Poster
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ZUMA-19: A Phase 1/2 Study of Axicabtagene Ciloleucel Plus Lenzilumab in Patients With Relapsed or Refractory Large B-cell Lymphoma

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BACKGROUND

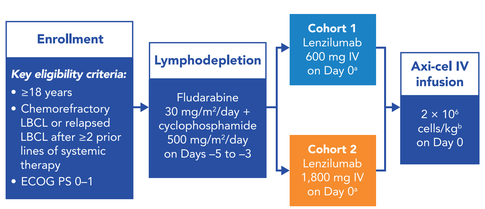
- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of adults with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy and recently, in the United States, for R/R LBCL within 12 months of first-line chemoimmunotherapy[1]
- Clinically significant Grade ≥3 neurologic events (NEs) and cytokine release syndrome (CRS) were reported in the registrational ZUMA-1 and ZUMA-7 studies[2,3]
  - ZUMA-1: NEs, 32% of patients; CRS, 11%
  - ZUMA-7: NEs, 21%; CRS, 6%
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) levels after axi-cel infusion were positively associated with Grade ≥3 NEs in ZUMA-1 and both Grade ≥3 NEs and CRS in ZUMA-7[4,5]
- Preclinical evidence indicates that inhibition of the GM-CSF axis with lenzilumab, a humanized anti–GM-CSF IgG1κ monoclonal antibody, may have the potential to suppress some CAR T-cell toxicities without impairing efficacy[6]

OBJECTIVE

- To evaluate the safety and efficacy of axi-cel in combination with lenzilumab in adult patients with R/R LBCL in the Phase 1 ZUMA-19 trial (NCT04314843)

METHODS

Figure 1. ZUMA-19 Study Design



Data cutoff date: May 9, 2022.

[a]Six hours prior to receiving axi-cel. [b]Flat dose of 2 × 10⁸ cells for patients with body weight >100 kg.
CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; LBCL, large B-cell lymphoma; NE, neurologic event; ORR, objective response rate.

- CRS was graded according to a revised system per Lee et al[7]
- Other adverse events (AEs) including NEs were graded according to National Cancer Institute Common Terminology Criteria for AEs (v4.03)
- CAR T-cell levels in the blood were assessed by qPCR
- Serum lenzilumab concentrations were measured by an enzyme-linked immunosorbent assay
- Soluble analytes/markers were measured in the serum by multiplex assays
  - Platforms used included MSD®, Ella®, or Luminex®

RESULTS

PATIENTS

- In Phase 1 of ZUMA-19, 6 patients received either lenzilumab 600 mg in Cohort 1 (n=3) or lenzilumab 1,800 mg in Cohort 2 (n=3) 6 hours prior to receiving axi-cel
- Median follow-up was 17.1 months (range, 14.7–22.3 months)
- Overall, the median age was 59.5 years (range, 51–80 years) and 50% of patients were refractory to ≥2 lines of therapy (**Table 1**)

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Axi-cel + lenzilumab 600 mg (n=3)	Axi-cel + lenzilumab 1,800 mg (n=3)	Overall (N=6)
Median age, years (range)	55 (51–80)	61 (58–77)	59.5 (51–80)
Male, n (%)	3 (100)	3 (100)	6 (100)
ECOG PS 1, n (%)	1 (33)	2 (67)	3 (50)
Age-adjusted IPI total score, n (%)[a]			
1	2 (67)	2 (67)	4 (67)
2	1 (33)	1 (33)	2 (33)
Disease stage, n (%)			
I	0	2 (67)	2 (33)
II	2 (67)	0	2 (33)
III	1 (33)	1 (33)	2 (33)
Histological DLBCL type, n (%)			
DLBCL NOS	2 (67)	1 (33)	3 (50)
DLBCL arising from FL	1 (33)	2 (67)	3 (50)
Cell of origin, n (%)			
GCB	1 (33)	3 (100)	4 (67)
Other	2 (67)	0	2 (33)
Lines of prior therapy, n (%)			
2	1 (33)	1 (33)	2 (33)
3	2 (67)	1 (33)	3 (50)
4	0	1 (33)	1 (17)
Refractory subgroup, n (%)[b]			
Primary refractory	1 (33)	0	1 (17)
Refractory to ≥2 lines of therapy	2 (67)	1 (33)	3 (50)
Double/triple hit status, n (%)[c]			
Double	1 (33)	1 (33)	2 (33)
Median tumor burden, mm² (range)[d]	5,502 (893–7,846)	1,495 (902–2,830)	2,162.5 (893–7,846)

[a]Age-adjusted IPI was based on second line of therapy. [b]Data were missing for 2 patients. [c]No patients had triple hit status; data were not available for 1 patient in Cohort 1. [d]Measured by the product of diameters of all target lesions at baseline.
Axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; IPI, International Prognostic Index; NOS, not otherwise specified.

SAFETY

- As of the data cutoff (May 9, 2022), no DLTs or Grade ≥3 CRS events were observed in either cohort (**Table 2**)
  - No lenzilumab-related AEs were observed in either cohort

Table 2. AE Summary

AE, n (%)	Axi-cel + lenzilumab 600 mg (n=3)	Axi-cel + lenzilumab 1,800 mg (n=3)	Overall (N=6)
Grade ≥3 AEs	3 (100)	3 (100)	6 (100)
Grade ≥3 serious AEs	2 (67)	2 (67)	4 (67)
Grade ≥3 axi-cel–related AEs	2 (67)	2 (67)	4 (67)
Any lenzilumab-related AEs	0	0	0
Any NE[a]	3 (100)	2 (67)	5 (83)
Worst Grade 1	2 (67)	1 (33)	3 (50)
Worst Grade 2	0	1 (33)	1 (17)
Worst Grade 3	1 (33)	0	1 (17)
Worst Grade 4	0	0	0
Worst Grade 5	0	0	0
Any CRS[a]	2 (67)	2 (67)	4 (67)
Worst Grade 1	0	1 (33)	1 (17)
Worst Grade 2	2 (67)	1 (33)	3 (50)
Worst Grade 3	0	0	0
Worst Grade 4	0	0	0
Worst Grade 5	0	0	0
Worst Grade ≥3 infections[a]	1 (33)	2 (67)	3 (50)
Cytopenia present on or after Day 30[a,b]	1 (33)	1 (33)	2 (33)
Any steroid use	2 (67)	2 (67)	4 (67)
Any tocilizumab use	1 (33)	2 (67)	3 (50)

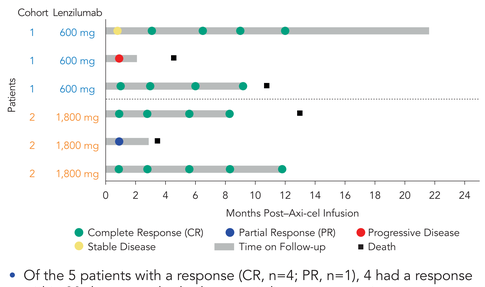
[a]All causality. [b]Included neutropenia, thrombocytopenia, or anemia; includes events started after 30 days from axi-cel infusion and those started earlier but still ongoing on or after 30 days from axi-cel infusion.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; NE, neurologic event.

- A single Grade ≥3 axi-cel–related NE (encephalopathy) was observed in Cohort 1
  - No Grade ≥3 NEs (any causality) were observed in Cohort 2
- Median earliest onset of worst grade NE (within first 30 days) in Cohort 1 and 2 was 8 and 9.5 days, respectively
- Median earliest onset of worst grade CRS (within first 30 days) in Cohort 1 and 2 was 3 and 4.5 days, respectively

EFFICACY

- Objective and complete response rates were 83% and 67%, respectively (**Figure 2**)

Figure 2. Objective Response and Survival Status Over Time

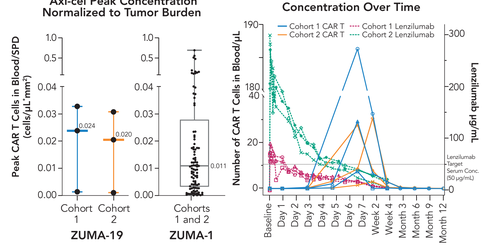


- Of the 5 patients with a response (CR, n=4; PR, n=1), 4 had a response within 30 days; none had subsequent disease progression
  - The patient with a PR died due to COVID-19–related pneumonia
- Four of 6 patients died (67%); no deaths were treatment related
  - COVID-19 pneumonia, n=3; refractory disease, n=1

PHARMACOKINETICS

- Peak concentrations of circulating CAR T cells, normalized to baseline tumor burden (sum of products of diameters; SPD), were comparable between Cohorts 1 and 2 (range, 0.001–0.03 cells/μL*mm² in both cohorts) (**Figure 3A**)
  - Peak CAR T-cell concentrations occurred between Days 7 and 14 after infusion
- Lenzilumab serum concentrations were dose proportional, with C_{max} values of 67.1–89.9 μg/mL in Cohort 1 and 249–299 μg/mL in Cohort 2 (**Figure 3B**)

Figure 3. Pharmacokinetics of Axi-cel and Lenzilumab



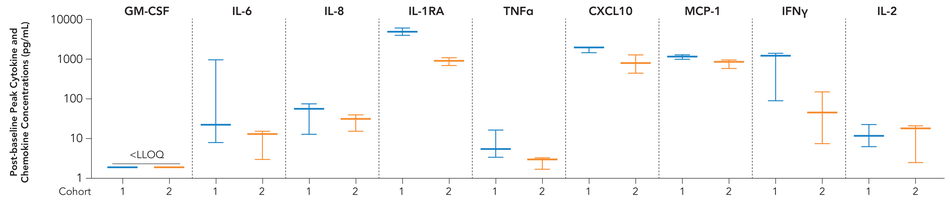
Medians are indicated by labeled horizontal bars, and error bars represent range (minimum, maximum). All comparisons between ZUMA-19 Cohorts 1 and 2 and combined ZUMA-1 Cohorts 1 and 2 are descriptive; no formal statistical analysis was conducted.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; SPD, sum of products of diameters.

- Lenzilumab was sustained above a target serum concentration of 50 μg/mL through Day 1 in Cohort 1 and through Day 4 in Cohort 2

BIOMARKERS

- GM-CSF levels were undetectable, based on an MSD® multiplex assay, in all patients at all time points through at least Week 4 in ZUMA-19 (**Figure 4**)
  - More than 50% of patients in ZUMA-1 Cohorts 1 and 2 had detectable levels of GM-CSF[4]
- Across Cohorts 1 and 2, there were lenzilumab dose-dependent reductions in serum concentrations of pro-inflammatory myeloid-related cytokines and chemokines and interferon gamma (IFNγ), compared with no reduction in interleukin-2 (IL-2)

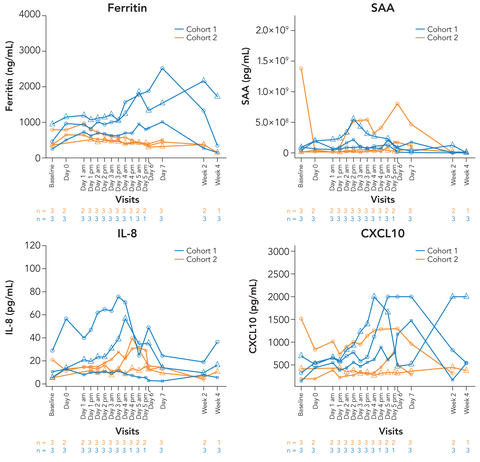
Figure 4. Peak Cytokine and Chemokine Concentrations in Patients Treated With Axi-cel Plus Lenzilumab



Peak concentrations were defined as the maximum post-baseline level from baseline to Week 4. Filled solid bars represent medians, and error bars represent range (minimum, maximum).
Axi-cel, axicabtagene ciloleucel; CXCL10, CXC motif chemokine ligand 10; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LLOQ, lower limit of quantitation; MCP-1, monocyte chemoattractant protein-1; TNF, tumor necrosis factor.

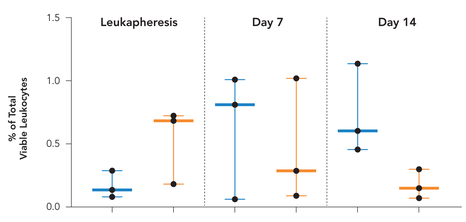
- Lenzilumab appeared to dose-dependently (in Cohort 2 compared with Cohort 1) reduce the serum concentration of ferritin, amyloid A (SAA), IL-8, and CXC motif chemokine ligand 10 (CXCL10) (**Figure 5**)
- The abundance of circulating intermediate monocytes on Day 14 was lower in Cohort 2 compared with Cohort 1 (**Figure 6**)

Figure 5. Serum Levels of Acute Phase and Pro-inflammatory Markers Over Time



CXCL10, CXC motif chemokine ligand 10; IL, interleukin; SAA, serum amyloid A.

Figure 6. Circulating Intermediate Monocytes in Patients Treated With Axi-cel Plus Lenzilumab



Circulating monocytes were evaluated by flow cytometry (CD66b⁻CD3⁻CD19⁻CD56⁻HLADR⁺CD14⁺CD16⁺). Filled solid bars represent medians, and error bars represent range (minimum, maximum).
Axi-cel, axicabtagene ciloleucel.

CONCLUSIONS

- No DLTs or new safety signals were observed in patients treated with axi-cel plus lenzilumab
- Addition of lenzilumab to the axi-cel regimen appeared to dose-dependently suppress the GM-CSF axis and reduce markers of systemic inflammation
  - Axi-cel in combination with lenzilumab may improve the inflammatory profile relative to single-agent axi-cel
- Inhibition of the GM-CSF axis to mitigate CAR T-cell toxicities may warrant further investigation

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ACKNOWLEDGMENTS

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and health care staff at each study site
- Preclinical research was funded in part by NIH R37CA266344
- Medical writing support was provided by Naomi Atkin, PhD, of Fishawack Health, funded by Kite, a Gilead Company

DISCLOSURES

Full author disclosures are available through the Quick Response (QR) code.