Yescarta® (axicabtagene ciloleucel, axi-cel) Retreatment Data from ZUMA-1

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Summary

Summary of Retreatment Data from ZUMA-1[1]

- Updated data from the pivotal ZUMA-1 study was presented at the ASCO 2020 conference on 14 patients retreated with axi-cel. As a limited number of patients were retreated with axi-cel, results should be interpreted with caution.
    - Based on the 4-year follow up data with a median follow up of 39.1 months, 5 patients achieved a complete response, 3 patients had partial response, 5 patients had progression of disease, and 1 patient had stable disease.
    - Median duration of first response was 3.3 months (range 1.8-10.9 months).
    - There were comparable rates of cytokine release syndrome (CRS) observed with retreatment as with first treatment.
    - Product characteristics at first treatment and retreatment were comparable.
- While limited by small sample size, authors concluded that retreatment with axi-cel may have clinical efficacy in some patients with LBCL, especially patients achieving CR upon first treatment.
- Further studies with additional patients are needed to confirm these results.
- Retreatment with axi-cel is at the discretion of the treating physician.

Background

ZUMA-1 Study Design[2-4]

ZUMA-1 (NCT02348216) was the pivotal, phase 2 open-label, multicenter, single-arm study that assessed the safety and efficacy of axi-cel for the treatment of patients with refractory, aggressive B-cell non-Hodgkin lymphoma.[2-4] Key eligibility criteria included adult patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL),or transformed follicular lymphoma (TFL) to DLBCL.[2] In the study, patients must have had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1 and adequate hematologic (absolute lymphocyte count [ALC] ≥100/µL,

absolute neutrophil count [ANC] ≥1000/µL, and a platelet count ≥75,000/µL), renal, hepatic, and cardiac function.[2] If patients showed signs and symptoms of a serious active infection, they were not allowed to receive treatment until the infection resolved.[2] As an exploratory component in the study, patients who had an initial response and then had disease progression at least 3 months after the first dose of axi-cel could be retreated if they met certain criteria outlined in the protocol.[3]

Treatment Process[3]

Patients underwent leukapheresis to obtain peripheral blood mononuclear cells (PBMCs) in order to manufacture axi-cel. Before receiving axi-cel, patients received a non-myeloablative, low-dose, lymphodepleting chemotherapy regimen of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 on Day -5, Day -4, and Day -3. On Day 0, hospitalized patients received a single intravenous (IV) infusion of axi-cel at a target dose of 2 x 10^6 CAR T cells/kg.

Retreatment Eligibility in ZUMA-1[2]

The key eligibility criteria for retreatment were no evidence of CD19 loss by local review and no dose-limiting toxicities, as defined in Phase 1 or comparable toxicities in Phase 2, during first treatment.

The decision to administer a second treatment with axi-cel was made in consultation with the Kite Medical Monitor. Patients were allowed to receive another course of lymphodepleting chemotherapy and axi-cel under the following conditions:

- Patient had a partial response (PR) or complete response (CR) and subsequently had disease progression greater than 3 months after axi-cel infusion
- CD19 tumor expression confirmed locally by biopsy after disease progression and prior to retreatment
- Patient continued to meet the original study eligibility criteria with exception of prior axi-cel use in this study. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility
- Patient had not received subsequent therapy for the treatment of lymphoma
- Patient had not experienced a dose-limiting toxicity with the initial infusion
- Toxicities related to lymphodepleting chemotherapy, with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to retreatment
- Patient did not have known neutralizing antibodies (exception: if a non-neutralizing HAMA or HABA antibody developed then the patient may be retreated if original study eligibility criteria were met)

Study Design and Baseline Characteristics[1]

In the analysis presented at ASCO, 14 patients were retreated in the ZUMA-1 study (Cohorts 1-4). The follow up period was:

- Cohorts 1+2: ≥30 months
- Cohort 3: ≥18 months
- Cohort 4: ≥6 months

The statistical analysis specified groups were compared with Wilcoxon signed-rank test. *P* values are descriptive and not adjusted for multiplicity and the Kaplan-Meier approach was used to estimate duration of response. Prior to first treatment, most of the 14 patients (64%)

had an IPI score 3-4, 86% had disease stage 3-4, and 71% had ≥ 3 prior therapies. Baseline characteristics prior to first treatment are described in Table 1.

Table 1. ZUMA-1 Study Retreated Patients: Baseline Characteristics Prior to First Treatment[1]

Characteristic	Retreated n=14	No Retreatment n=180
Median age (range), years	59 (28-75)	58 (19-77)
≥ 65, n (%)	5 (36)	45 (25)
Male, n (%)	11 (79)	117 (65)
ECOG 1, n (%)	8 (57)	98 (54)
Disease stage III/IV, n (%)	12 (86)	138 (77)
IPI score 3-4, n (%)	9 (64)	78 (43)
≥ 3 Prior therapies, n (%)	10 (71)	126 (70)
Prior ASCT, n (%)	0	49 (27)
Tumor histology, n (%)		
DLBCL	10 (71)	126 (70)
PMBCL	2 (14)	17 (9)
TFL	2 (14)	34 (19)

ASCT, autologous stem cell transplant; DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.

Efficacy[1]

Fourteen patients were retreated with axi-cel, according to the protocol. The decision to proceed with a transplant after retreatment was at the discretion of the treating physician. With 1st treatment, 7 patients achieved CR, 6 achieved PR, and 1 patient had SD prior to disease progression. Median duration of first response was 3.3 months (range, 1.8-10.9). Upon retreatment, 57% of patients achieved response (5 CR, 3 PR), 36% had progression of disease (5 PD) and 7% had stable disease (1 SD). Median duration of response to retreatment was 9.4 months (0.03-18.2+). Two patients remain in response 18.2 and 11.2 months after retreatment, respectively. Response to retreatment was more common among patients who achieved CR with 1st treatment (86%) than among patients who achieved PR with first treatment (33%), and no response was observed in the patient with SD with first treatment. One of the patients who were retreated converted from stable disease (SD) or PD.

Based on limited sample size, retreatment with axi-cel may have clinical efficacy in some patients with LBCL, especially patients who achieved CR with first treatment. However, durability of response remains to be determined in future studies, as several patients received consolidative allogeneic transplant, though 1 patient remains in ongoing CR without transplant at 18.2+ months. A listing of disease response following retreatment for each of the 10 patients is provided in Table 2.

Product characteristics were largely comparable between first and second infusions.

Table 2. ZUMA-1 Study Retreated Patients: Cytokine Release Syndrome and Neurologic Events[1]

Patient	First Treatment		Retreatment Source	Retreatment	
	Best Response	Duration of Response, months		Best Response	Duration of Response, months
1	CR	10.9	PBMC	CR	11.2+
2	CR	4.5	2nd bag	CR	2.7
3	CR	3.5	2nd bag	PD	-
4	CR	5.1	PBMC	CR	12.7
5	CR	1.8	PBMC	PR	0.03
6	CR	3.3	PBMC	CR	6
7	CR	9	2nd bag	CR	18.2+
8	PR	2.1	PBMC	PD	-
9	PR	2.1	PBMC	PR	3.5
10	PR	3	PBMC	PD	-
11	PR	2.1	PBMC	PR	1.4
12	PR	5	PBMC	SD	-
13	PR	1.9	Re-Aph	PD	-
14	SD	-	2nd bag	PD	-

[a] Patient received transplant while in response.
[b] Patient data were updated after dataset snapshot and the duration of response should be 3 months. Duration of response was calculated as the time from the initial response to disease progression. Disease assessments obtained on study prior to initiation of new anticancer therapy (excluding transplant) were included in duration of response calculation. PBMC refers to axi-cel manufactured from frozen PBMCs collected during initial apheresis and were used in a 2nd round of manufacturing prior to retreatment. 2nd bag refers to a second bag of axi-cel that was generated during the initial manufacturing. Re-Aph refers to axi-cel that was manufactured from a 2nd round of apheresis and manufacturing prior to retreatment. 2nd bag, the 2nd bag produced in the original manufacturing; CR, complete response; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PR, partial response; Re-Aph, second apheresis after progression from first treatment; SD, stable disease.

Safety[1]

The safety data following retreatment were analyzed independently and found to be consistent with that reported for the main analysis of data as previously published. There were no reported Cytokine Release Syndrome (CRS) events that were Grade ≥ 3 or higher during 1st treatment or during retreatment.1 However, 13 patients had CRS (Grade ≤2 or lower) upon 1st treatment and 12 patients had CRS (Grade ≤ 2 or lower) upon retreatment. Comparable rates of CRS were observed with retreatment as with first treatment as shown in Table 3. Fewer Grade ≥ 3 neurologic events (NEs) were reported with retreatment than with first treatment and there were no Grade 4 or 5 NEs. Seven patients had axi-cel related NEs that were Grade ≥ 3 with first treatment but only 3 patients reported Grade ≥ 3 events upon retreatment. However, 4 patients had NEs (Grade ≤2 or lower) upon 1st treatment and 5 patients had NEs (Grade ≤ 2 or lower) upon retreatment.

Table 3. ZUMA-1 Study Retreated Patients: Cytokine Release Syndrome and Neurologic Events[1]

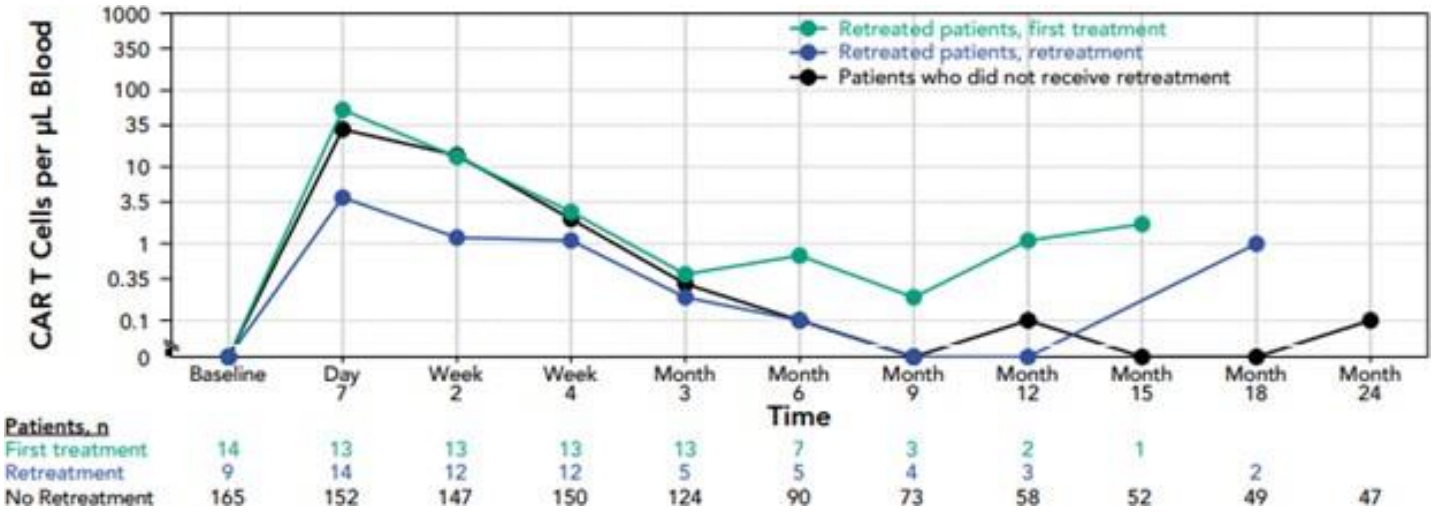
Adverse Event, n (%)	First Treatment n=14	Retreatment n=14
Cytokine Release Syndrome	13 (93)	12 (86)
Grade 1	7 (50)	8 (57)
Grade 2	6 (43)	4 (29)
Grade 3	0	0
Neurologic Events	11 (79)	8 (57)
Grade 1	3 (21)	4 (29)
Grade 2	1 (7)	1 (7)
Grade 3	7 (50)	3 (21)

There were no grade 4-5 CRS or NE events reported.

Pharmacokinetics[1]

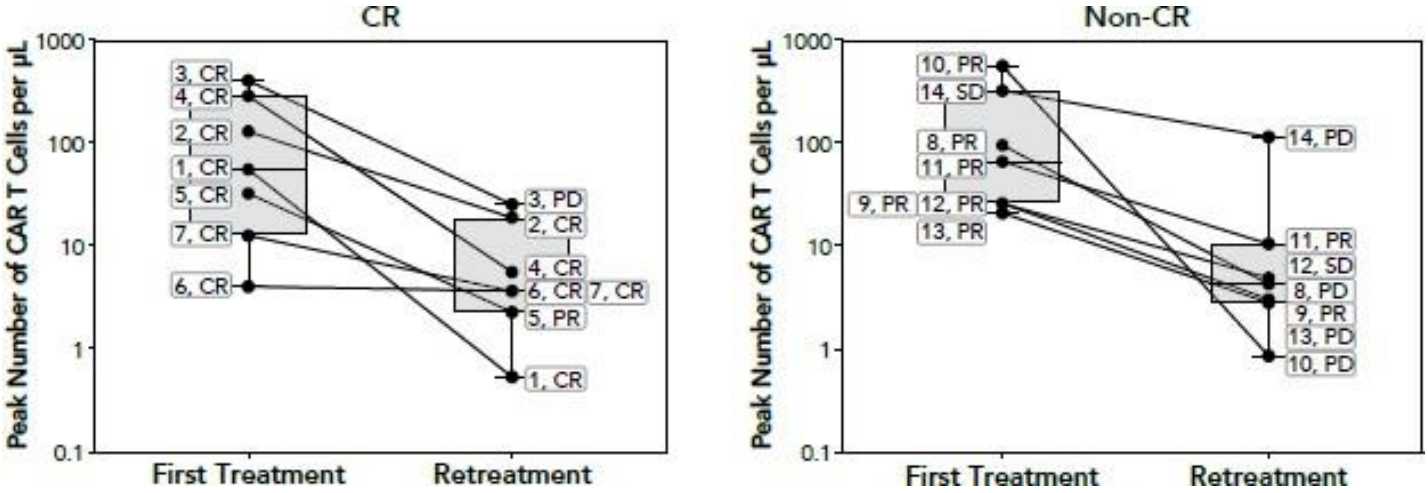
Levels of anti-CD19 CAR T cells were measured using a validated quantitative polymerase chain reaction (qPCR) assay after the first and second infusion in retreated patients. Peak CAR T cell expansion was lower with retreatment (median 4.3 cells/µL blood) compared with expansion at first treatment (median, 60.8 cells/µL blood) as shown in Figures 1 and 2.

Figure 1. CAR T Cell Levels Over Time[1]



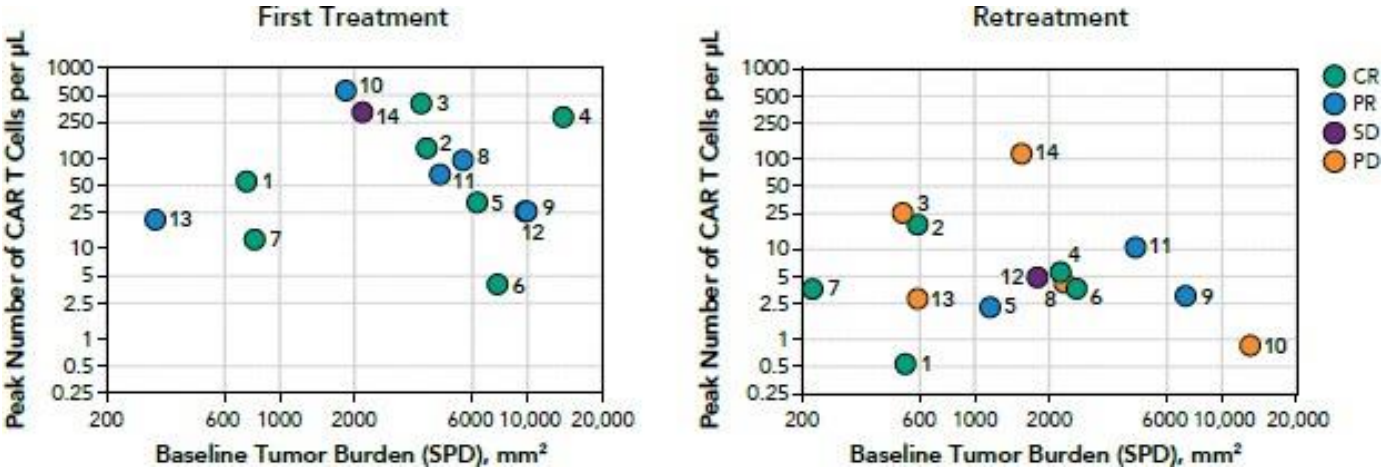
Retreatment baseline was calculated from the 9 patients who had CAR T cell level evaluation within 28 days prior to retreatment. Among those 9 patients, 8 had no detectible CAR T cells and 1 patient had 1.157 µL blood.
CAR, chimeric antigen receptor

Figure 2. Decreased CAR T Cell Expansion at Retreatment[1]



Each data point is annotated with the patient number 1 – 14 and best response at the indicated treatment period.
CAR, chimeric antigen receptor; CR, complete response; PD, progressive disease; PR; partial response; SD, stable disease.

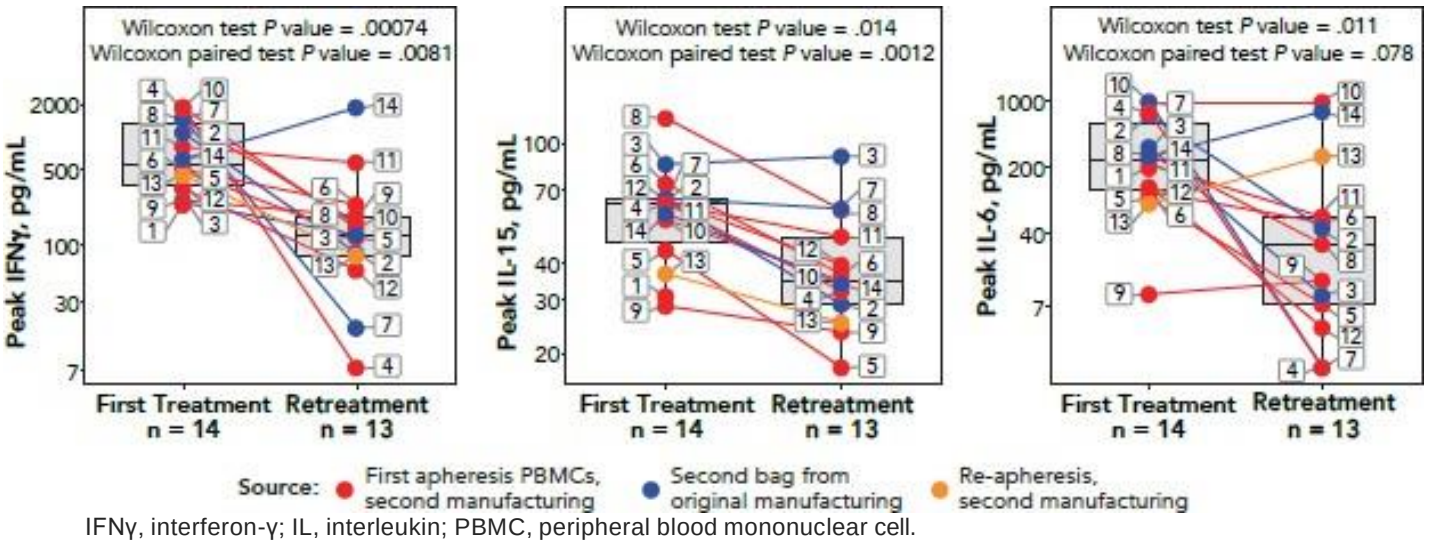
Figure 3. CAR T Cell Expansion by Tumor Burden: CAR T Cell Levels and Tumor Burden Were Lower at Retreatment[1]



CAR, chimeric antigen receptor; CR, complete response; PD, progressive disease; PR; partial response; SD, stable disease; SPD, sum of product diameters

Lower median CAR T cell expansion (4.0 [range, 0.5-115] vs 60.8 [4.0-562] CAR T cells/µL), commensurate with lower median tumor burden (1672 [range, 221-12,994] vs 4175 [315-13,936] mm^2), was observed with retreatment vs first treatment as shown in Figure 3.

Figure 4. Decreased Cytokine Levels in Serum Upon Retreatment[1]



IFNγ, interferon-γ; IL, interleukin; PBMC, peripheral blood mononuclear cell.

Significantly lower peak levels of interferon-γ and IL-15 were observed at retreatment compared with first treatment as shown in Figure 4. While not statistically significant, a similar trend was reportedly observed with IL-6.

References

1. Locke FL, Bartlett NL, Jacobson CA, Et Al., Retreatment of Patients with Refractory Large B Cell Lymphoma With Axicabtagene Ciloleucel in ZUMA-1. Presented at: American Society of Clinical Oncology. May 29-31, 2020; Chicago, Illinois.
2. [Redacted Protocol] Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. DOI: 10.1056/nejmoa1707447
3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. DOI: 10.1056/nejmoa1707447
4. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc.

Abbreviations

ASCT=autologous stem cell transplant
AE=adverse events
AUC=area under the curve
CAR=chimeric antigen receptor
CR=complete response
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
ECOG=Eastern Cooperative Oncology Group
IPI= International Prognostic Index
IV=intravenous
LBCL=large B-cell lymphoma
NE=neurologic event
PBMC=peripheral blood mononuclear cell
PD=progressive disease
PMBCL= primary mediastinal large B-cell lymphoma
PR=partial response
SCT=stem cell transplant
SD=stable disease
TFL=transformed follicular lymphoma

Product Label

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