Yescarta®(axicabtagene ciloleucel)
Persistence and Expansion of CAR T-Cells

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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.pdf

Relevant Prescribing Information[1]

According to the YESCARTA US Prescribing Information (USPI), following infusion of YESCARTA, anti-CD19 chimeric antigen receptor (CAR) T-cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T-cells occurred within the first 7–14 days after YESCARTA infusion.

Age (range: 21 to 80 years) and gender had no significant impact on AUC_{0-28} and C_{max} of YESCARTA.

Large B-cell Lymphoma

Among patients with large B-cell lymphoma (LBCL) in the ZUMA-1 study (n=96 evaluable), the number of anti-CD19 CAR T-cells in blood was positively associated with objective response (complete response [CR] or partial response [PR]). The median anti-CD19 CAR T-cell C_{max} levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/µL vs. 21.2 cells/µL). Median area under the curve from day 0-28 (AUC_{0-28}) in responding patients (n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days×cells/µL vs. 222.0 days×cells/µL).

Among patients with LBCL in the ZUMA-7 study (n=162 evaluable), the number of anti-CD19 CAR T-cells in blood was positively associated with objective response [CR or PR]. The median anti-CD19 CAR T-cell Cmax levels in responders (n=142) were 275% higher compared to the corresponding level in nonresponders (n=20) (28.9 cells/µL vs. 10.5 cells/µL). Median AUC_{0-28} in responding patients (n=142) was 418% of the corresponding level in nonresponders (n=20) (292.9 days×cells/µL vs. 70.1 days×cells/µL).

Follicular Lymphoma

Among patients with follicular lymphoma (FL) in the ZUMA-5 study (n=81 evaluable), the median anti-CD19 CAR T-cell C_{max} levels in responders (n=74) were 40.1 cells/µL and 46.0 cells/µL in nonresponders (n=7). The median $AUC_{0–28}$ in responding FL patients (n=74) were 465.8 days×cells/µL and 404.5 days×cells/µL in nonresponders (n=7).

Some patients required tocilizumab and corticosteroids for management of cytokine release syndrome (CRS) and neurologic toxicities. Patients treated with tocilizumab (n=44) had 262% and 232% higher anti-CD19 CAR T-cells as measured by $AUC_{0–28}$ and C_{max} respectively, as compared to patients who did not receive tocilizumab (n=57). Similarly, patients that received corticosteroids (n=26) had 217% and 155% higher $AUC_{0–28}$ and C_{max} compared to patients who did not receive corticosteroids (n=75).

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinemia was reported as an adverse reaction in 14% of all patients with non-Hodgkin lymphoma (NHL). Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Available Data

Large B-cell Lymphoma (LBCL)

ZUMA-1 Study

The pivotal ZUMA-1 study was a phase 1/2 multicenter, single-arm, open-label study which evaluated the safety and efficacy of Yescarta (axicabtagene ciloleucel) in patients with chemorefractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL).[2]

The presence, persistence, expansion, and immunophenotype of transduced anti-CD19 CAR T-cells were monitored in the blood primarily by polymerase chain reaction (PCR) analysis, complemented by flow cytometry.[3] Expansion and persistence in the peripheral blood were also monitored by a CD19 CAR-specific quantitative polymerase chain reaction assay (qPCR).[3] Based on a biomarkers analysis of the ZUMA-1 phase 2 study (N=101), CAR T levels peaked in the peripheral blood within 14 days after infusion of Yescarta and were detectable in most patients at 180 days after infusion.[2] The median $AUC_{0–28}$ was 462.3 cells/µL·days (interquartile range, 147.6–930.4).[4] Consistent with previously reported results for objective response, ongoing responses at 24 months was associated with higher CAR T-cell peak concentrations and $AUC_{0–28}$ after Yescarta infusion.[2,5,6]

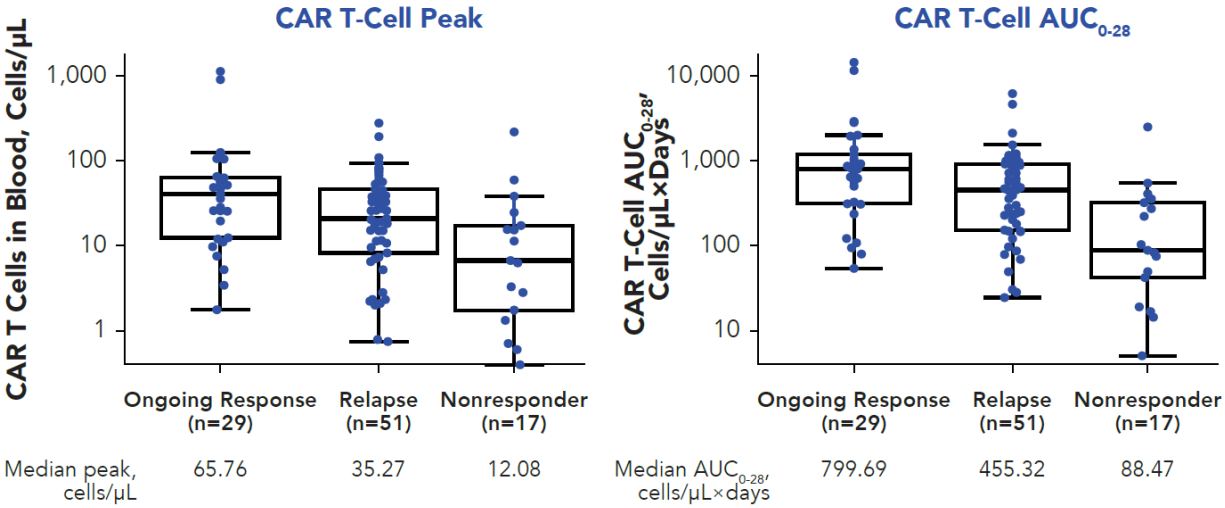
At the ZUMA-1 2-year analysis, 11 (34%) of 32 assessable patients maintained ongoing responses but no longer had detectable gene-marked CAR T-cells.[6] Additionally, 24 (75%) of 32 patients with ongoing responses showed evidence of B-cell recovery at 24 months, and initiation of B-cell recovery was noted in some patients at 9 months. Patients with ongoing responses and recovered B-cells suggest the possibility that durable responses in adults with lymphoma do not require long-term persistence of functional CAR T-cells.[3,6] These results are in accord with National Cancer Institute data showing that 3 of 4 patients with long-term ongoing responses had B-cell recovery.[7]

Updated 4-year follow-up data from the ZUMA-1 study were recently presented at the 2020 American Society of Hematology (ASH) Annual Meeting and included information on CAR T-cell and B-cell detection in patients with refractory LBCL treated with Yescarta.[8] From this study, blood samples from 21 patients in ongoing response at ≥3 years were available for analysis of CAR T-cells and evaluation of B-cell presence. All evaluable patients had detectable B-cells in the blood at 3 years after Yescarta treatment and 67% of patients (n=14/21) had detectable CAR gene-marked cells and polyclonal B-cells in blood at 3 years.

Furthermore, 91% (n=21/23) of patients with evaluable B-cells in ongoing response at the 3-year follow-up demonstrated polyclonal B-cell recovery.

Updated 5-year follow-up data from the ZUMA-1 study was presented at the 2021 ASH Annual Meeting.[9] Figure 1 shows peak CAR T-cell levels in blood and CAR T-cell $AUC_{0–28}$ at Month 60 according to response. Median peak CAR T-cell levels were numerically higher in patients with ongoing response and were lower in patients who relapsed and non-responders. A similar trend was observed with CAR T-cell expansion by $AUC_{0–28}$.

Figure 1. Measures of CAR T-Cell Levels at Month 60 According to Response[9]



Abbreviations: AUC_{0-28}=area under the curve from day 0 to 28.

ZUMA-7 Study

The ZUMA-7 study is an international, multicenter, randomized, phase 3 trial comparing Yescarta with standard care as second-line treatment in patients with early relapsed (≤12 months) or refractory LBCL.[10] Expansion and persistence of CAR T-cells were monitored by qPCR.[11] The median time to peak CAR T-cell levels post–Yescarta infusion was 7 days (range, 2–233) with median peak CAR T-cell level of 25.84 cells/mL^3.[10] CAR T-cells remained detectable in 12/30 (40%) evaluable patients by 24 months. Figure 2 shows that peak CAR T-cell expansion was significantly lower in patients who did not respond compared with patients in ongoing response or who relapsed ($P<0.05$). There was no association between ongoing responses and CAR T-cell peak, or CAR T-cell peak normalized to tumor burden, as shown in Figure 3.[12]

Figure 2. Relationship Between Peak CAR T-Cell Levels and Response[12]

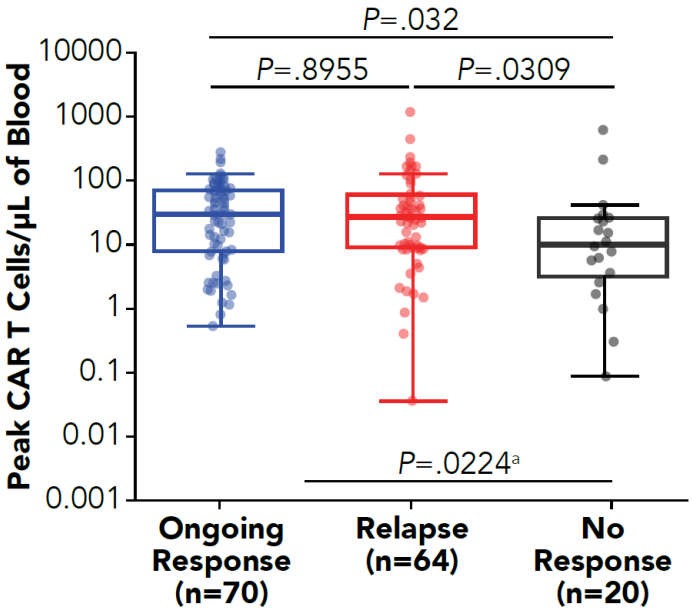
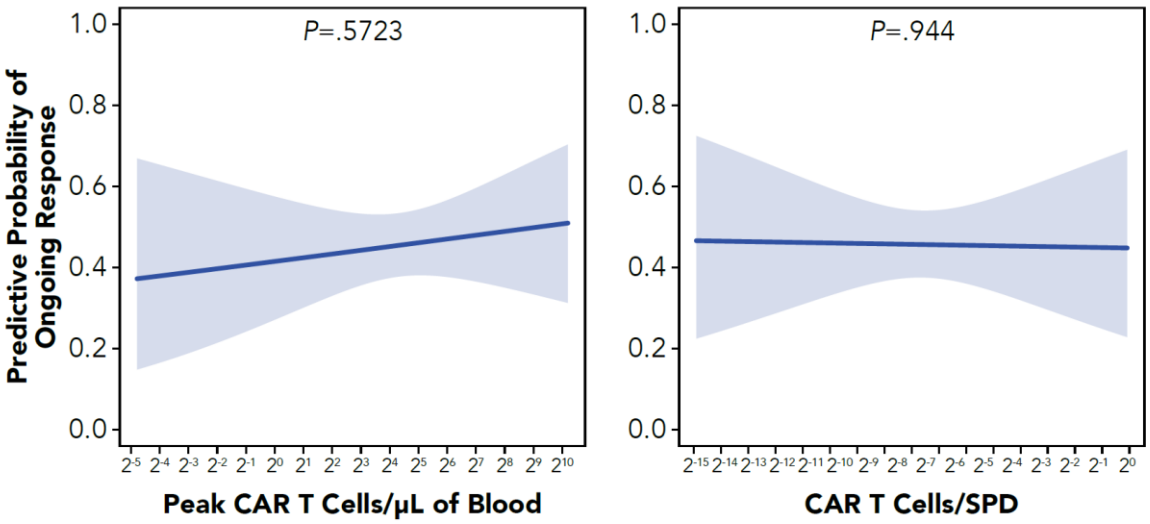


Figure 3. Relationship Between CAR T-Cell Levels and Predicted Probability of Ongoing Response[12]



Abbreviations: SPD=sum of product diameters.

Follicular Lymphoma

ZUMA-5 Study

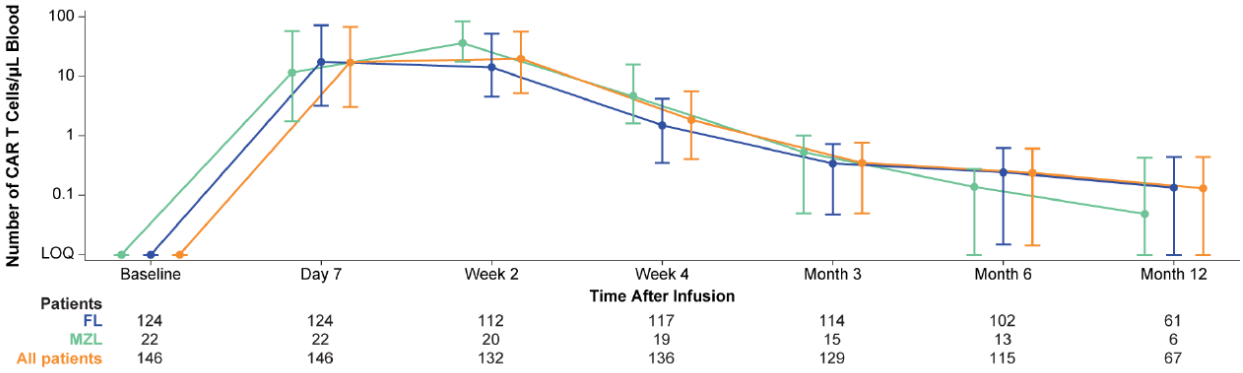
ZUMA-5 is a multicenter, single-arm, phase 2 study to evaluate the efficacy of axicabtagene ciloleucel in patients with relapsed/refractory indolent non-Hodgkin lymphoma (iNHL), including FL (Grades 1–3a) and marginal zone lymphoma (MZL, nodal or extranodal).[13]

In the ZUMA-5 study, expansion and persistence were monitored by anti-CD19 CAR specific qPCR and/or flow cytometry.[14] The median time to peak concentration of anti-CD19 CAR T-cells after infusion was 9 days (interquartile range [IQR], 8–15) in 148 treated patients (8 days [8–15] in those with FL, 15 days [8–16] in those with in MZL).[13] One (1%) patient with FL had a second CAR T-cell peak on day 371 in the context of relapse. CAR T-cell expansion by peak and AUC appeared slightly higher in patients with MZL than in those with FL. Most patients with assessable samples (70 [75%] of 93) had low levels of detectable CAR gene-marked cells 12 months after infusion; by 24 months, 18 (69%) of 26 patients with assessable samples still had detectable cells.

Of evaluable patients in ongoing response at 18 months, B cells were detectable in 20 (69%) of 29, of whom 11 (55%) had detectable CAR gene-marked cells.[13] All four non-responding patients with evaluable samples had detectable CAR T-cell expansion, but none had B-cell aplasia.

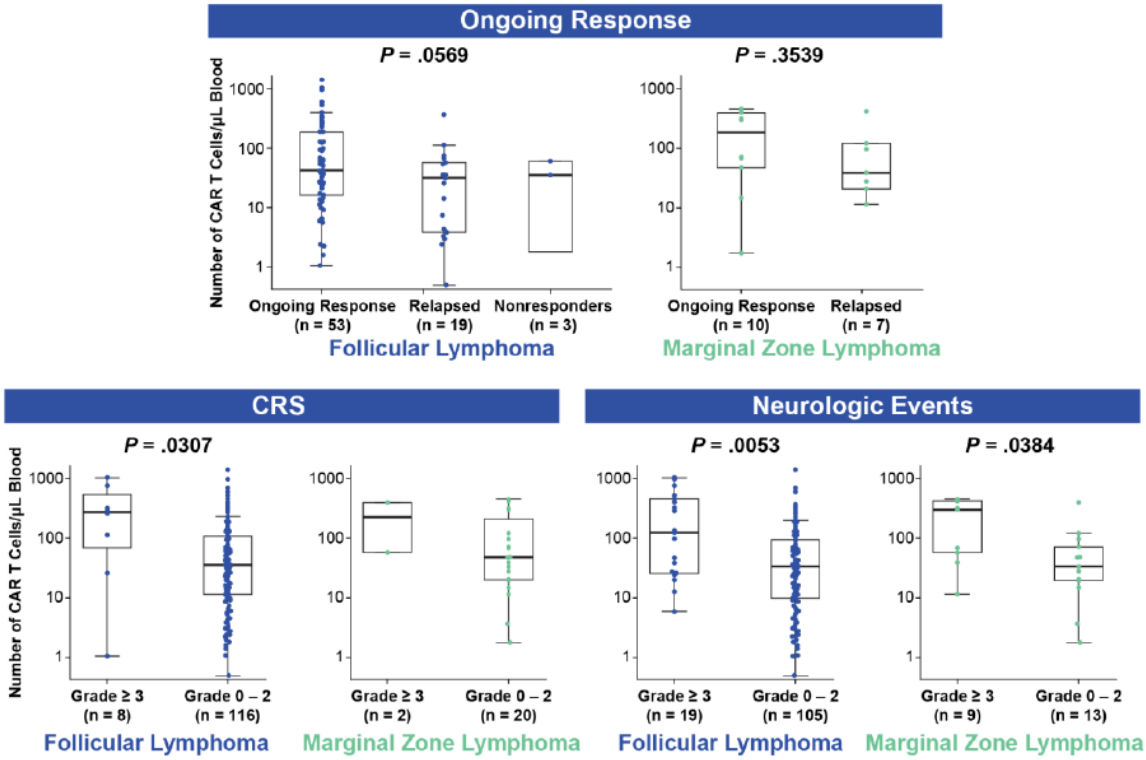
CAR T-cell expansion over time according to clinical outcomes in ZUMA-5 following Yescarta infusion is presented in Figures 4 and 5.

Figure 4. CAR T-Cell Expansion Through Month 12[15]



Abbreviations: FL=follicular lymphoma, MZL=marginal zone lymphoma.

Figure 5. CAR T-Cell Expansion According to Ongoing Response and Key Safety Outcomes[15]



Abbreviations: CRS=cytokine release syndrome.

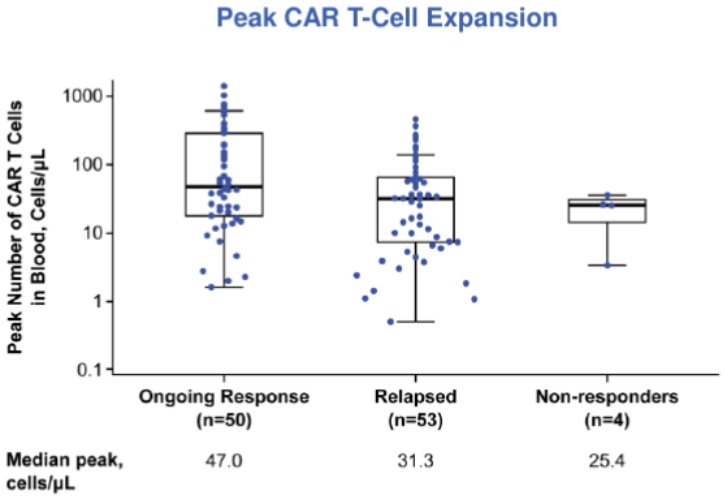
Additionally, those with ongoing response at 48 months continued to have higher CAR T-cell expansion by peak and AUC than those who relapsed or had no response.[16]

Updated 5-year follow-up data from the ZUMA-5 study was presented at the 2024 ASH Annual Meeting.[17] The 5-year analysis occurred after the median follow-up of all enrolled patients (N=159) reached ≥60 months post-infusion (data cutoff March 31, 2024). Of the enrolled patients, 127 patients had FL and 31 patients had MZL.[17]

Treated patients in ongoing response at the 60-months data cutoff had higher median post-infusion peak CAR T-cell expansion (59.41 cells/µL) and AUC within the first 28 days after treatment (AUC_{0-28}; 696.92 cells/µL×d) than those who relapsed (30.45 cells/µL and 362.68 cells/µL×d) or nonresponders (22.18 cells/µL and 269.82 cells/µL×d). The total number of infused CCR7+CD45RA+ T-cells, indicative of naive phenotype, was associated with improved response.[18]

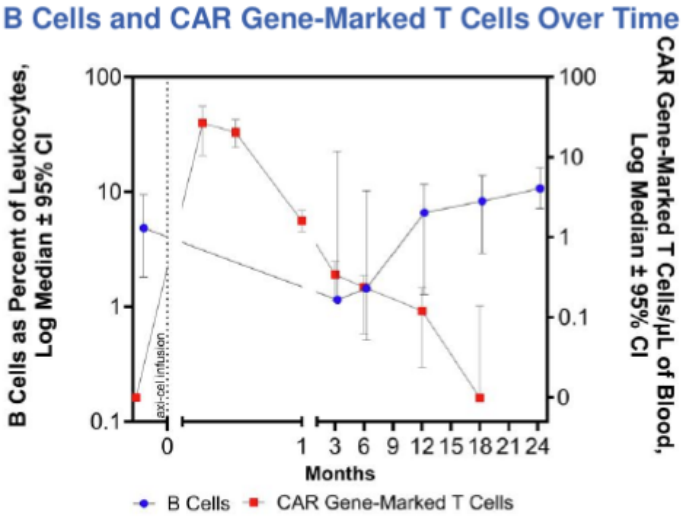
As shown in Figure 6, at ≥60 months post-infusion, the peak CAR T-cell levels in blood for treated patients with FL in ongoing response at data cutoff had greater CAR T-cell expansion than relapsed or non-responding patients. Consistent with the prior analysis,[16] levels of CAR gene-marked T-cells were inversely correlated with that of B-cells at each timepoint post-infusion (Figure 7).[17]

Figure 6. Peak CAR T-Cell Levels at ≥60 Months Post-Infusion According to Response[17]



Abbreviations: CAR, chimeric antigen receptor; FL, follicular lymphoma.

Figure 7. CAR Gene-Marked T-Cell Levels vs. B-Cell Levels Post-Infusion Over Time[17]



Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval.

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Abbreviations

$AUC_{0–28}$=area under the curve from Day 0–28
CAR=chimeric antigen receptor
C_{max}=maximum concentration
CI=confidence interval
CR=complete response
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
FL=follicular lymphoma
iNHL=indolent non-Hodgkin

lymphoma
IQR=interquartile range
LBCL=large B-cell lymphoma
MZL=marginal zone lymphoma
NHL=non-Hodgkin lymphoma
PCR=polymerase chain reaction
PMBCL=primary mediastinal B-cell lymphoma
PR=partial response
qPCR=quantitative polymerase chain reaction
SPD=sum of product diameters
TFL=transformed follicular lymphoma

Product Label

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

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