Yescarta® (axicabtagene ciloleucel)

Results of the ZUMA-5 Phase 2 Study

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Summary

Methods[1]

- The ZUMA-5 Phase 2 study is a single-arm, open-label, multicenter study to assess the safety and efficacy of Yescarta in patients with refractory indolent non-Hodgkin lymphoma (iNHL), including follicular lymphoma (FL) and marginal zone lymphoma (MZL) after ≥2 lines of therapy. Eligible patients underwent conditioning chemotherapy prior to receiving a single intravenous (IV) infusion of Yescarta at a target dose of 2×10^6 chimeric antigen receptor (CAR) T-cells/kg.

Disposition and Manufacturing[1]

- Of 153 patients enrolled, 148 received treatment with Yescarta as of the updated analysis of ZUMA-5 (September 14, 2020, data cutoff); Yescarta was successfully manufactured for all enrolled patients. The median turnaround time from leukapheresis to Yescarta delivery to the trial site was 17 days.

Patient Characteristics[1]

- Among all 148 patients treated in the updated analysis (September 14, 2020, data cutoff), patients were refractory to several lines of treatment with a median of 3 prior lines of therapy. Sixty-nine percent of patients were refractory to their last line of treatment. High-risk disease features were common, with 81 (55%) of 148 patients experiencing progression within 24 months after initiating their first chemoimmunotherapy (POD24).

Efficacy[2]

- At the 5-year follow-up analysis of ZUMA-5 (March 31, 2024, data cutoff), the overall response rate (ORR) for the 159 enrolled patients (127 FL, 31 MZL), who were all evaluated for efficacy, was 90%, with a complete response (CR) rate of 75%. The estimated 60-month rates of duration of response (DOR), progression-free survival (PFS), and overall survival (OS) for all enrolled patients were 53.4%, 50.4%, and 69%, respectively.

Safety

- In the updated analysis of ZUMA-5 (N=148; September 14, 2020, data cutoff), 99% of patients experienced adverse events (AEs) of any grade, and 86% of patients experienced AEs of Grade ≥3.[1]
- Grade ≥3 cytokine release syndrome (CRS) occurred in 7% and Grade ≥3 neurologic events in 19% of iNHL patients as of the September 14, 2020, data cutoff.1 As of the 3-year follow-up analysis (March 31, 2022, data cutoff), 1 additional Grade ≥3 neurologic event had occurred.[3]
- As of the 5-year follow-up analysis (N=152; March 31, 2024 data cutoff), non-relapse mortalities were due to secondary malignancy (4%), cardiac-related (2%), infection-related (7%), and other (2%; 1 death due to CRS and multi-organ failure, 2 deaths were due to unknown causes).[2] Two deaths due to AEs were described in the 3-year analysis as being attributable to Yescarta treatment in FL patients (including 1 due to progressive multifocal leukoencephalopathy (PML) and 1 due to coronavirus disease 2019 (COVID-19) pneumonia.).[3]

Pharmacokinetics and Persistence

- In all treated patients in the updated analysis (N=148; September 14, 2020, data cutoff), the median time to peak concentration of anti-CD19 CAR T-cell levels after infusion was 9 days, and CAR T-cell expansion by peak and area under the curve (AUC) appeared slightly higher in patients with MZL than in patients with FL.[1]
- As of the 3-year long-term follow-up analysis (March 31, 2022, data cutoff), the majority of patients with FL had detectable B-cells by Month 12, and half of patients had low levels of detectable CAR gene-marked cells by Month 24.[3]
- At the 5-year follow-up analysis (N=154, March 31, 2024, data cutoff), treated patients with FL in ongoing response had greater CAR T-cell expansion than relapsed or non-responding patients. Additionally, consistent with prior analysis, elevated early CAR T-cell expansion and a naive product phenotype continued to be associated with durable response.[2]

ZUMA-5 Phase 2 Study Design

Methods

Study Design and Participants

ZUMA-5 is a single-arm, open-label, multicenter, Phase 2 study conducted at 15 sites in the United States and 2 sites in France to evaluate the safety and efficacy of Yescarta in patients with relapsed or refractory iNHL, including FL and MZL.[1]

Key eligibility criteria:[5,6]

- Age 18 or older
- Histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to FL Grade 1, Grade 2, or Grade 3a or MZL nodal or extranodal, based on criteria established by the WHO 2016 classification
- Relapsed/refractory disease after 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. Patients with stable disease (without relapse) >1 year from completion of last therapy

were not eligible
- At least 1 measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma
- No known history or suspicion of central nervous system (CNS) involvement by lymphoma
- At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy and enrollment, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy and enrollment
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Adequate renal, hepatic, pulmonary, and cardiac function

Key exclusion criteria: [5,6]

- Transformed FL or MZL
- Small lymphocytic lymphoma
- FL Histological Grade 3b
- Autologous stem cell transplant (ASCT) transplant ≤6 weeks of planned Yescarta infusion
- History of allogeneic stem cell transplant (allo-SCT)
- Cardiac atrial or cardiac ventricular lymphoma involvement
- Possible requirement for urgent therapy ≤6 weeks after leukapheresis due to ongoing or impending oncologic emergency
- Prior CD19 targeted therapy, with the exception of subjects who received Yescarta in this study and are eligible for retreatment

Procedures[1]

Eligible patients underwent leukapheresis to obtain T-cells for Yescarta manufacturing. Prior to Yescarta, patients received conditioning chemotherapy that consisted of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day on Days -5, -4, and -3. On Day 0 (i.e., the day of Yescarta infusion), patients received a single IV infusion of Yescarta at a target dose of 2×10^6 CAR T-cells/kg. Bridging therapy was administered per investigator discretion before conditioning chemotherapy. Patients were required to stay in the hospital on Days 0–7, and were monitored after Yescarta infusion. Disease response was assessed by investigators using PET-CT and were required at baseline (i.e., before conditioning therapy was started) and at Week 4 after infusion, every 3 months for Months 3–24, and at any subsequent scheduled or unscheduled visit if there was clinical concern for disease progression. For assessment of safety and biomarker analysis, blood and serum samples were taken within 28 days of enrollment; on Days -5, -4, -3, and 0, during the 7 days of in-hospital stay; during Week 2; during Month 1–3; and then every 3 months until Month 24. Patients who had disease progression after a response at the Month 3 disease assessment could have received retreatment with Yescarta, if eligible.

Endpoints

The primary endpoint was ORR (CR and partial response [PR]), as assessed by an independent radiology review committee (IRRC) per the Lugano Classification.[1]

Key secondary endpoints included:[1,4]

- CR rate per IRRC
- Investigator-assessed ORR
- DOR, PFS, and OS

- Incidence of AEs
- Levels of anti-CD19 CAR T-cells in blood, and levels of cytokines in serum

Summary of Analyses

The ZUMA-5 primary analysis, updated analysis, and 5-year long-term follow-up analysis are summarized in Table 1 below. The updated analysis was a prespecified analysis to assess the durability of response to Yescarta when at least 80 patients with FL had been followed for ≥18 months after infusion and included patients with MZL that had been followed ≥4 weeks after infusion.[1] The 5-year long-term follow-up analysis provided updated clinical and pharmacologic outcomes from ZUMA-5 after the median follow-up of all enrolled patients reached ≥60 months.[2] In the primary and updated analyses, disease response was assessed by an IRRC, whereas in the 5-year long-term follow-up analysis, efficacy assessments were performed per investigator.[2,4,6]

Table 1. Summary of Analyses

	Primary Analysis[4]	Updated Analysis[1]	5-Year Follow-Up Analysis[2]
Data cutoff date	March 12, 2020	September 14, 2020	March 31, 2024
Minimum follow-up period	FL: ≥12 months[b] MZL: ≥4 weeks[b]	FL: ≥18 months[c] MZL: ≥4 weeks[c]	No minimum follow-up period[d]
Duration of follow-up for efficacy in the overall population, median (range), months	17.5 (1.4–31.6)	23.3 (20.0–28.0)[e]	64.6 (32.3–81.4)
Duration of follow-up for patients with FL median (range), months	Not reported	24.4 (21.2–29.0)[e]	65.7 (56.7–81.4)
Duration of follow-up for patients with MZL median (range), months	Not reported	17.3 (8.3–21.1)[e]	55.8 (32.3–76.4)
Duration of follow-up for safety in the overall population, median (range), months	15.1 (0.5–31.6)	Not reported	Not reported
Number of efficacy-evaluable patients	104 (84 FL, 20 MZL)	109 (86 FL, 23 MZL)	159[f] (127 FL, 31 MZL)
Number of safety-evaluable patients (all treated patients)	146 (124 FL, 22 MZL)	148 (124 FL, 24 MZL)	152 (124 FL, 28 MZL)

[a]The analyses were performed when ≥80 treated patients with FL had the minimum follow-up required for each respective analysis and also included MZL patients who met the minimum required follow-up.
[b]After first response assessment. [c]After infusion. [d]No minimum, median reached ≥60 mo. [e]Interquartile range (IQR). [f]All enrolled patients.

Disposition and Manufacturing

Disposition and Manufacturing

At the September 14, 2020, data cutoff date for the updated analysis, 153 patients (127 FL; 25 MZL; 1 diffuse large B-cell lymphoma [DLBCL]) were enrolled, underwent leukapheresis, and Yescarta was successfully manufactured for all 153 enrolled patients.[1] One hundred forty-eight patients received conditioning chemotherapy and Yescarta infusion, and 5 patients were not treated due to the following reasons: DLBCL identified via pretreatment biopsy (n=1), low

platelet levels (n=1), CR before conditioning chemotherapy (n=1), partial withdrawal (n=1), and death due to cardiac arrest (n=1).

As of the March 31, 2024, data cutoff date, 159 patients with iNHL were enrolled, and 152 patients (124 FL, 28 MZL) were treated with Yescarta.[2]

Time from Leukapheresis to Yescarta Delivery

At the September 14, 2020, data cutoff for the updated analysis, the median time from leukapheresis to Yescarta delivery to the trial site was 17 days (IQR, 16–20).[1]

Results

Patient Characteristics

Baseline Characteristics

Among all 148 patients treated in the updated analysis (September 14, 2020, data cutoff), patients were refractory to several lines of treatment, with a median of 3 prior lines of therapy.[1] One hundred and two (69%) of patients were refractory to their last line of treatment and 81 (55%) experienced POD24. Additionally, 4% of patients (6 patients, 4 FL, 2 MZL) received bridging therapy, and all 6 patients had measurable disease after bridging. Details of baseline patient characteristics from the primary and updated analyses are summarized in Table 2 below.

Table 2. Baseline Patient Characteristics in All Treated Patients

Characteristic	Primary Analysis[6]			Updated Analysis[1]		
	FL (n=124)	MZL (n=22)	All Patients (N=146)	FL (n=124)	MZL (n=24)	All Patients (N=148)
Age, median (IQR), years	60 (53–67)	66 (62–72)	61 (53-68)	60 (53–67)	65 (61–72)	61 (53–68)
≥65 years, n (%)	38 (31)	13 (59)	51 (35)	38 (31)	13 (54)	51 (34)
Male sex, n (%)	73 (59)	10 (45)	83 (57)	73 (59)	11 (46)	84 (57)
ECOG PS of 1, n (%)	46 (37)	9 (41)	55 (38)	46 (37)	10 (42)	56 (38)
FL histological category, n (%)						
Grade 1	33 (27)	NA	33 (23)	33 (27)	NA	NA
Grade 2	61 (49)	NA	61 (42)	61 (49)	NA	NA
Grade 3a	30 (24)	NA	30 (21)	30 (24)	NA	NA
MZL histological category, n (%)						
Nodal	NA	6 (27)	6 (4)	NA	7 (29)	NA
Extranodal	NA	16 (73)	16 (11)	NA	17 (71)	NA
Stage 3-4 disease	106 (85)	20 (91)	126 (86)	106 (85)	22 (92)	128 (86)
High-risk FLIPI (≥3)	54 (44)	14 (64)	68 (47)	54 (44)	NA	NA
High tumor burden (GELF criteria)[a]	64 (52)	8 (36)	72 (49)	64 (52)	10 (42)	74 (50)
Prior lines of therapy						

Characteristic	Primary Analysis[6]			Updated Analysis[1]		
	FL (n=124)	MZL (n=22)	All Patients (N=146)	FL (n=124)	MZL (n=24)	All Patients (N=148)
Number of prior therapies, median (IQR)[b]	3 (2–4)	3 (2–5)	3 (2-4)	3 (2–4)	3 (2–5)	3 (2–4)
≥3 prior lines of therapy, n (%)	78 (63)	15 (68)	93 (64)	78 (63)	16 (67)	94 (64)
Prior therapies, n (%)						
Prior PI3Ki therapy	34 (27)	9 (41)	43 (29)	34 (27)	9 (38)	43 (29)
Prior ASCT	30 (24)	3 (14)	33 (23)	30 (24)	3 (13)	33 (22)
Prior anti-CD20 mAb + alkylating agent	123 (99)	21 (95)	144 (99)	123 (99)	23 (96)	146 (99)
Prior anti-CD20 mAb single agent	39 (31)	10 (45)	49 (34)	39 (31)	10 (42)	49 (33)
Prior alkylating single agent	16 (13)	6 (27)	22 (15)	16 (13)	6 (25)	22 (15)
Prior lenalidomide	38 (31)	7 (32)	45 (31)	38 (31)	8 (33)	46 (31)
Refractory subgroup, n (%)[c]						
Refractory to last prior therapy	84 (68)	16 (73)	100 (68)	84 (68)	18 (75)	102 (69)
POD24 from first anti-CD20 mAb-containing therapy[d]	68 (55)	11 (52)	79 (55)	68 (55)	13 (57)	81 (55)
Positive CD19 status[e]	93/104(89)	14/16 (88)	107/120 (89)	93/103 (90)	15/16 (94)	108/119 (91)
Lymphoma present in bone marrow[f]	33 (27)	11 (50)	44 (30)	33 (27)	11 (46)	44 (30)

[a]Tumor burden, as defined by any of the following 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. [b]One patient received prior therapy for DLBCL, not for the primary disease of FL. [c]Patients who progressed <6 months of completion of the most recent prior therapy were defined as refractory. [d]POD24 defined as 24 months from initiation of the first line of anti-CD20–containing immunochemotherapy to progression. Percentages are based on the number of patients who ever received anti-CD20-chemotherapy combination therapy. [e]CD19 status of the tumor assessed by immunohistochemistry at a central laboratory, with a positive score defined as the H-score of staining ≥5. [f]Bone marrow was assessed by the investigator at baseline for lymphoma presence per Lugano 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.

Efficacy

Response

Response rates as assessed by IRRC (primary and updated analysis) and investigators (5-year follow-up) were similar for all analyses, as shown in Table 3.[1,2,6] In the primary analysis, the ORR was 92% (95% CI, 85–97) in all iNHL efficacy-evaluable patients (n=104), with a median follow-up of 17.5 months.[1] The ORR rate (90-92%) was generally consistent through the updated and long-term follow-up analyses.[2,6] Additionally, the ORR was consistent across key high-risk subgroups, including POD24, in the updated analysis.[1] The median time to initial response was 1 month (IQR, 1–1), and was consistent across diseases.[1] The median time to initial CR was 1 month (IQR, 1–3) in patients with FL and 3 months (IQR, 1–5) in patients with MZL.[1]

Table 3. Response Rates in ZUMA-5

Response Rates	Primary Analysis[6]			Updated Analysis[6]			5-Year Follow-up Analysis[2]		
	FL (n=84)	MZL (n=20)	All Patients[a] (n=104)	FL (n=86)	MZL (n=23)	All Patients[a] (n=109)	FL (n=127)	MZL (n=31)	All Patients[a] (n=159)
ORR, n (%)	79 (94)	17 (85)	96 (92)	81 (94)	19 (83)	100 (92)	119 (94)	24 (77)	143 (90)
CR[b] rate, n (%)	66 (79)	11 (55)	77 (74)	68 (79)	15 (65)	83 (76)	100 (79)	20 (65)	120 (75)
PR rate, n (%)	13 (15)	6 (30)	19 (18)	13 (15)	4 (17)	17 (16)	19 (15)	4 (13)	23 (14)

[a] Efficacy eligible. [b] CR rates through the updated analysis include 13 patients assessed with PET-CT alone without a post-treatment biopsy. A subsequent protocol amendment required a negative bone marrow biopsy after Yescarta treatment to confirm a CR for those patients who did not have a negative baseline bone marrow biopsy.

The median DOR, PFS, and OS rates from the primary, updated, and 5-year follow-up analyses are presented in Table 4.

Table 4. Median DOR, PFS, and OS Rates at the Primary, Updated, and Long-Term Analyses

	Primary Analysis[6]			Updated Analysis[6]			5-Year Follow-up Analysis[2]		
	FL (n=84)	MZL (n=20)	All Patients (n=104)	FL (n=86)	MZL (n=23)	All Patients (n=109)	FL (n=127)	MZL (n=31)	All Patients (n=159)
DOR, median (95% CI), months	NR (20.8–NE)	10.6 (8.1–NE)	NR (20.8–NE)	NR (NE–NE)	11.1 (8.1–NE)	NR (NE–NE)	60.4 (36.6–NE)	NR (13.9–NE)	60.4 (39.7–NE)
Estimated DOR rate (95% CI)	12-month DOR Rate			18-month DOR Rate			60-month DOR Rate		
	77.0 (65.6–85.1)	NE (NE–NE)	71.7 (60.7–80.1)	69.4 (56.7–79.1)	45.8 (19.6–68.7)	65.6 (53.9–75.0	52.2 (41.8–61.6)	60.0 (36.3–77.3)	53.4 (43.9–62.0)
PFS, median (95% CI), months	NR (23.5–NE)	11.8 (9.1–NE)	NR (23.5–NE)	NR (23.5–NE)	12.0 (9.1–NE)	NR (23.5–NE)	57.3 (30.9–NE)	NR (12.4–NE)	62.2 (34.9–NE)
Estimated PFS rate (95% CI)	12-month PFS Rate			18-month PFS Rate			60-month PFS Rate		
	77.5 (66.6–85.2)	45.1 (15.2–71.4)	73.7 (63.3–81.6)	68.8 (57.4–77.8)	43.1 (18.4–65.8)	64.8 (54.2–73.5)	49.8 (39.8–59.0)	53.9 (32.9–71.0)	50.4 (41.3–58.7)
OS, median (95% CI), months	NR (NE–NE)	NR (NE–NE)	NR (NE–NE)	NR (31.6–NE)	NR (18.7–NE)	NR (NE–NE)	NR (NE–NE)	NR (NE–NE)	NR (NE–NE)
Estimated OS rate (95% CI)	12-month OS Rate			18-month OS Rate			60-month OS Rate		
	92.8 (84.7–96.7)	92.9 (59.1–99.0)	92.9 (85.6–96.5)	88.3 (79.4–93.5)	82.8 (54.7–94.3)	87.4 (79.2–92.5)	68.9 (59.8–76.3)	71.1 (50.1–84.5)	69.0 (60.8–75.8)

NE=not estimable, NR=not reached.

The 24-month PFS rates in patients with FL determined at an earlier analysis (March 31, 2021, data cutoff) were generally consistent across key subgroups, which included age, sex, ECOG performance status, high tumor burden, relapsed/refractory disease, and prior therapy.[2,7]

As of the March 31, 2024 data cutoff for the 5-year long-term follow-up analysis, 43% of patients

with FL and 48% with MZL had ongoing responses.[2] Among the patients who had achieved CR, 58% remained in CR at data cutoff. The median OS was not reached in patients with FL or MZL.[2] The 60-month OS rate was 69% overall. Among patients with FL, the 60-month lymphoma-specific survival rate was 83.4%. Kaplan-Meier curves for DOR, PFS, and OS from the 5-year follow-up analysis (March 31, 2024, data cutoff) are shown in Figures 1, 2, and 3.

Figure 1. Duration of Response[2]

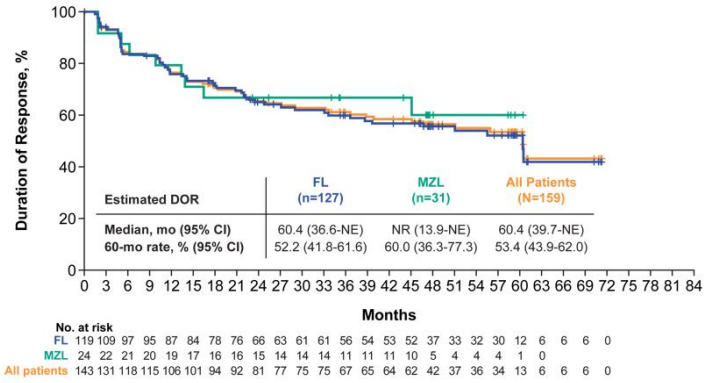


Figure 2. Progression-Free Survival[2]

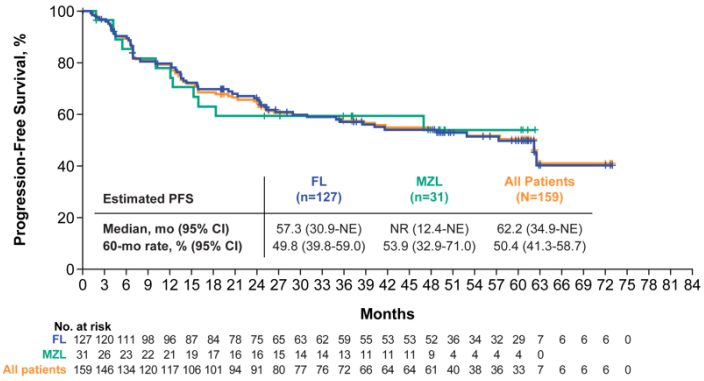
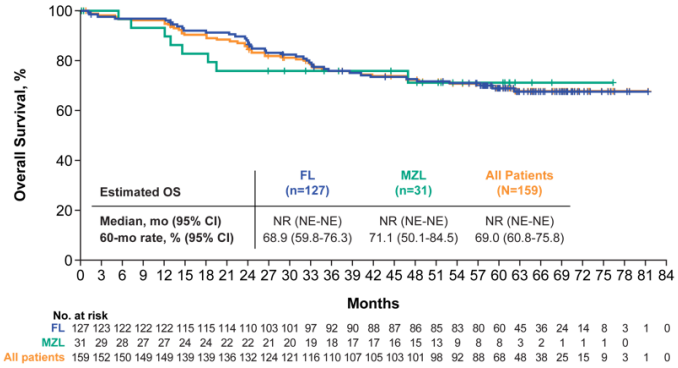


Figure 3. Overall Survival[2]



Safety

Adverse Events

At the updated analysis (September 14, 2020, data cutoff), 99% (147 of 148) of treated patients experienced treatment-emergent AEs of any grade (86% Grade ≥3), and 50% (57 FL, 17 MZL) experienced serious AEs of any grade.[1] The most frequently reported Grade ≥3 AEs in Yescarta treated patients were cytopenias (70%) and infections (18%). Thirty-four percent of patients had Grade ≥3 cytopenias that were present on or after Day 30 (33% with FL, 38% with MZL), and were mostly neutropenias (27% with FL, 33% with MZL). Infections of Grade ≥3 occurred in 26 (18%) patients (19 FL, 7 MZL).[1,6] Two deaths were described to be attributable to Yescarta treatment (PML, with death occurring 23.8 months after enrollment, and COVID-19 pneumonia, with death occurring 26.6 months after enrollment; both in patients with FL).[8]

Safety events that occurred in ≥20% of patients as of the updated analysis data cutoff are summarized in Table 5 below.

Table 5. AEs of Any Grade That Occurred in ≥20% of All Patients in ZUMA-5 (September 14, 2020, Data Cutoff)[6]

Treatment-Emergent AEs, n (%)	FL (n=124)		MZL (n=24)		All Patients (n=148)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	123 (99)	105 (85)	24 (100)	23 (96)	147 (99)	128 (86)
Pyrexia	103 (83)	9 (7)	22 (92)	2 (8)	125 (84)	11 (7)
Neutropenia	79 (64)	75 (60)	17 (71)	16 (67)	96 (65)	91 (61)
Hypotension	59 (48)	3 (2)	15 (63)	3 (13)	74 (50)	6 (4)
Headache	54 (44)	2 (2)	12 (50)	0	67 (45)	2 (1)
Fatigue	51 (41)	1 (1)	15 (63)	0	66 (45)	1 (1)
Nausea	45 (36)	0	15 (63)	0	60 (41)	0
Anemia	44 (35)	29 (23)	12 (50)	7 (29)	56 (38)	36 (24)
Thrombocytopenia	44 (35)	29 (23)	6 (25)	5 (21)	50 (34)	34 (23)
Sinus tachycardia	41 (33)	2 (2)	8 (33)	0	49 (33)	2 (1)
Tremor	36 (29)	1 (1)	9 (38)	0	45 (30)	1 (1)
Chills	33 (27)	0	10 (42)	0	43 (29)	0
Diarrhea	33 (27)	0	9 (38)	0	42 (28)	0
Constipation	35 (28)	0	6 (25)	0	41 (28)	0
Vomiting	29 (23)	1 (1)	9 (38)	0	38 (26)	1 (1)
Decreased appetite	28 (23)	2 (2)	9 (38)	0	37 (25)	2 (1)
Hypoxia	27 (22)	8 (6)	9 (38)	4 (17)	36 (24)	12 (8)
Confusional state	28 (23)	6 (5)	7 (29)	2 (8)	35 (24)	8 (5)
Cough	27 (22)	0	6 (25)	0	33 (22)	0
Encephalopathy	24 (19)	10 (8)	6 (25)	3 (13)	30 (20)	13 (9)
White blood cell count decreased	23 (19)	21 (17)	6 (25)	6 (25)	29 (20)	27 (18)

Note: all treated patients include the 146 patients in the primary analysis and 2 patients with MZL who were treated with Yescarta after the data cutoff for the primary analysis.

Between the updated analysis and the 3-year long-term follow-up analysis (N=152, March 31, 2022, data cutoff), additional Grade ≥3 AEs were reported in 11% of patients, including cytopenias (5%), infections (5%), and neurologic events (1%); serious AEs were reported in 10% of patients (Grade ≥3, 9%).[3] Six of the serious AEs were considered related to Yescarta (COVID-19/COVID-19 pneumonia, pyrexia, cellulitis, myelodysplastic syndrome, febrile neutropenia, and pneumonia). No new safety signals were observed among the treated patients at the 3-year long-term follow-up analysis.

Through the 5-year long-term follow-up analysis (March 31, 2024, data cutoff), non-relapse mortalities were due to infection-related events (7%), secondary malignancy (4%), cardiac-related events (2%), and other (2%; including 1 death due to CRS and multiorgan failure and 2 deaths of unknown causes).[2]

Cytokine Release Syndrome

In the updated analysis (September 14, 2020, data cutoff), 82% of all 148 Yescarta-treated patients (78% with FL; 100% with MZL) experienced CRS of any grade, per the Lee et al. criteria.[1] Most cases were of Grade 1 or 2 (75% in all 148 treated patients, 72% with FL,

92% with MZL), and Grade ≥3 cases in 7% of treated patients (6% with FL; 8% with MZL). All events in the setting of CRS resolved except 1 event of multisystem organ failure, leading to death on Day 7 in a patient with FL who had bulky disease at baseline per GELF criteria. For the management of CRS, tocilizumab was administered to 74 (50%) of 148 patients, corticosteroids to 27 (18%) patients, and vasopressors to 8 (5%) patients. The CRS events from the updated analysis are summarized in Table 6 below.

Table 6. Summary of CRS Events (September 14, 2020, Data Cutoff)

Parameter	FL (n=124)		MZL (n=24)		All Patients (N=148)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS, n (%)[6]	97 (78)	8 (6)	24 (100)	2 (8)	121 (82)	10 (7)
Most common CRS symptoms [a,b], n (%)[6]						
Pyrexia	94 (97)	6 (6)	22 (92)	2 (8)	116 (96)	8 (7)
Hypotension	39 (40)	3 (3)	12 (50)	2 (8)	51 (42)	5 (4)
Chills	25 (26)	0	7 (29)	0	32 (26)	0
Hypoxia	23 (24)	6 (6)	8 (33)	4 (17)	31 (26)	10 (8)
Sinus tachycardia	25 (26)	2 (2)	6 (25)	0	31 (26)	2 (2)
Headache	19 (20)	0	1 (4)	0	20 (17)	0
Median time to onset (IQR), days[1]	4 (2–6)		4 (2–7)		-	
Median duration of events (IQR), days[1]	6 (4–8)		5 (3–9)		-	

[a] Included are CRS events of any grade occurring in ≥15% of patients. [b] Percentage calculated out of 121 patients that experienced CRS

As of the 2-year follow-up analysis (March 31, 2021, data cutoff), Grade ≥3 CRS events occurred in 7% of patients (6% FL; 8% MZL), and most cases of CRS (120 of 121) of any grade resolved by data cutoff.[7]

As of the 3-year follow-up analysis (March 31, 2022, data cutoff), CRS of any grade was reported in 2% of patients (0% FL; 11% MZL). No Grade ≥3 CRS events were reported.[3]

Neurologic Events

Neurologic events of any grade, as of the updated analysis (September 14, 2020, data cutoff), occurred in 59% of patients (56% with FL; 71% with MZL) of all 148 Yescarta-treated patients.[1] Grade 1 or 2 events occurred in 40% of patients (41% in FL, 33% in MZL), Grade 3 or 4 events occurred in 19% of patients (15% in FL, 38% in MZL), and no Grade 5 neurologic events occurred. Two patients with FL had ongoing neurologic events (1 had Grade 1 memory impairment and 1 had intermittent paresthesia), and 2 patients with MZL had ongoing neurologic events (1 had Grade 1 memory impairment and 1 had ongoing Grade 1 tremor). For management of neurologic events, corticosteroids were used in 53 (36%) patients and tocilizumab was used in 9 (6%; 7 of 9 patients had concurrent CRS). The neurologic events are summarized in Table 7 below.

Table 7. Summary of Neurologic Events (September 14, 2020, Data Cutoff)

Parameter	FL (n=124)		MZL (n=24)		All Patients (N=148)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neurologic events, n (%)[6]	70 (56)	19 (15)	17 (71)	9 (38)	87 (59)	28 (19)
Most common neurologic event symptoms [a], n (%)[6]						
Tremor	36 (29)	1 (1)	9 (38)	0	45 (30)	1 (1)

Parameter	FL (n=124)		MZL (n=24)		All Patients (N=148)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Confusional state	28 (23)	6 (5)	7 (29)	2 (8)	35 (24)	8 (5)
Encephalopathy	24 (19)	10 (8)	6 (25)	3 (13)	30 (20)	13 (9)
Median time to onset (IQR), days[1]	7 (6–10)		7 (6–11)		-	
Median duration of events (IQR), days[1]	14 (5–43)		10 (5–28)		-	

[a] Included are neurologic events of any grade occurring in ≥15% of patients

As of the March 31, 2021 data cutoff, Grade ≥3 neurologic events occurred in 19% of patients (15% FL; 36% MZL), and most cases of neurologic events (82 of 87) of any grade resolved by data cutoff.[7] Nearly half of all neurologic events (49%) resolved ≤2 weeks after onset, and most neurologic events (76%) resolved ≤8 weeks after onset.

As of the 3-year follow-up analysis (March 31, 2022, data cutoff), 1 additional Grade ≥3 neurologic event had occurred.[3]

Pharmacokinetics

CAR T-Cell Expansion and Persistence

The median time to peak anti-CD19 CAR T-cell levels, for the 148 patients included in the updated analysis (September 14, 2020, data cutoff) was 9 days (IQR, 8–15) post-infusion.[1] The median time to peak concentration of anti-CD19 CAR T-cells for patients with FL and MZL was 8 days (IQR 8–15) and 15 days (IQR 8–16), respectively. One patient with FL experienced a second CAR T-cell peak on Day 371 in association with a relapse. CAR T-cell expansion appeared slightly higher in patients with MZL than patients with FL by peak and AUC. CAR T-cell expansion, persistence, and association with response are illustrated in Figure 4 and Figure 5.

Figure 4. CAR T-Cell Expansion and Persistence[6]

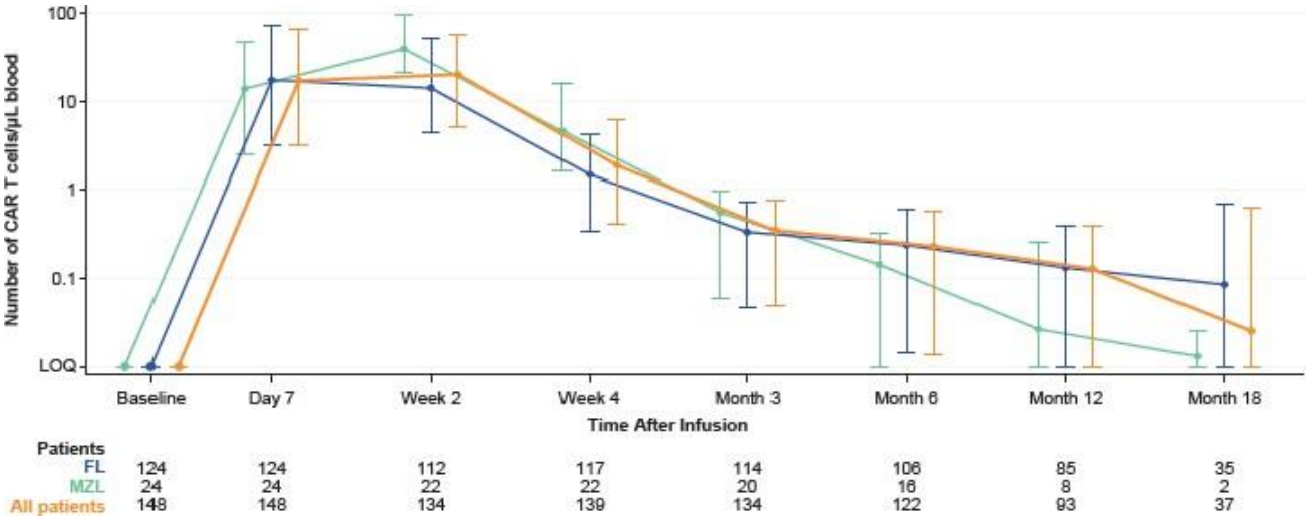


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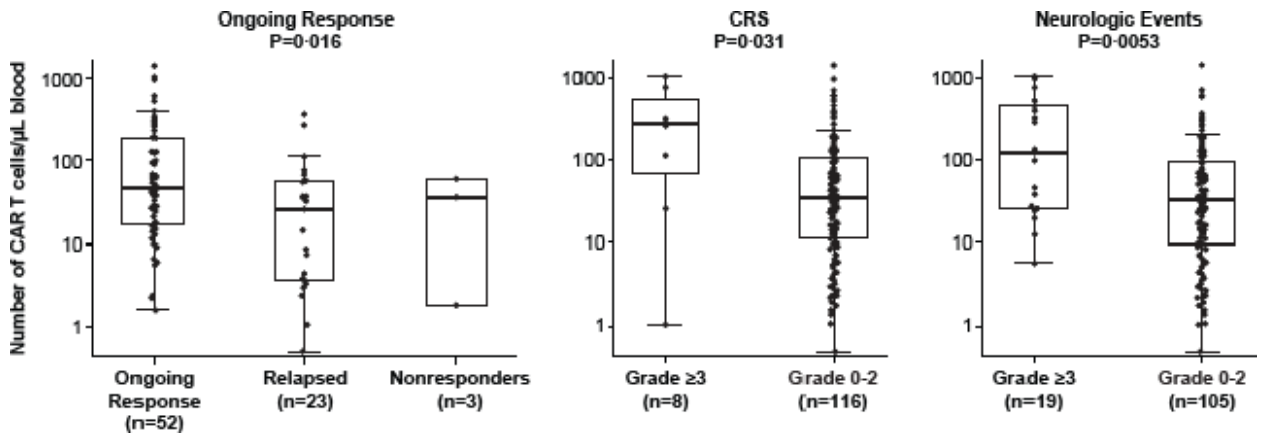
Figure 5. CAR T-Cell Expansion and Association with Ongoing Response, CRS, and Neurological Events in Patients with FL[6]



P-values were calculated using the Wilcoxon rank sum test and were not adjusted for multiplicity. The median is represented by the horizontal line within each box, and the 25th and the 75th percentiles are represented by the lower and upper borders of each box. The numbers of patients in some groups are small and may limit comparison.

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Patients with FL who had an ongoing response at the 5-year follow-up (March 31, 2024, data cutoff) had significantly higher CAR T-cell expansion than patients with FL who relapsed or did not respond to treatment.[2]

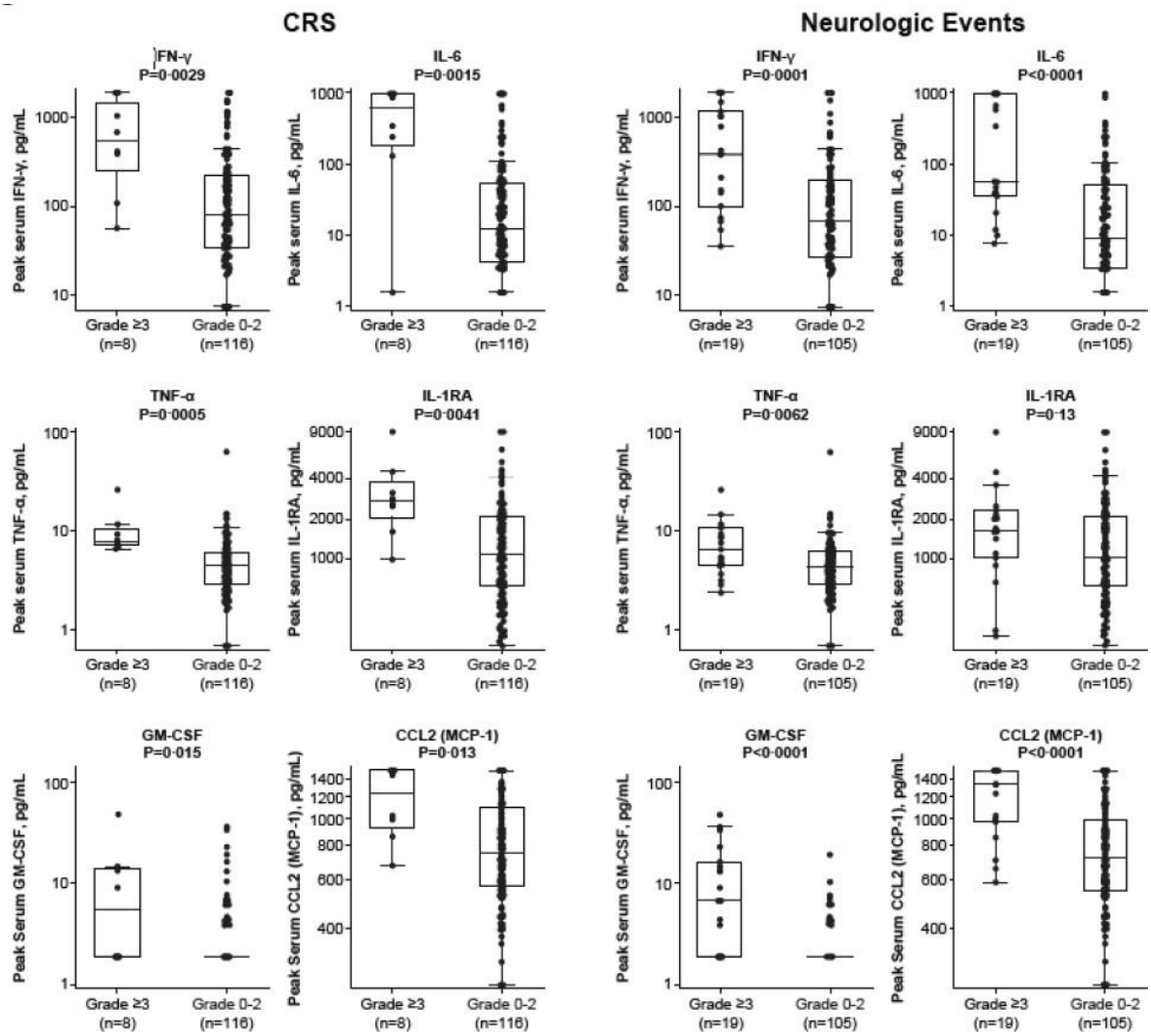
Patients with MZL were noted at the March 31, 2021 data cutoff to have similar pharmacokinetic findings to patients with FL. [7]

Of the patients with FL and an ongoing response at the March 31, 2021 data cutoff, 90% (43 of 45) had detectable CAR gene-marked T-cells at Month 3, and 42% (20 of 37) had detectable CAR T-cells at Month 24.[7] As of 3-year long-term follow-up analysis (March 31, 2022, data cutoff), the majority of treated patients had low levels of detectable CAR gene-marked cells by Month 12, and half of the patients had low levels of detectable CAR gene-marked cells by Month 24.[3] An inverse correlation between CAR gene-marked cells and B cells was noted at the 3-year analysis (March 31, 2022, data cutoff) and remained evident at the 5-year follow-up analysis (March 31, 2024 data cutoff).[2,3]

Serum Cytokines

In the updated analysis, after Yescarta infusion, concentrations of most cytokines peaked by Day 8 and resolved by Week 4.[1] Peak levels of key serum analytes were associated with Grade ≥3 CRS and neurological events.[6] In patients with MZL, *P*-values for associations with CRS were not calculated, and an association between peak levels of key serum analytes and neurologic events was not identified (data not shown).[6] Associations between peak serum biomarkers and adverse events in patients with FL are illustrated in Figure 6.

Figure 6. Associations Between Peak Serum Biomarkers and Adverse Events in All Treated Patients with FL[6]



P values were calculated using the Wilcoxon rank sum test and were not adjusted for multiplicity. The median is represented by the horizontal line within each box, and the 25th and the 75th percentiles are represented by the lower and upper borders of each box. The numbers of patients in some groups are small and may limit comparison

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Abbreviations

AE = adverse event
ASCT= autologous stem-cell transplantation
AUC=area under the curve
CAR=chimeric antigen receptor
CNS=central nervous system
COVID-19=coronavirus disease 2019
CR=complete response
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
DOR=duration of response
ECOG PS=Eastern Cooperative Oncology Group performance status
FL=follicular lymphoma
FLIPI= Follicular Lymphoma International Prognostic Index
GELF=Groupe d'Etude des Lymphomes Folliculaires
iNHL=indolent non-Hodgkin lymphoma
IQR=interquartile range
IRRC=independent radiology review committee
IV=intravenous
mAb= monoclonal antibody
MZL=marginal zone lymphoma
NA=not applicable
NE=not estimable
NR=not reached
ORR=overall response rate
OS=overall survival
PET-CT= Positron emission tomography-computed tomography
PFS=progression free survival
PI3Ki=phosphatidylinositol 3-kinase inhibitor
PML=progressive multifocal leukoencephalopathy
POD24=progression of disease <24 months from initiating the first anti-CD20– containing chemoimmunotherapy
PR=partial response
WHO=World Health Organization

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉ MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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