Poster
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Updated Outcomes With Axicabtagene Ciloleucel (Axi-Cel) Retreatment in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma in ZUMA-5

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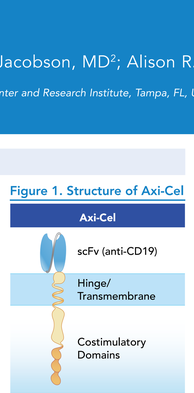
BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (**Figure 1**) approved in the United States (US) for the treatment of adults with relapsed/refractory (R/R) follicular lymphoma (FL) after ≥2 lines of systemic therapy, and in the US and European Union for adults with R/R large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy[1,2]
  - In a long-term follow-up analysis of axi-cel in refractory LBCL, the 4-year overall survival rate was 44%[3]
- ZUMA-5 is a multicenter, single-arm Phase 2 study of axi-cel in patients with R/R indolent non-Hodgkin lymphoma (iNHL) including FL and marginal zone lymphoma (MZL)[4]
  - In the primary analysis, 11 patients (9 FL; 2 MZL) were retreated with axi-cel, achieving an overall response rate (ORR) of 100% (91% complete response [CR] rate) at a median follow-up of 2.3 months post-retreatment[5]
  - No patients experienced Grade ≥3 cytokine release syndrome (CRS) or Grade ≥3 neurologic events with axi-cel retreatment[5]

Figure 1. Structure of Axi-Cel



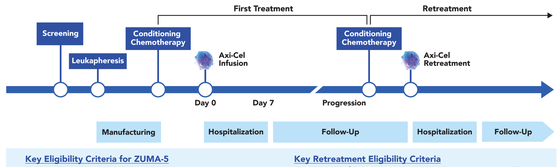
Axi-cel, axicabtagene ciloleucel; scFv, single-chain variable fragment.

OBJECTIVE

- To examine updated clinical outcomes, product attributes, and pharmacologic characteristics in patients with R/R iNHL retreated with axi-cel in ZUMA-5, with longer follow-up after retreatment

METHODS

Figure 2. ZUMA-5 Treatment Schema at First Treatment and Retreatment



Key Eligibility Criteria for ZUMA-5
- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)[a]
- ≥2 Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent

Conditioning Regimen
- Cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 for 3 days prior to first treatment and retreatment

Axi-Cel
- 2×10^6 CAR T cells/kg at first treatment and retreatment

Key Retreatment Eligibility Criteria
- Response of a CR or PR per investigator assessment at the Month 3 disease assessment with subsequent progression
- No evidence of CD19-negative relapse after after first treatment by local review of progression biopsy
- No axi-cel–neutralizing antibodies
- No Grade 4 CRS or neurologic events, or life-threatening toxicities with first treatment

- **N=13 retreated patients (11 FL; 2 MZL)**
- **Median retreatment follow-up: 11.4 months**

[a] Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; FL, follicular lymphoma; mAb, monoclonal antibody; MZL, marginal zone lymphoma; PR, partial response.

Statistical Analyses

- Specified groups were compared using the Wilcoxon signed-rank test
- *P* values were descriptive and not adjusted for multiplicity
- The Kaplan-Meier approach was used to estimate duration of response (DOR)

RESULTS

Table 1. Baseline Characteristics Prior to First Treatment

Characteristic	Nonretreated (n=135)	Retreated (n=13)	All Patients (N=148)
Disease type, n (%)			
FL	113 (84)	11 (85)	124 (84)
MZL	22 (16)	2 (15)	24 (16)
Median age (range), y	60 (34–79)	63 (49–71)	61 (34–79)
≥65, n (%)	46 (34)	5 (38)	51 (34)
Male, n (%)	76 (56)	8 (62)	84 (57)
Disease stage III-IV, n (%)	117 (87)	11 (85)	128 (86)
≥3 FLIPI score, n/n (%)	45/113 (40)	9/11 (82)	54/124 (44)
High tumor bulk (GELF criteria), n (%)[a]	63 (47)	11 (85)	74 (50)
Median no. of prior therapies (range)	3 (1–10)[b]	4 (2–7)	3 (1–10)[b]
POD24 from first anti-CD20 mAb-containing therapy, n/n (%)[c]	75 (56)	6 (46)	81 (55)
Refractory disease at study entry, n (%)[d]	92 (68)	10 (77)	102 (69)

[a] Disease burden, per GELF criteria: involvement of ≥3 nodal sites (≥3 cm diameter each); any nodal or extranodal tumor mass with ≥7 cm diameter; B symptoms; splenomegaly; pleural effusions or peritoneal ascites; cytopenias; or leukemia.
[b] Enrollment of 3 patients with FL who had 1 prior line of therapy occurred before a protocol amendment requiring ≥2 prior lines of therapy.
[c] <24 months from initiation of 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.
[d] Patients with iNHL who progressed <6 months after completion of the most recent prior treatment.
FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; iNHL, indolent non-Hodgkin lymphoma; mAb, monoclonal antibody; MZL, marginal zone lymphoma; POD24, progression of disease <24 months.

- Median follow-up after retreatment in the updated analysis was 11.4 months
  - Two of 13 patients were retreated with axi-cel between the cutoff dates for the primary analysis and updated analysis
- Most retreated patients had high-risk disease characteristics at baseline (**Table 1**)
- Of the 14 patients in the broader ZUMA-5 population with available data at relapse after axi-cel, including all retreated patients, 100% had detectable CD19

RESULTS (CONT.)

Table 2. IRRC-Assessed Response at First Treatment and Retreatment

Patient No.	Tumor Type	First Treatment: Best Response	First Treatment: DOR, months	Retreatment Source	Retreatment: Best Response	Retreatment: DOR, months
1	FL	PR	8.3	2nd bag	CR	12.0+
2	FL	CR	11.8	Re-Aph	CR	0.03+
3	FL	CR	5.3	PBMCs	PR	5.2
4	FL	CR	11.5	Re-Aph	CR	11.4+
5	FL	CR	5.0	Re-Aph	CR	2.1[a]
6	FL	CR	1.9	2nd bag	CR	4.9[a]
7	FL	CR	10.9	2nd bag	CR	13.9+
8	FL	CR	5.4	PBMCs	CR	5.0
9	FL	CR	5.0	Re-Aph	CR	7.7+
10	MZL	CR	10.6	2nd bag	CR	14.5+
11	MZL	CR	8.2	2nd bag	CR	0.03[b]
12	FL	CR	18.0	Re-Aph	PR	1.0
13	FL	SD[c]	–	PBMCs	PR	2.3

Response was assessed by an IRRC according to the Lugano Classification.[6] Duration of response was calculated as the time from initial overall response after retreatment to disease progression per the Lugano Classification[6] or death from any cause. Patients not meeting criteria by data cutoff were censored at their last disease assessment before data cutoff or new anticancer therapy start date (including SCT), whichever was earlier. PBMCs refer 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.
[a] Initiated a new anti-cancer therapy.
[b] Initiated SCT.
[c] Patient had an SD to first treatment per IRRC assessment and a PR per investigator assessment.
2nd bag, second bag produced from original manufacturing; axi-cel, axicabtagene-ciloleucel; CR, complete response; DOR, duration of response; FL, follicular lymphoma; IRRC, independent radiology review committee; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cell; PR, partial response; Re-Aph, re-apheresis; SD, stable disease; SCT, stem cell transplantation.

- At first treatment, the IRRC-assessed CR rate was 85% (**Table 2**)
  - Median first DOR was 8.2 months (range, 1.9–18.0)
- Median time between first treatment and retreatment was 10.6 months
- At retreatment, the ORR was 100% (77% CR rate; **Table 2**)
  - Response rates were similar irrespective of retreatment product source
- After a median of 11.4 months of follow-up post-retreatment, the median DOR to retreatment was not reached
  - The 12-month estimated DOR rate post-retreatment was 58%
  - Responses were ongoing for 6 patients (46%) at data cutoff
- The median progression-free survival (PFS) after first treatment was 9.2 months; the median PFS after retreatment was not reached
  - The 12-month estimated PFS rate post-retreatment was 58%

Table 3. CRS and Neurologic Events

Adverse Event, n (%)	First Treatment (n=13)	Retreatment (n=13)
CRS	9 (69)	8 (62)
Grade 1	5 (38)	6 (46)
Grade 2	4 (31)	2 (15)
Grade 3	0	0
Grade 4	0	0
Neurologic events	5 (38)	4 (31)
Grade 1	3 (23)	3 (23)
Grade 2	1 (8)	1 (8)
Grade 3	1 (8)	0
Grade 4	0	0

CRS, cytokine release syndrome.

- Incidences of CRS and neurologic events were comparable at first treatment and at retreatment (**Table 3**)
  - With additional patients and longer follow-up, no Grade ≥3 CRS or neurologic events occurred with retreatment

Table 4. Peak Cytokine Levels

Peak Cytokine Levels (Range)	First Treatment (n=13)	Retreatment (n=13)
IL-6, pg/mL	5.7 (1.6[a]–533.5)	7.7 (1.6[a]–976.0[b])
IL-2, pg/mL	0.9[a] (0.9[a]–15.8)	1.8 (0.9[a]–6.9)
IFN-γ, pg/mL	64.2 (7.5[a]–1876.0[b])	62.9 (7.5[a]–1876.0[b])
CXCL10, pg/mL	1085.8 (402.6–2000.0[b])	1179.4 (168.4–2000.0[b])
TNF-α, pg/mL	5.8 (1.8–20.8)	3.7 (2.2–21.4)
IL-1RA, pg/mL	708.1 (377.1–9000.0[b])	583.0 (204.0–9000.0[b])
GM-CSF, pg/mL	1.9[a] (1.9[a]–11.6)	1.9[a] (1.9[a]–10.1)
CCL2 (MCP-1), pg/mL	906.1 (402.7–1500.0[b])	707.4 (355.9–1500.0[b])
CCL22 (MDC), pg/mL	1485.1 (417.7–2.2×10^3)	991.2 (88.3[a]–3671.7)
IL-15, pg/mL	35.5 (26.3–64.3)	38.1 (15.2–49.2)
Ferritin, ng/mL	746.4 (245.2–9799.5)	490.9 (178.9–1.2×10^3)

[a] Lower limit of quantification in assay used.
[b] Upper limit of quantification in assay used.
CCL, chemokine (C-C motif) ligand; CXCL, C-X-C motif chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MDC, macrophage-derived chemokine; RA, receptor agonist; TNF, tumor necrosis factor.

- Median peak levels of cytokines typically associated with severe CRS and neurologic events were numerically similar at both treatments (**Table 4**)

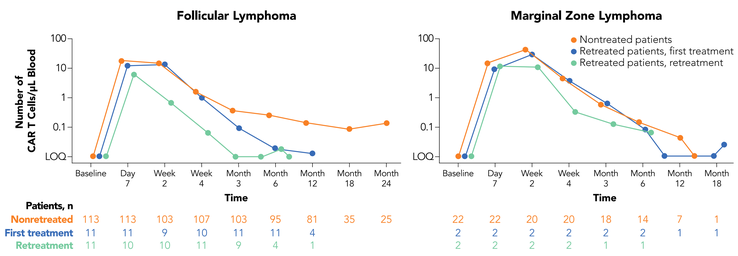
Table 5. Axi-Cel Product Characteristics by Retreatment Source

Characteristic, Median (Range)	2nd Bag (n=5): First Treatment	2nd Bag (n=5): Retreatment	Frozen PBMCs (n=3): First Treatment	Frozen PBMCs (n=3): Retreatment	Re-Apheresis (n=5): First Treatment	Re-Apheresis (n=5): Retreatment
No. CCR7+CD45RA+ T cells, 10^6	17.7 (11.1–98.8)	42.2 (28.3–97.3)[a]	38.5 (36.6–40.3)[b]	23.1 (5.3–40.8)[b]	27.4 (20.3–71.1)[c]	98.6 (42.2–143.5)[c]
CD4/CD8 ratio	0.8 (0.3–1.2)	0.6 (0.4–1.6)[a]	0.4 (0.2–0.5)[b]	0.8 (0.3–1.2)[b]	1.6 (0.6–9.9)[c]	1.3 (0.3–2.2)[c]
Transduction rate, %	77.0 (63.0–83.0)	N/A[d]	26.0 (18.0–50.0)	63.0 (53.0–66.0)	66.0 (41.0–76.0)	61.0 (39.0–65.0)
IFN-γ in coculture, pg/mL	4738.0 (4400.0–6721.0)	N/A[d]	2384.0 (2311.0–1.3×10^4)	6544.0 (3229.0–1.3×10^4)	6203.0 (2691.0–8852.0)	4882.0 (2338.0–1.4×10^4)

[a] Data were available for 4 patients who received product from a 2nd bag.
[b] 2 patients who received product from frozen PBMCs.
[c] 4 patients who received product from re-apheresis.
[d] Transduction efficiency and IFN-γ in coculture were only measured after initial manufacturing.
2nd bag, second bag produced from original manufacturing; axi-cel, axicabtagene ciloleucel; IFN, interferon; N/A, not applicable; PBMC, peripheral blood mononuclear cell.

- Axi-cel product characteristics were generally similar at both treatments (**Table 5**)
  - The total number of infused naïve T cells (CCR7+CD45RA+ cells) appeared higher in product from patients who had re-apheresis at retreatment, compared with product at first treatment
  - Higher numbers of infused CCR7+CD45RA+ cells are associated with ongoing response in patients with FL[7]
  - CD4/CD8 ratio, transduction efficiency, and interferon-γ in coculture were similar at both treatments

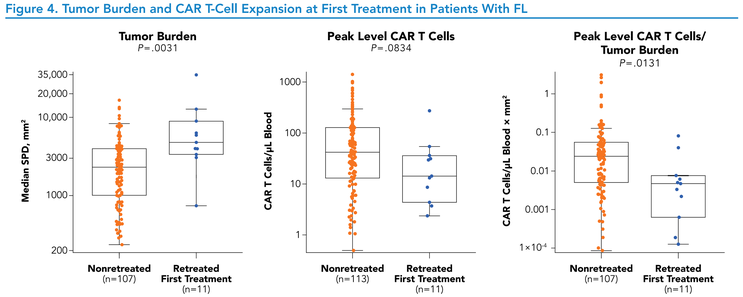
Figure 3. CAR T-Cell Levels Over Time



CAR, chimeric antigen receptor; LOQ, limit of quantification.

- Median peak CAR T-cell levels appeared lower in patients with FL at retreatment than at first treatment (5.2 vs 14.3 cells/µL blood; **Figure 3**)
- CAR T-cell expansion by area under the curve between Day 0 and 28 was lower in patients with FL at retreatment compared with first treatment (59.3 vs 246.9 cells/µL × days; **Figure 3**)
  - Similar trends in CAR T-cell expansion were observed in patients with MZL

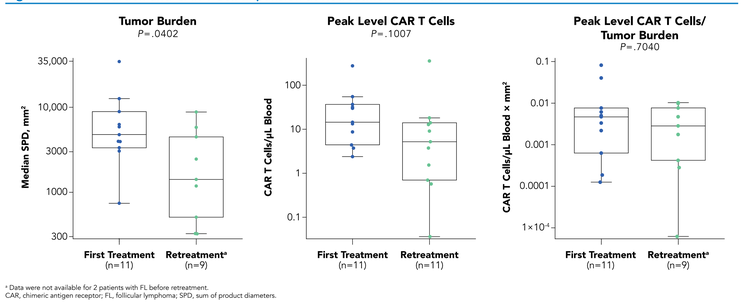
Figure 4. Tumor Burden and CAR T-Cell Expansion at First Treatment in Patients With FL



CAR, chimeric antigen receptor; FL, follicular lymphoma; SPD, sum of product diameters.

- Patients with FL who were retreated had higher tumor burden (by sum of product diameters [SPD]) before first treatment than nonretreated patients (4770 vs 2303 mm^2; **Figure 4**)
- Among patients with FL, those who received retreatment appeared to have lower median peak CAR T-cell levels at first treatment than nonretreated patients (14.3 vs 41.9 cells/µL; **Figure 4**)
- Engraftment index (CAR T-cell expansion relative to SPD) was lower at first treatment in patients who were retreated than in nonretreated patients (0.005 vs 0.020 cells/µL × mm^2; **Figure 4**)
  - Engraftment index is an indirect proxy for effector:target ratio and a key covariate of response to axi-cel[7,8]

Figure 5. Tumor Burden and CAR T-Cell Expansion at Retreatment in Patients With FL



[a] Data were not available for 2 patients with FL before retreatment.
CAR, chimeric antigen receptor; FL, follicular lymphoma; SPD, sum of product diameters.

- Patients with FL had lower median tumor burden before retreatment than before first treatment (1416 vs 4770 mm^2; **Figure 5**)
- Though median peak CAR T-cell levels appeared lower in patients with FL at retreatment than at first treatment, engraftment index was similar (0.003 vs 0.005 cells/µL × mm^2; **Figure 5**)

CONCLUSIONS

- After a median of 11.4 months of follow-up, axi-cel retreatment achieved deep and durable responses in patients with R/R iNHL
  - Axi-cel retreatment demonstrated a 100% ORR in patients with iNHL, most of whom had high-risk disease characteristics
  - Responses were ongoing in nearly half of patients at data cutoff
- The safety profile of axi-cel was similarly acceptable at both treatments
- Tumor CD19 positivity was confirmed at relapse in all evaluable patients in ZUMA-5
- Pharmacologic findings in retreated patients compare favorably with previous reports in aggressive lymphomas and suggest patients with FL may potentially benefit from axi-cel dosing optimization[9]
  - Axi-cel product characteristics and engraftment index, factors that previously demonstrated association with durable response to axi-cel in FL, were similar at both treatments[7]
  - Cytokines typically associated with T-cell activation were also similar at both treatments[7]
- These data suggest retreatment with axi-cel may be a potential option for patients with R/R iNHL

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