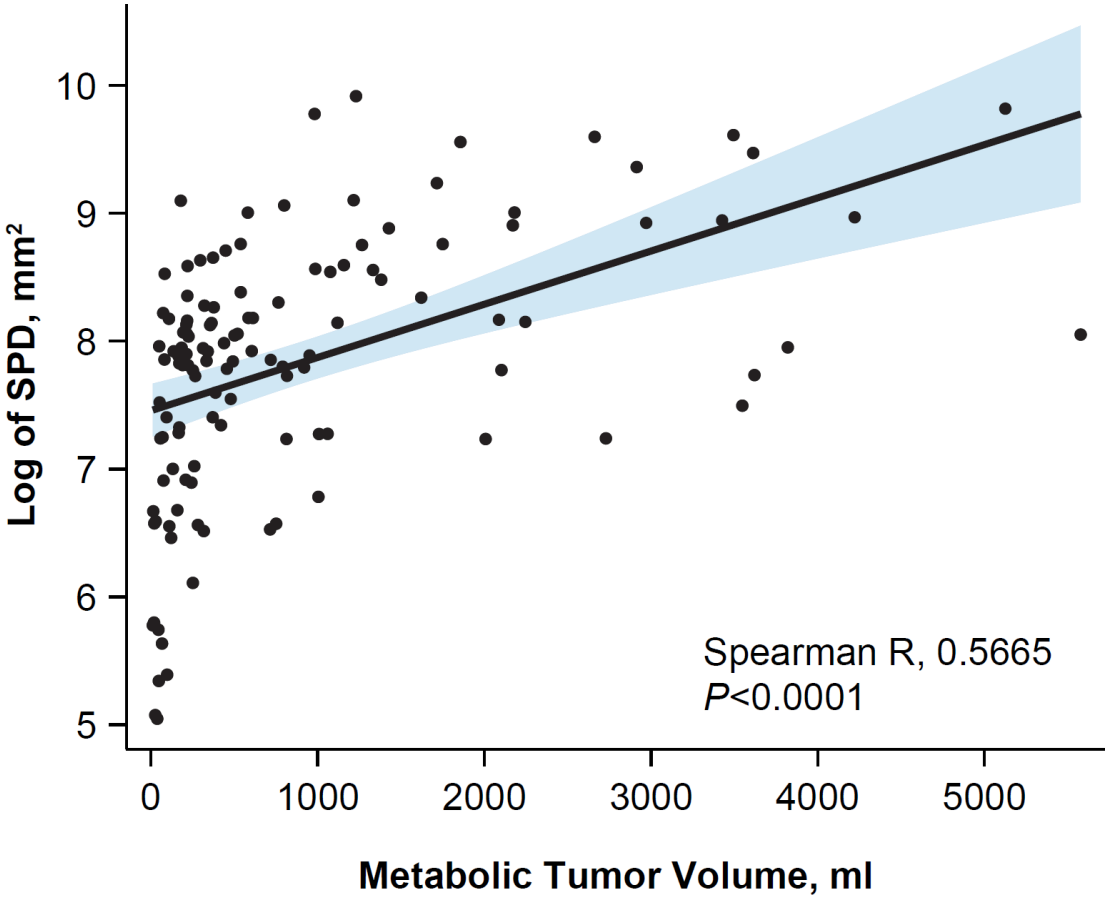

Figure S2. Duration of Response in Enrolled Patients and in Patients With FL by Response

Kaplan-Meier estimates of duration of response to axi-cel per investigator assessment among (A) enrolled patients with iNHL, assessed by disease type and (B) patients with FL assessed by best response (CR or PR). Axi-cel, axicabtagene ciloleucel; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; partial response; PR, partial response.

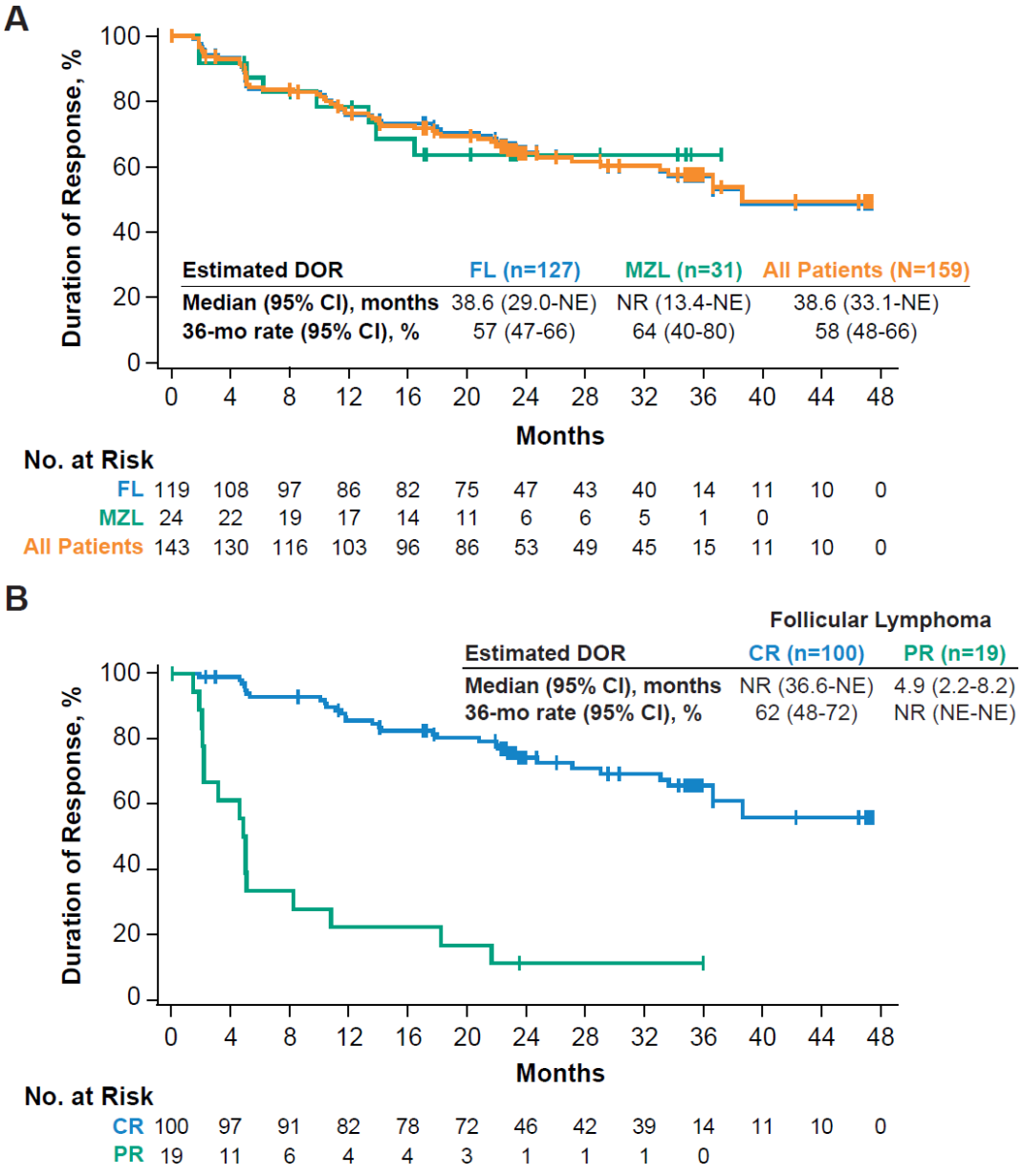

Figure S3. Cumulative Incidence of Progression or Death Due to Lymphoma in Patients With Follicular Lymphoma With Non-Lymphoma Mortality as a Competing Risk

Cumulative incidence plots of competing risk lymphoma-specific PFS by investigator assessment in enrolled patients with FL. Main events included those due to lymphoma. Events due to study treatment or not otherwise attributed to lymphoma were considered competing risks. FL, follicular lymphoma; progression-free survival.

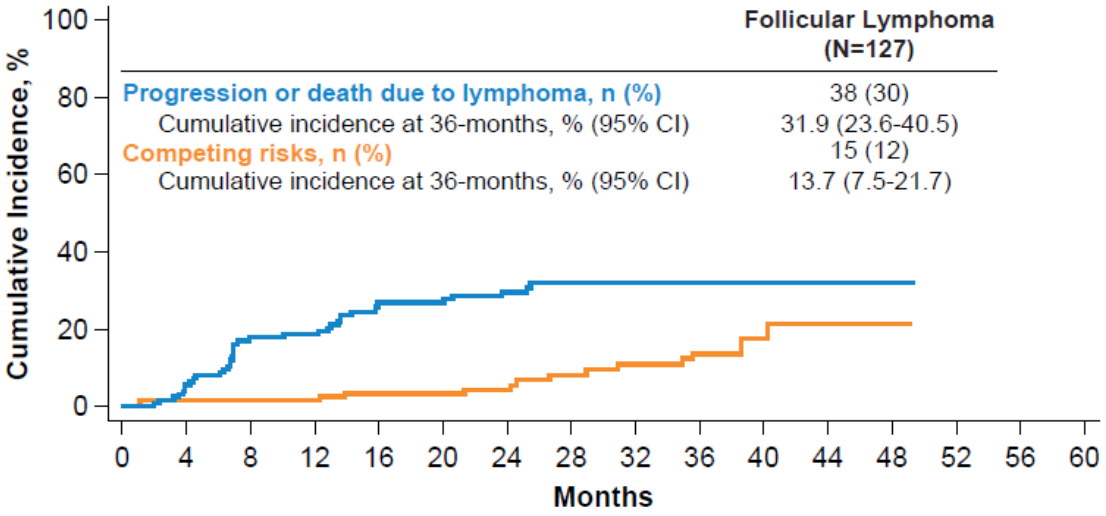

Figure S4. Progression-Free Survival Among Patients With FL With or Without POD24

Kaplan-Meier estimates of progression-free survival per investigator assessment in enrolled patients with FL by POD24 status at baseline. FL, follicular lymphoma; NE, not estimable; NR, not reached; PFS, progression-free survival; POD24, progression <24 months from initiating the first anti-CD20–containing chemoimmunotherapy.

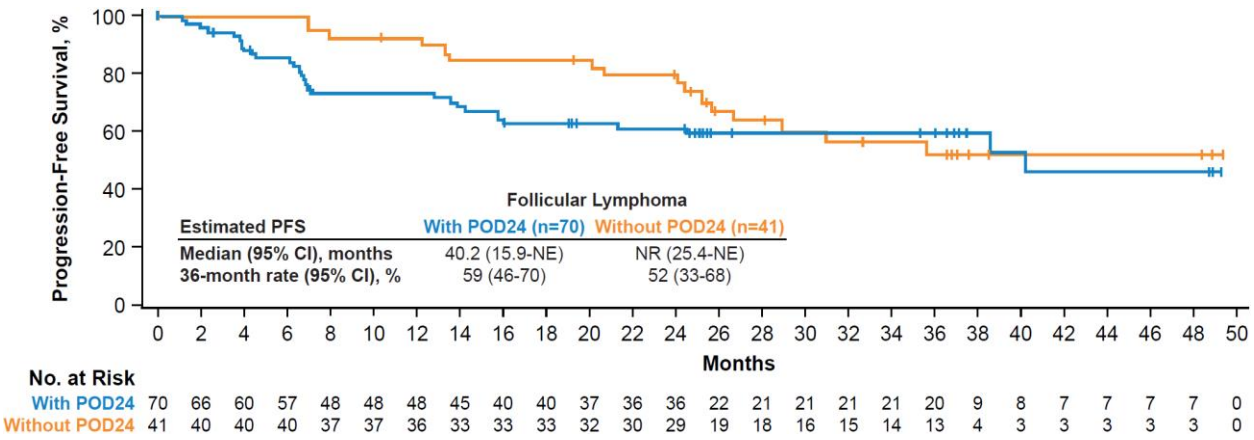

Figure S5. Subanalysis of 36-Month PFS Rate Among Patients With FL

A subgroup analysis of estimated progression-free survival at 36 months in enrolled patients with FL by key patient baseline and clinical covariates. The Clopper-Pearson method was used to calculate the 95% CI. FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF Groupe d'Etude des Lymphomes Folliculaires; PFS, progression-free survival; PI3K phosphoinositide 3-kinase; POD24 progression <24 months from initiating first anti-CD20 mAb–containing therapy; SCT stem-cell transplantation.

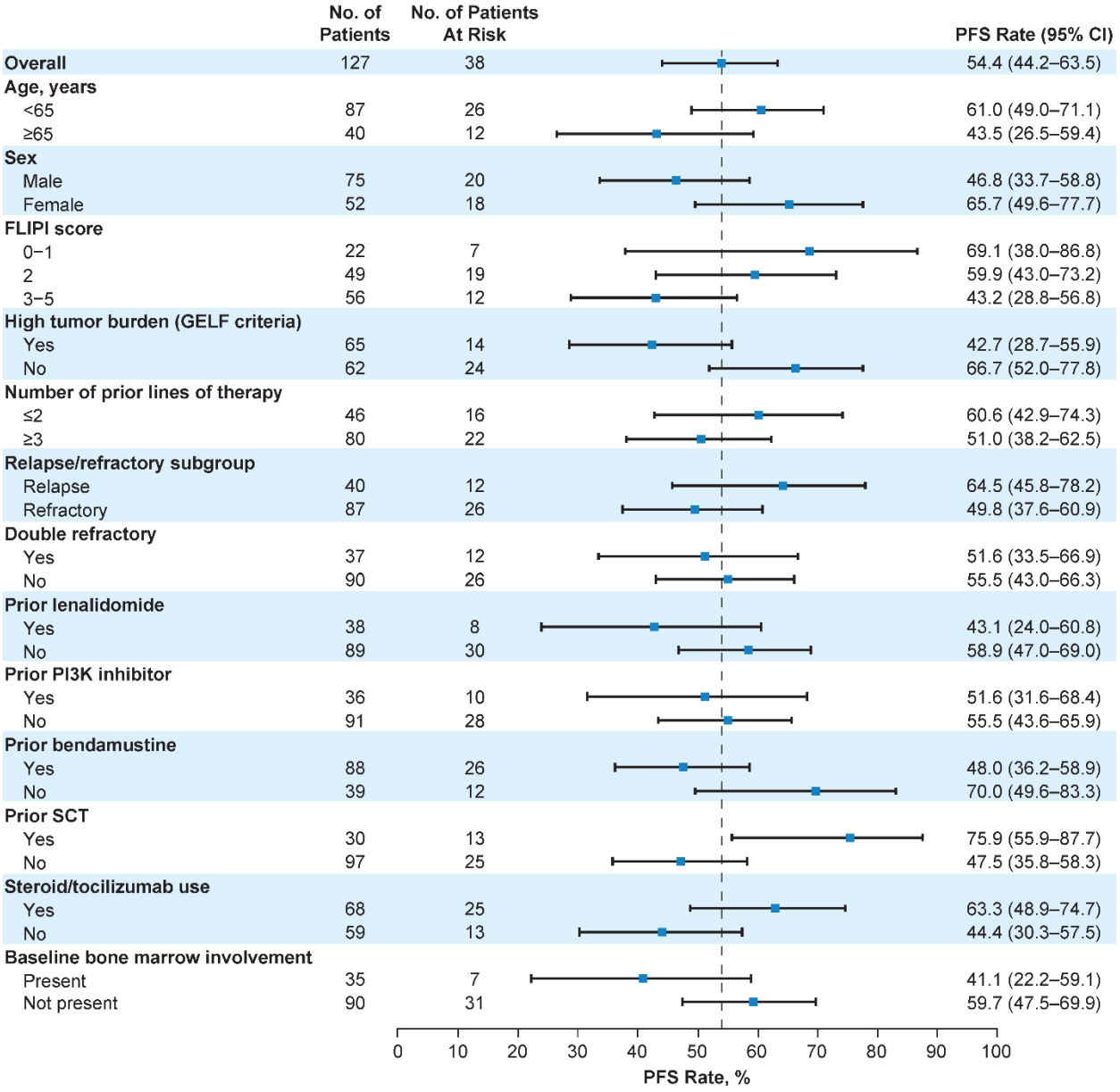

Figure S6. Subanalysis of 24-Month PFS Rate Among Patients With MZL

A subgroup analysis of estimated progression-free survival at 24 months in enrolled patients with MZL by key patient baseline and clinical covariates. The Clopper-Pearson method was used to calculate the 95% CI. GELF Groupe d'Etude des Lymphomes Folliculaires; MZL, marginal zone lymphoma; PFS, progression-free survival; PI3K phosphoinositide 3-kinase.

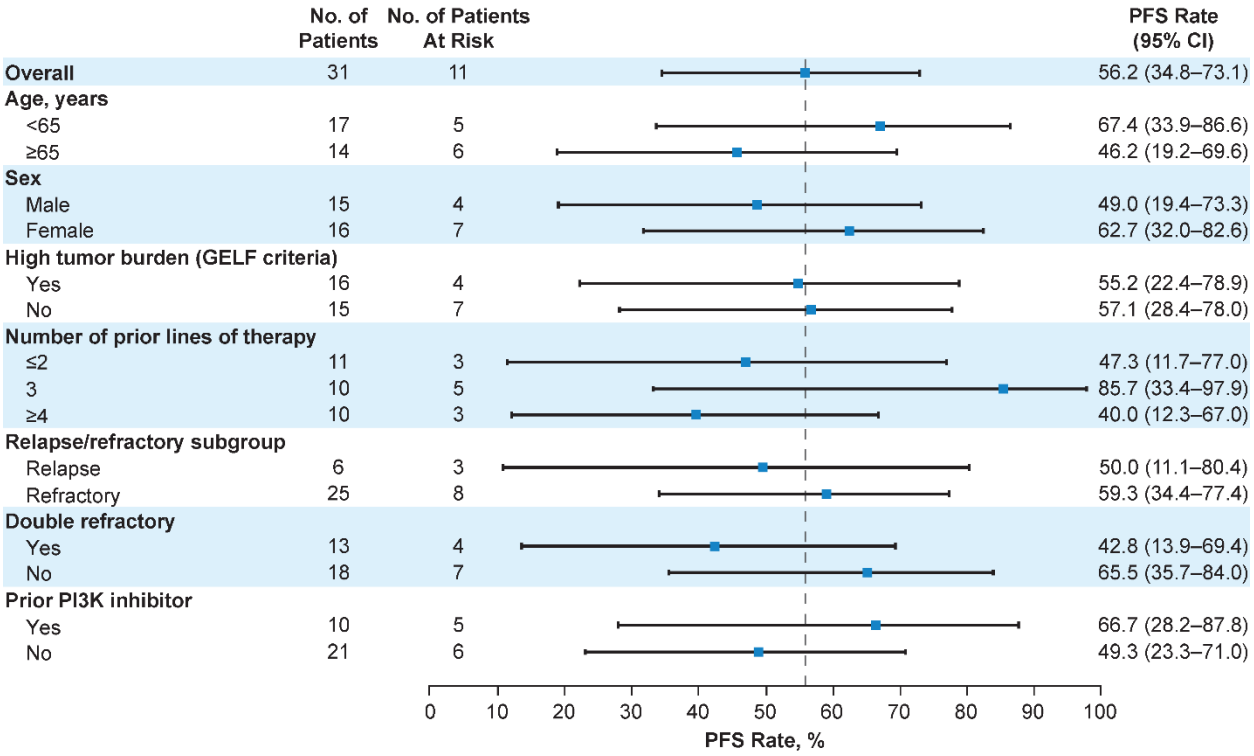

Figure S7. CAR T-cell Expansion in Treated Patients With FL and MZL by Ongoing Response at 36 Months

Association between peak CAR T-cell expansion and ongoing response versus relapse or nonresponse at 36-months post axi-cel infusion in enrolled patients with FL and MZL, shown as box and whisker plots. Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; FL, follicular lymphoma; MZL, marginal zone lymphoma.

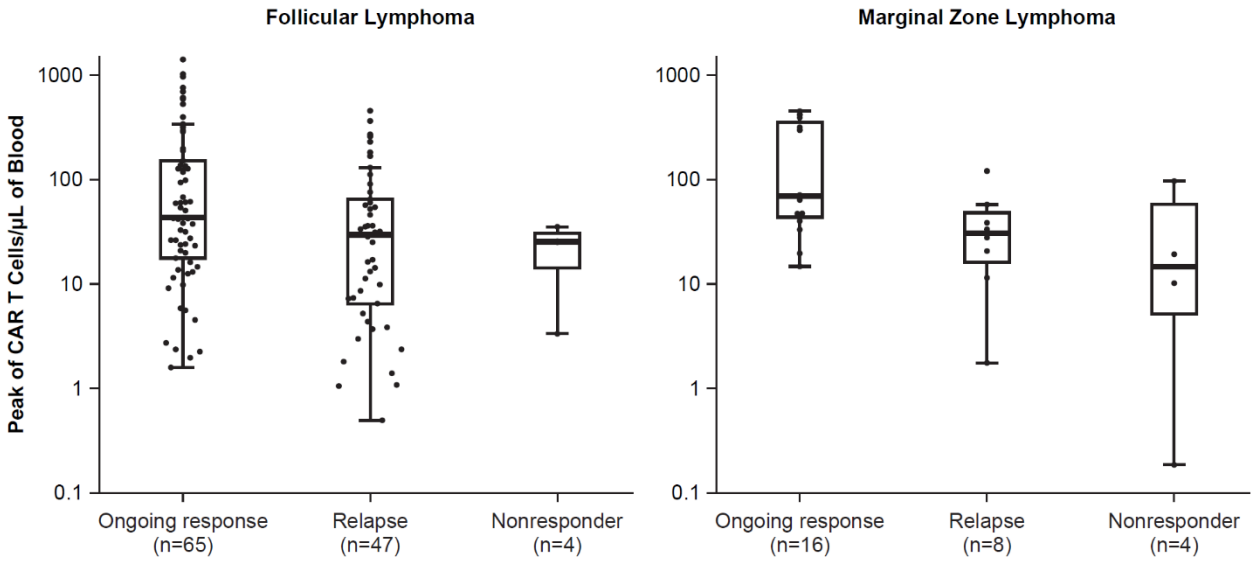

Figure S8. Detectable B Cells and CAR T Cells Over Time

Graphical representation of treated patients with FL and with an ongoing response at 36 months who had detectable B cells and CAR gene–marked T cells at baseline and at timepoints specified. CAR, chimeric antigen receptor; FL, follicular lymphoma.

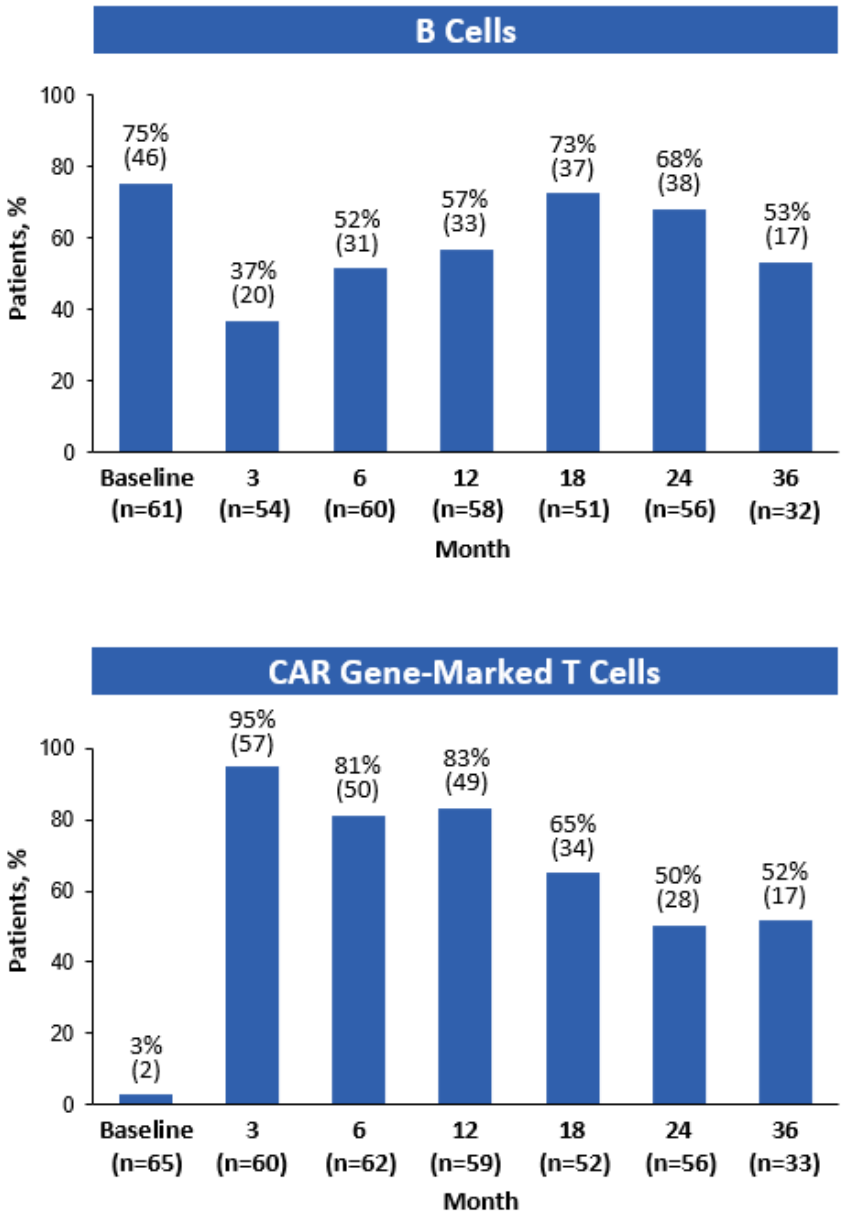

Table S1. Baseline Patient Characteristics in Enrolled Patients in the 2-Year Analysis

Characteristic	FL n=127	MZL n=29	All Patients N=157*
Age, median (range), years	60 (34-79)	64 (43-77)	60 (34-79)
≥65 years, n (%)	40 (31)	14 (48)	54 (34)
Male sex, n (%)	75 (59)	15 (52)	90 (57)
FL histological category, n (%)			
Grade 1	34 (27)	-	-
Grade 2	63 (50)	-	-
Grade 3a	30 (24)	-	-
MZL histological category, n (%)			
Nodal	-	9 (31)	-
Extranodal	-	20 (69)	-
ECOG PS of 1, n (%)	48 (38)	15 (52)	64 (41)
Stage III-IV disease, n (%)	109 (86)	27 (93)	137 (87)
High-risk FLIPI (≥3), n (%)	56 (44)	-	-
High tumor bulk (GELF criteria), n (%)†	65 (51)	14 (48)	80 (51)
Number of prior therapies, median (range)‡	3 (1-10)	3 (2-8)	3 (1-10)
≥3 prior lines of therapy, n (%)	80 (63)	20 (69)	101 (64)
Relapsed/refractory subgroup, n (%)			
Refractory to last prior therapy	87 (69)	23 (79)	111 (71)
POD24 from initiating first anti-CD20 mAb–containing therapy§	70 (56)	16 (57)	87 (56)
Lymphoma present in bone marrow, n (%)¶	35 (28)	13 (45)	48 (31)

Data cutoff date for the 2-year analysis: March 31, 2021.

* One patient was found to have disease type DLBCL after enrollment via pretreatment biopsy. This patient did not receive axi-cel and discontinued the study.

† High tumor bulk, as defined by any of GELF criteria: Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm, any nodal or extranodal tumor mass with a diameter of ≥7 cm, B symptoms, splenomegaly, pleural effusions or peritoneal ascites, cytopenias, or leukemia.

‡ One patient received prior therapy for DLBCL, not for the primary disease of follicular lymphoma.

§ Proportions are based on the number of patients who ever received anti-CD20–chemotherapy combination therapy.

¶ Bone marrow was assessed by the investigator at baseline for lymphoma presence per Lugano[2] bone marrow assessment/bone marrow assessment using aspirate or core biopsy at screening. If these were not available, lymphoma presence was based on diagnosis history of bone marrow involvement.

Axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d Etude des Lymphomes Folliculaires; mAb, monoclonal antibody; MZL, marginal zone lymphoma; POD24, progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy.

Table S2. Baseline Characteristics in Patients With Follicular Lymphoma by Prior Bendamustine Use Before and After Propensity Score Matching

	Before Matching		After Matching*	
Bendamustine Use Prior to Leukapheresis	≤12 Months (n=17)	None (n=38)	≤12 Months (n=15)	None (n=15)
MTV, median (IQR), mL	799.3 (212.3-2007.4)	359.3 (220.8-777.6)	981.7 (212.6-2089.0)	553.2 (247.1-1114.5)
Age, median (IQR), years	54 (39-59)	57 (52-62)	57 (50-60)	54 (50-63)
ECOG PS=1, n (%)	6 (35.3)	9 (23.7)	6 (40.0)	3 (20.0)
FLIPI ≥3, n (%)	10 (58.8)	11 (28.9)	10 (66.7)	7 (46.7)
Number of prior lines of chemotherapy, n (%)†				
≤2	6 (35.3)	21 (55.3)	5 (33.3)	8 (53.3)
3	6 (35.3)	9 (23.7)	5 (33.3)	4 (26.7)
≥4	5 (29.4)	7 (18.4)	5 (33.3)	3 (20.0)
Double refractory to prior anti-CD20 mAb and alkylating agent, n (%)	14 (82.4)	12 (31.6)	12 (80.0)	9 (60.0)
Last systemic therapy administered within 12 months of enrollment, n (%)	17 (100.0)	24 (63.2)	15 (100.0)	15 (100.0)
POD24 from initiating first anti-CD20 mAb–containing therapy, n (%)†	13 (76.5)	19 (50.0)	11 (73.3)	8 (53.3)

* Propensity score matching was performed after 1:1 matching with log2 MTV Calipers=1 and age Calipers=1.5, with exact statement on PTR12MFL.

† 1 observation for number of prior lines of therapy was missing before and after matching in patients exposed to bendamustine ≤12 months prior to leukapheresis. 8 observations were missing for POD24 before and after matching in patients with no prior bendamustine exposure. 2 observations were missing for POD24 before and after matching in patients exposed to bendamustine ≤12 months prior to leukapheresis.

ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; IQR, interquartile range; mAb, monoclonal antibody; MTV, metabolic tumor volume; POD24, progression of disease <24 months from initiating the first anti-CD20–containing.

Table S3. IRRC-Assessed Efficacy Outcomes Among Enrolled Patients in the 2-Year Analysis

	Follicular Lymphoma n=127	Marginal Zone Lymphoma n=29	All Patients N=157*
ORR, n (%)	117 (92)	20 (69)	137 (87)
CR	99 (78)	15 (52)	114 (73)
PR	18 (14)	5 (17)	23 (15)
SD, n (%)	5 (4)	0 (0)	5 (3)
PD, n (%)	0 (0)	1 (3)	1 (1)
Undefined/no disease, n (%)†	1 (1)	3 (10)	4 (3)
Not done, n (%)	4 (3)	5 (17)	10 (6)
Median DOR (95% CI), months	38.6 (NE-NE)	NR (8.2-NE)	38.6 (24.7-NE)
Estimate at 24 months (95% CI), %	69.5 (59-78)	NE (NE-NE)	67 (58-75)
Median duration of CR (95% CI, months)	38.6 (NE-NE)	NE (10.6-NE)	38.6 (NE-NE)
Estimate at 24 months (95% CI), %	73.7 (60.5-83.1)	NR (NE-NE)	72.3 (60.2-81.3)
Median duration of PR (95% CI, months)	3.0 (2.1-8.2)	3.1 (1.9-NE)	3.1 (2.1-8.1)
Estimate at 24 months (95% CI), %	NE (NE-NE)	0 (NE-NE)	NE (NE-NE)
Median PFS (95% CI), months	40.2 (28.9-NE)	18.3 (12.1-NE)	40.2 (26.6-NE)
Estimate at 24 months (95% CI), %	70.5 (61-78)	46 (22-68)	67 (58.5-75)
Median OS (95% CI), months	NR (40.2-NE)	NR (19.5-NE)	NR (40.2-NE)
Estimate at 24 months (95% CI), %	88 (80-92)	71 (46-86)	85 (78-90)
Median TTNT (95% CI), months	40.2 (40.2-NE)	18.3 (12.1-NE)	40.2 (40.2-NE)
Estimate at 24 months (95% CI), %	70 (61.5-78)	48.5 (25-68)	67.5 (59-74)

* One patient was found to have disease type DLBCL after enrollment via pretreatment biopsy. This patient did not receive axi-cel and discontinued the study.

† No disease at baseline or postbaseline per IRRC but were considered with disease by the investigator.

Axi-cel, axicabtagene ciloleucel; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; IRRC, independent radiology review committee; NE, not estimable; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; OS, overall survival; SD, stable disease; TTNT, time to next treatment.

Table S4. DOR, PFS, and OS in Patients With Follicular Lymphoma in the 3-Year Analysis by Timepoint of Bendamustine Use Prior to Leukapheresis

	Follicular Lymphoma (n=127)			
Bendamustine Use Prior to Leukapheresis	**≤6 Months (n=8)**	**>6-≤12 Months (n=10)**	**>12 Months (n=70)**	**None (n=39)**
Median DOR (95% CI), months	10.5 (2.2-NE)	NR (2.2-NE)	38.6 (22.7-NE)	NR (33.6-NE)
Estimate at 36 months (95% CI), %	40.0 (5.2-75.3)	55.6 (20.4-80.5)	51.8 (37.7-64.2)	69.7 (49.3-83.2)
Median PFS (95% CI), months	6.4 (1.1-38.6)	NR (2.3-NE)	40.2 (24.6-NE)	NR (35.5-NE)
Estimate at 36 months (95% CI), %	25.0 (3.7-55.8)	50.0 (18.4-75.3)	50.4 (36.7-62.6)	70.0 (49.6-83.3)
Median OS (95% CI), months	35.5 (1.1-NE)	NR (22.2-NE)	NR (NE-NE)	NR (NE-NE)
Estimate at 36 months (95% CI), %	50.0 (15.2-77.5)	39.8 (33.4-45.8)	70.6 (58.1-79.9)	88.7 (72.4-95.6)

CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Table S5. Clinical and Translational Outcomes by Prior Bendamustine Use in Patients With Follicular Lymphoma After Propensity Score Matching

Bendamustine Use Prior to Leukapheresis	≤12 Months (n=15)	None (n=15)	*P* Value
ORR, n (%)	12 (85.7)	15 (100.0)	.2241
CR	8 (57.1)	12 (80.0)	.2451
Ongoing response at 36 months, n (%)	4 (28.6)	9 (60.0)	.1394
Grade ≥3 neurologic events, n (%)	1 (6.7)	2 (13.3)	1
Grade ≥3 CRS, n (%)	1 (6.7)	2 (13.3)	1
Peak CAR T-cell level, median (IQR), cells/µL	17.1 (3.0-48.4)	42.5 (5.7-62.6)	.3046
AUC CAR T-cell level, median (IQR), cells/µL×days	181.1 (45.3-414.4)	507.0 [99.1-745.9)	.1485
Total number of CD4 cells infused, median (IQR), n×10^6	149.3 (70.0-176.1)	121.1 (93.0 -205.0)	.5409
Total number of CD8 cells infused, median (IQR), n×10^6	131.9 (90.0-183.5)	130.4 (92.2-176.0)	.8743
Total number of CCR7+CD45RA+ T cells infused, median (IQR), n×10^6	21.7 (17.4-45.5)	44.9 (24.0-89.7)	.1781
IFN-γ in co-culture, median (IQR), pg/mL	2871.0 (2272.5-4360.0)	6973.0 (5348.0-10403.0)	.001665

Propensity score matching was performed after 1:1 matching with log2 MTV Calipers=1 and age Calipers=1.5. with exact statement on PTR12MFL.

AUC, area under the curve; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; IFN, interferon, IQR, interquartile range; MTV, metabolic tumor volume; ORR, overall response rate.

Table S6. Efficacy Outcomes in the 3-Year Analysis by Study Median and Historical Threshold of Metabolic Tumor Volume

	Follicular Lymphoma (n=127)		Marginal Zone Lymphoma (N=31)	
Study median	≤438.5 mL (n=63)	>438.5 mL (n=62)	≤368.8 mL (n=14)	>368.8 mL (n=13)
ORR, n (%)	61 (97)	56 (90)	12 (86)	11 (85)
CR	55 (87)	44 (71)	10 (71)	9 (69)
Median DOR (95% CI), months	NE (36.6-NE)	23.5 (11.8-NE)	NE (1.9-NE)	NE (5.1-NE)
Estimate at 36 months (95% CI), %	73.3 (58.4-83.5)	40.4 (26.1-54.3)	56.3 (24.4-79.1)	NE (NE-NE)
Median PFS (95% CI), months	NE (38.6-NE)	24.2 (13.4-40.2)	NE (5.5-NE)	NE (7.0-NE)
Estimate at 36 months (95% CI), %	71.2 (56.8-81.6)	37.3 (23.9-50.7)	51.9 (22.5-75.0)	55.9 (24.0-79.0)
Historical threshold	≤510 mL (n=68)	>510 mL (n=57)	≤510 mL (n=16)	>510 mL (n=11)
ORR, n (%)	66 (97)	51 (89)	14 (88)	9 (82)
CR	57 (84)	42 (74)	11 (69)	8 (73)
Median DOR (95% CI), months	NE (36.6-NE)	24.7 (11.8-NE)	NE (5.1-NE)	NE (6.2-NE)
Estimate at 36 months (95% CI), %	70.7 (56.6-81.0)	40.6 (25.5-55.1)	55.6 (26.4-77.2)	NE (NE-NE)
Median PFS (95% CI), months	NE (38.6-NE)	25.2 (13.6-NE)	NE (5.5-NE)	NE (10.1-NE)
Estimate at 36 months (95% CI), %	68.9 (55.1-79.2)	37.1 (23.1-51.1)	51.9 (24.5-73.6)	56.8 (21.3-81.3)

CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; ORR, overall response rate; PFS, progression-free survival.

Table S7. Efficacy Outcomes in Patients With Follicular Lymphoma in the 3-Year Analysis by Quartiles of Metabolic Tumor Volume

	Follicular Lymphoma (n=127)			
Quartile of MTV, mL	**Min-Q1 (11.2-183.9)**	**Q1-Median (183.9-438.5)**	**Median-Q3 (438.5-1076.0)**	**Q3-Max (1076.0-5576.6)**
ORR, n/n (%)	30/32 (94)	31/31 (100)	27/28 (96)	29/30 (97)
CR	26/32 (81)	29/31 (94)	20/28 (71)	24/30 (80)
Median DOR (95% CI), months	NR (22.7-NE)	NR (36.6-NE)	29.0 (10.4-NE)	22.0 (11.5-NE)
Estimate at 36 months (95% CI), %	63.3 (40.1-79.6)	81.5 (60.1-92.1)	45.1 (23.9-64.1)	36.2 (17.7-55.2)
Median PFS (95% CI), months	NR (24.4-NE)	NR (38.6-NE)	25.4 (7.0-NE)	24.2 (12.8-NE)
Estimate at 36 months (95% CI), %	60.4 (39.0-76.3)	81.5 (60.1-92.1)	41.9 (22.2-60.5)	33.0 (15.8-51.4)

CR, complete response; DOR, duration of response; max, maximum; min, minimum; NE, not estimable; NR, not reached; ORR, overall response rate; PFS, progression-free survival.

Table S8. Efficacy Outcomes at 2 and 3 Years Among Enrolled Patients With FL With ≥3 Prior Lines of Therapy, Excluding Those With Non-FL Histology Per Central Assessment

	Follicular Lymphoma (N=75)	
	2-Year*	**3-Year***
ORR, n (%)	68 (91)	70 (93)
CR	58 (77)	58 (77)
PR	10 (13)	12 (16)
SD, n (%)	3 (4)	0
PD, n (%)	0 (0)	2 (3)
Undefined/no disease, n (%)†	1 (1)	0
Not done, n (%)	3 (4)	3 (4)
Median DOR (95% CI), months	38.6 (24.7-NE)	38.6 (22.7-NE)
Estimate (95% CI), %	68 (53-79)	54 (40-66)
Median PFS (95% CI), months	40.2 (26.6-NE)	40.2 (24.2-NE)
Estimate (95% CI), %	72 (59-81)	52 (39-64)
Median OS (95% CI), months	NR (40.2-NE)	NR (NE-NE)
Estimate (95% CI), %	86 (75-92)	74 (62-82)
Median TTNT (95% CI), months	40.2 (26.6-NE)	NR (26.6-NE)
Estimate (95% CI), %	67 (55-77)	56 (44-67)

A total of 5 patients with FL were excluded. Of those, 3 patients were found to have DLBCL transformed in background of FL, one had small B-cell lymphoma, and one had MZL per central pathology.

* Assessment of response was per IRRC at 2 years and per investigator at 3 years.

† No disease at baseline or postbaseline per independent radiology review but considered with disease by the investigator.

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; IRRC, independent radiology review committee; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; OS, overall survival; SD, stable disease; TTNT, time to next treatment.

Table S9. Efficacy Outcomes in the Updated Analysis in Patients With Marginal Zone Lymphoma by Histological Category

	Marginal Zone Lymphoma (n=31)	
	Nodal (n=10)	**Extranodal (n=21)**
Overall response rate, n (%)	7 (70)	17 (81)
Complete response	7 (70)	13 (62)
Partial response	0	4 (19)
Median DOR (95% CI), months	NR (NE-NE)	NR (6.2-NE)
Estimate at 36 months (95% CI), %	100 (100-100)	NE (NE-NE)

DOR, duration of response; NE, not estimable; NR, not reached.

Table S10. Incidence of Grade ≥3 Prolonged Cytopenias by Time Postinfusion Among Treated Patients

	Follicular Lymphoma (N=124)	Marginal Zone Lymphoma (N=28)	Overall (N=152)
Patients with any grade ≥3 prolonged cytopenia	41 (33)	10 (36)	51 (34)
Month 3 postinfusion*	8 (6)	2 (7)	10 (7)
Month 6 postinfusion	9 (7)	0 (0)	9 (6)
Month 9 postinfusion	6 (5)	1 (4)	7 (5)
Month 12 postinfusion	5 (4)	0 (0)	5 (3)
Month 18 postinfusion	5 (4)	0 (0)	5 (3)
Month 24 postinfusion	4 (3)	0 (0)	4 (3)

Prolong cytopenia includes events (neutropenia, thrombocytopenia or anemia) present on or after day 30 postinfusion and prior to any subsequent anti-lymphoma therapy

* One patient who received subsequent therapy and who had grade 4 neutropenia had no end date recorded. The event began on day 71, and subsequent therapy began on day 107. This patient was included at the month 3 timepoint (day 91), but the patient was not included in subsequent timepoints.

Table S11. Summary of Deaths Among Enrolled Patients

Disease Type	Primary Cause of Death	Time from Enrollment to Death (Months)	Related to Lymphoma or Study Treatment per Investigator (Y/N)
Follicular Lymphoma	Adverse event: multiple organ dysfunction syndrome, cytokine release syndrome	1.1	Y
	Other: cardiac arrest	1.3	N
	Progressive disease	2.5	Y
	Progressive disease	5.0	Y
	Second primary malignancy	12.2	N
	Progressive disease	12.9	Y
	Progressive disease	13.2	Y
	Adverse event: aortic dissection	13.9	N
	Progressive disease	14.6	Y
	Progressive disease	14.9	Y
	Progressive disease	18.0	Y
	Other new malignancy: mixed lineage acute leukemia	21.3	N
	Progressive disease	22.2	Y
	Other: unknown, found via public record	23.6	N
	Adverse event: progressive multifocal leukoencephalopathy	23.8	Y
	Other: unknown*	24.0	Y
	Other: infection†	24.2	Y
	Adverse event: COVID-19	24.4	N
	Other new malignancy: anal/rectal cancer	24.6	N
	Other: E-bacteremia/*E. coli* sepsis with superimpose or diarrhea due *to C. difficile* infection	26.4	N
	Adverse event: COVID-19 pneumonia‡	26.6	Y
	Other: COVID-19	28.9	N
	Second primary malignancy	30.9	N
	Progressive disease	32.0	Y
	Other: complications of GVHD	32.5	N
	Other: unknown*	32.8	Y
	Progressive disease	33.1	Y
	Other: COVID pneumonia with hypoxic respiratory failure	33.3	N
	Other: sepsis	34.9	N
	Other: lung infection	35.5	N
	Second primary malignancy	38.6	N
	Adverse event: sepsis	40.2	N
	Adverse event: sepsis	5.5	N

Marginal Zone Lymphoma	Progressive disease	7.3	Y
	Adverse event: coccidioidomycosis	12.1	N
	Other: infection	12.9	N
	Other: unknown§	14.6	Y
	Other: unknown	18.3	N
	Progressive disease	19.5	Y

Death due to lymphoma includes death due to disease progression or determined to be disease-related per investigator assessment. Death due to study treatment complications includes death determined to be related to axicabtagene ciloleucel or lymphodepleting therapy per investigator assessment.

Patients with cause of death of "unknown" whose death was ultimately determined not to be related to lymphoma or study treatment were in ongoing response as of their last alive disease assessment and the treating physician did not suspect any relation to lymphoma or study treatment.

* Upon further questioning, investigator suspected patient likely died of lymphoma-related complications.

Only 2 patients with death due to infections had documented concurrent high-grade neutropenia or any grade hypogammaglobulinemia at the time of infection.

† Patient had concurrent grade 2 hypogammaglobulinemia and grade 3 neutropenia at the time of death.

‡ Patient had concurrent grade 1 decreased blood IgG at the time of death.

§ Upon further questioning, investigator suspected death was likely due to disease progression.

E. coli, Escherichia coli; GVHD, graft-versus-host disease; IgG, immunoglobulin G; N, no; Y, yes.

Table S12. AEs Among Treated Patients With FL With ≥3 Prior Lines of Therapy, Excluding Those With Non-FL Histology Per Central Assessment

	Follicular Lymphoma (N=73)	
Adverse Event, n (%)	**Any Grade**	**Grade ≥3**
Any	72 (99)	64 (88)
Pyrexia	58 (79)	7 (10)
Hypotension	34 (47)	2 (3)
Fatigue	32 (44)	1 (1)
Headache	32 (44)	2 (3)
Neutropenia	28 (38)	25 (34)
Anemia	24 (33)	16 (22)
Sinus tachycardia	23 (32)	1 (1)
Chills	22 (30)	0
Tremor	22 (30)	0
Neutrophil count decreased	21 (29)	20 (27)
Constipation	19 (26)	0
Decreased appetite	19 (26)	2 (3)
Diarrhea	18 (25)	0
Nausea	18 (25)	0
Vomiting	18 (25)	0
Confusional state	17 (23)	4 (5)
Hypokalemia	17 (23)	2 (3)
Cough	16 (22)	0
Hypoxia	16 (22)	7 (10)
Insomnia	15 (21)	0
Thrombocytopenia	15 (21)	13 (18)
White blood cell count decreased	15 (21)	15 (21)
Serious AEs	37 (51)	29 (40)
Cytopenias	55 (75)	51 (70)
CRS	57 (78)	5 (7)
Neurologic events	41 (56)	11 (15)
Infections	43 (59)	13 (18)
Hypogammaglobulinemia	13 (18)	0

Data included are AEs of any grade occurring in ≥20% of patients as well as select AEs of clinical interest.

AE, adverse event; CRS, cytokine release syndrome; FL, follicular lymphoma.

Table S13. CAR T-cell Expansion and Axi-Cel Product Characteristics in Treated Patients With Follicular Lymphoma by the Timeline of Prior Bendamustine Use

Bendamustine Exposure Prior to Leukapheresis	<6 months (n=7)	≥6 months and ≤12 months (n=10)	>12 months (n=69)	None (n=38)
Median CAR T-cell expansion (range)				
Peak, cells/µL	35.4 (3.34-112.8)	18.8 (2.7-53.9)	32.9 (11.3-112.1)	60.2 (23.7-182.5)
AUC_{0-28}, cells/ µL×days	337.6 (53.2-410.9)	236.9 (37.4-527.2)	404.5 (143.6-1037.2)	614.4 (303.2-1918.6)
Product characteristics (range)				
Total no. T cells infused × 10^6, n	271.9 (250.0-298.5)	311.1 (244.3-387.8)	268.7 (239.4-344.8)	292.9 (237.3-384.6)
CCR7+CD45RA+ T cells, %	6.6 (4.9-46.5)	11.9 (7.0-16.0)	14.9 (10.1-25.8)	26.8 (17.4-36.9)
CCR7+CD45RA- T cells, %	15.8 (6.1-21.0)	11.4 (6.7-26.9)	19.6 (11.8-24.6)	22.9 (14.2-28.9)
CCR7-CD45RA+/- T cells, %	74.9 (35.2-89.0)	71.4 (50.2-79.8)	62.5 (48.2-72.7)	52.0 (32.2-59.4)

AUC_{0-28}, area under the curve between days 0 and 28; CAR, chimeric antigen receptor.

REFERENCES

1. Meignan M, Cottereau AS, Versari A, et al. Baseline Metabolic Tumor Volume Predicts Outcome in High-Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies. *J Clin Oncol*. 2016;34(30):3618-3626.

2. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.