Yescarta® (axicabtagene ciloleucel)

Results from Safety Management Cohort 6 of the ZUMA-1 Study

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The full indication, important safety information, and boxed warnings for cytokine release syndrome, neurologic toxicities and secondary hematological malignancies are available at: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.

Summary

Methods[1,2,3]

Cohort 6 of the ZUMA-1 study investigated the management of cytokine release syndrome (CRS) and neurologic toxicities (NTs) with prophylactic levetiracetam and corticosteroids, and earlier corticosteroid and tocilizumab intervention. Forty eligible patients underwent conditioning chemotherapy prior to receiving a single intravenous infusion of YESCARTA at a target dose of $2x10^6$ anti-CD19 CAR T cells/kg, prophylactic treatment with corticosteroids with once-daily oral dexamethasone 10mg for 3 days beginning on the day of infusion with YESCARTA prior to infusion of YESCARTA, and prophylactic levetiracetam (750 mg PO or IV). As part of the FDA adjudication, one patient in Cohort 6 did not receive all three dosages of oral dexamethasone on day 0, 1, and 2, and was thus excluded from the analysis in the US Prescribing Information. Thirty-nine patients were included in the FDA's adjudicated safety analysis. Primary endpoints were the incidence and severity of CRS and NTs. Secondary endpoints were investigator-assessed objective response rate, duration of response, progression-free survival, overall survival, incidence of adverse events, and levels of CAR T-cells and cytokines in blood.

Safety[1,2,4,5]

Adverse events (AEs) were reported for all treated patients. All patients reported Grade 3 or higher AEs. Of the 39 patients, CRS occurred in 31 patients (79%), with all cases reported as Grade 1 or Grade 2. NTs occurred in 33 patients (85%), including 5 patients (13%) with Grade $\geq$3 NTs. Four patients (10%) had fatal treatment emergent AEs. The use of prophylactic corticosteroids and earlier corticosteroid and/or tocilizumab intervention for toxicity management resulted in no cases of Grade 3 or higher CRS, delayed CRS onset, and had similar neurologic toxicities. Per the YESCARTA US Prescribing Information, consider the use of prophylactic corticosteroid in patients after weighing the potential benefits and risks. At the 1-year and 2-year analyses, there were no new cases of CRS.

There were 4 new cases of NTs (in 2 patients) between the 6-month and 1-year analysis, and 2 new cases of NTs (in 2 patients) at the 2-year analysis.

Efficacy[4,5]

No formal statistical analysis was conducted and end-points were analyzed descriptively, including efficacy outcomes. The investigator-assessed objective response rate (ORR) and complete response (CR) rate in Cohort 6 were 95% and 80%, respectively, at a median follow-up of 14.9 months; ORR and CR rate remained unchanged at a median follow-up of 26.9 months.

Propensity Score Matching (PSM)[2,4]

The safety management cohorts were not designed or powered for statistical comparisons with each other or with the pivotal cohorts. To overcome these limitations and reduce bias, PSM was applied to Cohorts 1+2 and Cohort 6. The differences in CRS and NTs observed between patients in Cohort 6 and Cohorts 1+2 remained comparable before and after PSM. Clinical efficacy (ORR) in Cohort 6 remained comparable to Cohort 1+2 before and after PSM.

ZUMA-1 Study

Study Description and Cohorts

ZUMA-1 Pivotal Cohorts 1+2

ZUMA-1 is a phase 1/2, multicenter, single-arm, open-label study which evaluated the safety and efficacy of YESCARTA (axicabtagene ciloleucel [axi-cel]) in patients with chemorefractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (FL).[6] Table 1 below provides the incidence and severity of CRS and NTs for ZUMA-1 Cohorts 1+2, as reported in the US Prescribing Information.[1]

Table 1. Incidence of CRS and NTs for LBCL patients in Pivotal ZUMA-1 Cohorts 1+2 (N=108)[1]

Adverse Reaction	Cytokine Release Syndrome (CRS)	Neurologic Toxicities (NTs)
Any Grade	101 (94%)	94 (87%)
Grade ≥3	14 (13%)[7]	34 (31%)[7]
Median Onset (days)	2 (1–12)	4 (1–43)
Median Duration (days)	7 (2-58)	17 (N/A)

The most common Grade ≥3 CRS symptoms included pyrexia, hypoxia and hypotension. The most common Grade ≥3 NTs were encephalopathy, confusional state, aphasia and somnolence.[6]

ZUMA-1 Cohort 6

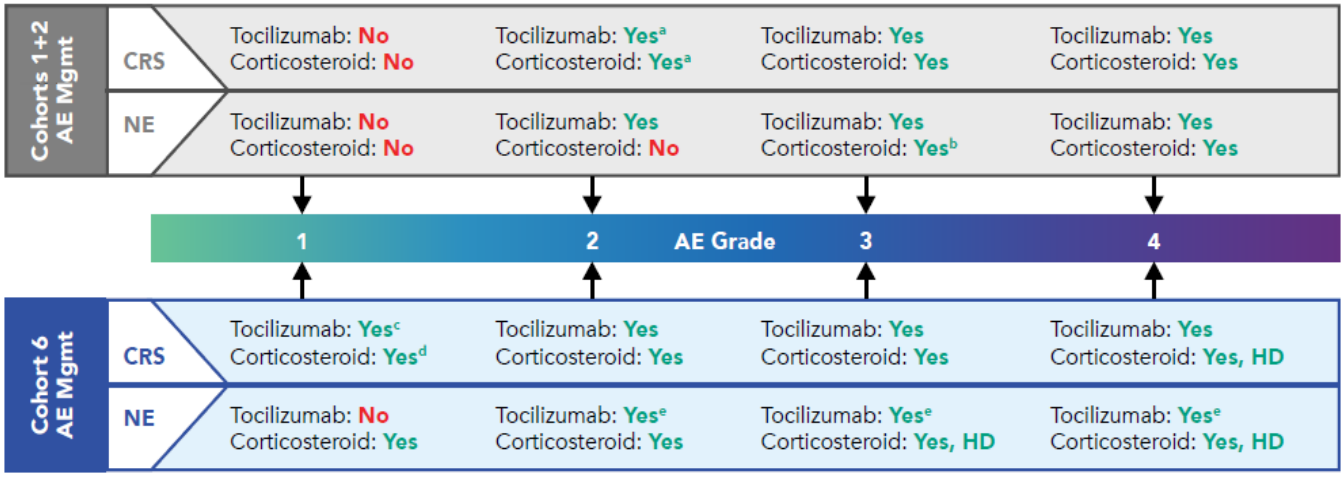
Since minimizing CRS and NT incidence and severity are important goals in CAR T-cell therapy related toxicity management, Kite investigated ways to improve the safety profile of YESCARTA in LBCL with the addition of exploratory safety cohorts.

Cohort 4 was an open-label safety management cohort from ZUMA-1 study which evaluated the rates and severity of CRS and NT with earlier corticosteroid and tocilizumab use. In the study, numerically lower rates of Grade ≥3 CRS and NTs were observed and did not appear to affect CAR T-cell expansion or ongoing response rates.[8] To build on these findings, Cohort 6 evaluated the addition of prophylactic corticosteroids to Cohort 4 toxicity management regimen on the incidence and severity of CRS and NTs.[2]

The safety management Cohort 6 evaluated the safety and efficacy of YESCARTA with the use of prophylactic corticosteroids (oral dexamethasone 10 mg once daily for 3 days, starting prior to YESCARTA infusion on Day 0) and prophylactic levetiracetam (750 mg PO or IV).[1,2] Cohort 6 included 40 patients with relapsed/refractory LBCL who were treated with YESCARTA.[2] Primary endpoints included incidence and severity of CRS and NTs. Secondary endpoints included investigator-assessed ORR, duration of response (DOR), progression-free survival (PFS), overall survival (OS), incidence of AEs, and levels of anti-CD19 CAR T-cells and cytokines in blood. Cohort 6 primarily differed from Cohorts 1+2 in that patients received levetiracetam and corticosteroid prophylaxis, and earlier corticosteroids and tocilizumab for toxicity management. Note that the safety management cohorts were not designed for comparative purposes and no formal hypotheses were tested.[2,8]

Figure 1 provides the protocol-specified management of CRS and neurologic events in ZUMA-1 Cohorts 1+2 and Cohort 6.

Figure 1. Adverse Event Management of CRS and NE in ZUMA-1 Cohorts 1+2 and Cohort 6[4]



[a]Only in case of comorbidities or older age. [b]Only if no improvement with tocilizumab; use standard dose. [c]If no improvement after 24 hours of supportive care in Cohort 6. [d]If no improvement after 3 days. [e]Only for Grade ≥2 NEs with concurrent CRS in Cohort 6.
AE, adverse event; CRS, cytokine release syndrome; HD, high dose; Mgmt, management; NE neurologic event.

Safety

Adverse Events

The incidence and severity of CRS and NTs in Cohort 6 of the ZUMA-1 study are presented in Table 2 below.[1] According to the YESCARTA US Prescribing Information, prophylactic corticosteroids for management of CRS and neurologic toxicities may result in higher grade of neurologic toxicities or prolongation of neurologic toxicities, delay the onset and decrease

the duration of CRS. The healthcare provider should consider the risk and benefits of prophylactic corticosteroids in the context of pre-existing comorbidities for the individual patient and the potential for the risk of Grade 4 and prolonged neurologic toxicities.

Table 2. Incidence and Severity of CRS and NTs (N=39[a])[1]

Adverse Event	Cytokine Release Syndrome (CRS)	Neurologic Toxicities (NT)
Any Grade, n (%)	31 (79)	33 (85)
Worst Grade 3, n (%)	0 (0)	3 (8)
Worst Grade 4, n (%)	0 (0)	2 (5)
Median Onset, days (range)	5 (1–15)	6 (1–274)
Median Duration, days (range)	4 (1–10)	12 (1–107)

[a]As part of the FDA adjudication, one patient in Cohort 6 did not receive all three dosages of oral dexamethasone on day 0,1, and 2, and was thus excluded from the analysis in the US Prescribing Information.[3] Thirty-nine patients were included in the FDA's adjudicated safety analysis.

Additionally, the results from six-month analysis of Cohort 6 have been previously presented and published.[2,9] AEs were reported in all of the 40 patients receiving YESCARTA, which comprised the safety analysis set.[2] The most frequent any-grade AEs were pyrexia (85%), hypotension (55%), and neutropenia (50%). Grade 3 or higher AEs were reported in all treated patients — the most frequent were neutropenia (45%), neutrophil count decreased (33%), anemia (20%) and white blood cell count decreased (20%). The most common CRS symptoms included pyrexia (97%), hypotension (53%), and hypoxia (19%). The most common NTs included confusional state (38%), tremor (23%), aphasia (15%), and somnolence (15%). Notably, 68% of patients had no NTs or CRS within 72 hours of infusion. Fifteen patients received corticosteroids only as prophylaxis with no additional corticosteroids for AE management. Excluding prophylaxis, corticosteroids were used to treat CRS, NTs and other events in 17 patients (43%), 16 patients (40%) and 1 (3%) patient respectively.

A 1-year updated analysis of Cohort 6 was subsequently presented at the 2021 American Society of Hematology (ASH) Annual Meeting.[4] Between the 6-month and 1-year analyses, there were no new cases of CRS. There were four new YESCARTA-related NTs in 2 patients – one patient had Grade 2 mental status changes and seizure-like phenomena both on Day 441 (duration, 2 days and 1 day, respectively), and the other patient had Grade 1 dementia on Day 93 (duration, 277 days) and Grade 5 toxic encephalopathy on Day 369 (resultant from a Grade 4 event that stated on Day 351). The investigator believed that a mild case of dementia may have predated the study in this patient. Additionally, there were two new infections of Grade 2 pneumonia on Day 474 (resolved on Day 479; unrelated to YESCARTA) and Grade 1 bronchitis on Day 459 (resolved on Day 459; related to YESCARTA), and one death due to progressive disease. With the addition of the one new Grade 5 event, a total of four patients (10%) had fatal treatment-emergent AEs: one respiratory failure due to ongoing respiratory infection (Day 91; related to YESCARTA), one urosepsis (Day 107; unrelated to YESCARTA), one toxic encephalopathy (Day 369; related to YESCARTA), and one unknown AE.[2,4]

Results from a 2-year analysis of Cohort 6 have also been reported. Between the 1-year and 2-year analyses, there were no new cases of CRS. Two new NTs occurred in 2 patients

– one patient had Grade 2 dementia unrelated to YESCARTA on Day 685 that remained ongoing at the time of data cutoff, and the other patient had Grade 5 YESCARTA-related leukoencephalopathy on Day 758 that eventually led to death on Day 815. With the addition of the new Grade 5 event, the incidence of Grade ≥3 NTs increased from 15% to 18% between the 1-year and the 2-year analyses. There were six new infections (Grades 1, 2, and 5 COVID-19 [n=1 each; unrelated to YESCARTA]; Grade 3 *Pneumocystis jirovecii* pneumonia [related to YESCARTA]; Grade 3 unknown infectious episode with inflammatory syndrome [related to YESCARTA]; and Grade 2 herpes zoster [related to YESCARTA]) and eight deaths (due to progressive disease [n=5], COVID-19 [n=2], and leukoencephalopathy [n=1]).[5]

Efficacy

Overall Response Rate, Duration of Response, Progression-Free Survival, and Overall Survival

Table 3 presents the efficacy outcomes of Cohort 6 at the 6-month analysis (data cut-off date: June 16, 2020), 1-year analysis (data cut-off date: Dec 16, 2020), and 2-year analysis (data cut-off date: December 16, 2021).[2,4,5,10]

Table 3. Efficacy Outcomes at 6-Month, 1-Year, and 2-Year Analysis

Efficacy	6-month Analysis (N=40)[2,10]	1-year Analysis (N=40)[4]	2-year Analysis (N=40)[5]
Median Follow-up Time, months	8.9	14.9	26.9
Objective Response, *n* (%)	38 (95)	38 (95)	38 (95)
Complete Response, *n* (%)	32 (80)	32 (80)	32 (80)
Ongoing response at data cut-off, *n* (%)	25 (62.5)	21 (53)	18 (45)
Kaplan-Meier DOR Rate, % (95% CI)	62.4 (41.6, 77.6)	60 (41, 74)	53 (36, 68)
Kaplan-Meier PFS Rate, % (95% CI)	72.2 (54.1, 84.1)	63 (46, 77)	53 (36, 67)
Kaplan-Meier OS Rate, % (95% CI)	87.3 (72.1, 94.5)	82 (66, 91)	62 (45, 75)

CI, confidence interval; DOR, duration of response; OS, overall survival; PFS, progression-free survival.

Additionally, at the 6-month analysis, authors reported the ORR and CR rates were 92% and 84%, respectively, in the 25 patients who received corticosteroids for prophylaxis and toxicity management. The ORR and CR rates were 100% and 73%, respectively, in the 15 patients who received corticosteroid prophylaxis only.[2] At the 2-year analysis, rates for ORR and CR remained unchanged; median DOR and PFS were 25.9 (95% CI, 7.8–NE) and 26.8 (95% CI, 8.7–NE) months, respectively, and median OS was not reached (95% CI, 18.9–NE).[5]

Propensity Score Matching (PSM)

Comparison Between Patients in ZUMA-1 Pivotal Cohorts 1+2 and Cohort 6

As Cohort 6 of ZUMA-1 was not designed for a statistical comparison with the pivotal ZUMA-1 Cohorts 1+2, an exploratory retrospective PSM analysis was performed to descriptively compare results for Cohort 6 and Cohorts 1+2.[2] As shown in Table 4, the following key baseline disease characteristics were balanced to perform PSM analysis: tumor burden, International Prognostic Index score, number of prior lines of chemotherapy, disease stage and lactate dehydrogenase level.[2,10] In total, 32 matched patients each in Cohort 6 and Cohorts 1+2 were identified in PSM analysis.[2,4] Eight patients from Cohort 6 were not included due to nonavailability of matched patients in Cohorts 1+2.

As shown in Table 5, the differences in incidence of Grade ≥3 CRS and time to onset of CRS observed between Cohorts 1+2 and Cohort 6 were maintained before and after PSM.[2,4] The incidence and severity were found to be generally similar between Cohorts 1+2 and Cohort 6 after PSM. Median time to onset of Grade ≥3 NTs appeared to be delayed in Cohort 6 versus Cohorts 1+2 before and after matching. Additionally, ongoing response rates in Cohort 6 also remained comparable to that observed in Cohorts 1+2 before and after PSM.

Table 4. Propensity-Score-Matched Baseline Patient and Product Characteristics[10]

Characteristic	Cohorts 1+2 Overall (N=101)	Cohort 6 Overall (N=40)	Cohorts 1+2 After Matching (n=32)	Cohort 6 After Matching (n=32)
Patient characteristics				
Disease stage III or IV, *n* (%)	86 (85.1)	26 (65.0)	23 (71.9)	21 (65.6)
IPI score 3–4, *n* (%)	48 (47.5)	18 (45.0)	12 (37.5)	15 (46.9)
Number of prior lines of chemotherapy, *n* %				
≤2	31 (30.7)	25 (62.5)	20 (62.5)	17 (53.1)
3	30 (29.7)	12 (30.0)	10 (31.3)	12 (37.5)
≥4	40 (39.6)	3 (7.5)	2 (6.3)	3 (9.4)
Median tumor burden by SPD[a] (Q1, Q3), mm^2	3723 (2200, 7138)	1184 (498, 3391)	2212 (816, 4245)	1973 (632, 4641)
Median LDH (Q1, Q3), U/l	356 (219, 743)	236 (209, 329)	240 (192, 369)	247 (215, 504)
Product characteristics,[b] median (Q1–Q3)				
CD8+ T cells, %	53.6 (34.9, 65.1)	56.0 (37.3, 69.2)	54.4 (40.6, 64.5)	57.0 (37.3, 71.5)
Naive (CCR7+CD45RA+) T cells, %	13.9 (8.1, 24.4)	27.8 (19.9, 39.1)	20.0 (12.2, 26.7)	29.4 (19.8, 38.4)
Percent transduction, %	52.6 (44.3, 63.6)	62.0 (54.0, 69.0)	55.0 (38.6, 64.6)	62.0 (53.5, 68.5)

[a]Measured before conditioning therapy. For patients in Cohort 6, baseline tumor burden was measured after bridging therapy, for patients who received bridging therapy, but before conditioning therapy. [b]Product characteristics parameters were not used for propensity score matching and are presented descriptively here in before matching and after matching subgroups.

IPI, International Prognostic Index; LDH, lactate dehydrogenase; Q, quartile; SPD, sum of the products of diameters.

Table 5. Propensity-Score-Matched Safety and Efficacy Outcomes[4]

Characteristic	Cohorts 1+2 Overall (N=101)	Cohort 6 Overall (N=40)	Cohorts 1+2 After Matching (n=32)	Cohort 6 After Matching (n=32)
Safety				
CRS				
Worst Grade ≥3, *n* (%)	12 (12)	0 (0)	4 (13)	0 (0)
Median (Q1, Q3) time to onset of any grade CRS, days	2 (2, 3)	5 (4, 6)	2 (2, 4)	5 (4, 6)
NTs				
Worst Grade ≥3, *n* (%)	29 (29)	6 (15)	7 (22)	6 (19)
Median (Q1, Q3) time to onset of any grade NT, days	5 (3, 7)	6 (5, 9)	6 (3, 7)	6 (5, 8)
Infections				
Worst Grade ≥3, *n* (%)	23 (23)	8 (20)	6 (19)	8 (25)[a]
Cumulative cortisone-equivalent corticosteroid dose (including prophylaxis), n	25	40	6	32
Median (Q1, Q3), mg	6390 (2817, 15,760)	1252 (939, 6291)	7418 (2504, 11,579)	1252 (939, 6604)
Cumulative tocilizumab use, n	43	23	11	19
Peak median (Q1, Q3), mg	1300 (800, 1800)	1000 (700, 1760)	1339 (772, 3310)	1000 (600, 1680)
Efficacy				
Responses				
Objective response, *n* (%)	84 (83)	38 (95)	30 (94)	30 (94)
Complete response, *n* (%)	59 (58)	32 (80)	25 (78)	24 (75)
Ongoing response at data cutoff,[b] *n* (%)	42 (42)	21 (53)	19 (59)	15 (47)
Median DOR (95% CI), mo	11.1 (3.9, NE)	NR (7.8, NE)	NR (8.1, NE)	13.1 (5.5, NE)
KM 12-month (95% CI), %	49 (37, 59)	60 (41, 74)	65 (45, 80)	56 (36, 72)
Median PFS (95% CI), mo	5.9 (3.3, NE)	NR (8.7, NE)	NR (5.6, NE)	14.3 (6.5, NE)
KM 12-month (95% CI), %	44 (34, 54)	63 (46, 77)	61 (42, 76)	61 (41, 76)
Median OS (95% CI), mo	NR (12.8, NE)	NR (NE, NE)	NR (15.4, NE)	NR (NE, NE)
KM 12-month (95% CI), %	60 (50, 69)	82 (66, 91)	81 (63, 91)	78 (59, 89)

[a]Worst Grade 4 or 5 infections occurred in 3 patients (patient 1: Grade 4 sepsis [unrelated to treatment]; patient 2: Grade 4 human herpesvirus 6 encephalitis [related to conditioning chemotherapy] and Grade 5 urosepsis [unrelated to treatment]; and patient 3: Grade 4 aspergillus infection and respiratory tract infection [related to conditioning chemotherapy and YESCARTA]). [b]Represents the number of patients in response at the data cutoff date among all treated patients.

CRS, cytokine release syndrome; DOR, duration of response; KM, Kaplan-Meier; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; Q, quartile.

In the PSM analysis, the 2-year cumulative incidence rate of lymphoma-related deaths were 26% (95% CI, 12–42%) in Cohort 6 and 25% (95% CI, 12–41%) in Cohorts 1+2. Six patients in Cohort 6 died from non-lymphoma causes compared with none in Cohorts 1+2 at the 2-year analysis.[5]

Pharmacokinetics and CAR T-Cell Levels Between Patients in ZUMA-1 Pivotal Cohorts 1+2 and Cohort 6

As shown in Table 5 above and Table 6 below, clinical efficacy (ongoing response rates) in Cohort 6 remained comparable to that observed in Cohorts 1+2 before and after PSM and was corroborated by lower levels of soluble inflammatory biomarkers and comparable peak CAR T-cell levels versus those in Cohorts 1+2 before and after PSM.[2,4] There was no negative impact of prophylactic and earlier corticosteroid use on CAR T-cell pharmacokinetics noted in the Cohort 6 study.

Median peak CAR-T cell expansion was observed within 2 weeks post-YESCARTA infusion (64.4 cells/µL blood).[2] Median levels of inflammatory serum biomarkers previously shown to be associated with severe NTs and/or CRS (such as interferon-γ [IFN-γ], interleukin-2 [IL-2], granulocyte-macrophage colony-stimulating factor [GM-CSF], and ferritin) peaked within 8 days post YESCARTA infusion. Median peak CAR T-cell levels were comparably high in patients with ongoing response and relapse (64 cells/µL [n=21] and 66 cells/µL [n=15], respectively) at 12 months and considerably lower in nonresponders (18 cells/µL [n=2]).[4] A similar trend was observed with CAR T-cell expansion by area under the curve from Day 0 to 28. Peak CAR T-cell levels were comparable and peak inflammatory biomarkers associated with CAR T-cell treatment-related AEs, including IFN-γ, IL-2, GM-CSF, and ferritin, were lower in Cohort 6 versus Cohorts 1+2 before and after PSM.

Table 6. Propensity-Score-Matched Comparison of CAR T-Cell and Cytokine Levels[a,4]

Median (Q1, Q3)	Cohorts 1+2 Overall (N=101)	Cohort 6 Overall (N=40)	Cohorts 1+2 After Matching (n=32)	Cohort 6 After Matching (n=32)
Peak CAR T-cell levels				
CAR T-cell expansion cells/µL	38 (15, 83)	64 (6, 131)	43 (14, 107)	65 (18, 146)
Peak cytokine levels				
IFN-γ, pg/mL	477 (196, 1097)	208 (87, 446)	481 (120, 1096)	227 (103, 424)
IL-2, pg/mL	22 (10, 38)	8 (3, 23)	23 (10, 58)	8 (3,16)
GM-CSF, pg/mL	7 (2, 16)	2 (2, 5)	9 (2, 21)	2 (2, 4)
Ferritin, ng/mL	3001 (1326, 6683)	904 (489, 1529)	2312 (1225, 4777)	809 (489, 1529)
CRP, mg/L	214 (141, 353)	76 (39, 136)	175 (124, 345)	78 (44, 131)

[a]Data from the 1-year follow up of ZUMA-1 Cohort 6
CAR, chimeric antigen receptor; CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon, IL, interleukin; Q, quartile.

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Abbreviations

AE=adverse event
ASH=American Society of Hematology
Axi-cel=axicabtagene ciloleucel
CAR=chimeric antigen receptor
CR=complete response
CRP=C-reactive protein
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
DOR=duration of response
GM-CSF=granulocyte-macrophage colony stimulating factor
HD=high dose
IFN-γ=interferon-γ
IL-2=interleukin-2
IPI=International Prognostic Index
IV=intravenous
KM=Kaplan-Meier
LBCL=large B-cell lymphoma
LDH=lactate dehydrogenase
Mgmt=management
NE=not estimable
NR=not reached
NT=neurologic toxicity
ORR=objective response rate
OS=overall survival
PMBCL=primary mediastinal B-cell lymphoma
PFS=progression-free survival
PO=orally
PSM=propensity score matching
Q=quartile
SPD=sum of the products of diameters

Product Label

For the full indication, important safety information, and Boxed Warning(s), please refer to the YESCARTA US Prescribing Information available at:
https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf

Follow Up

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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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