Poster
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3-Year Follow-Up Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

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BACKGROUND

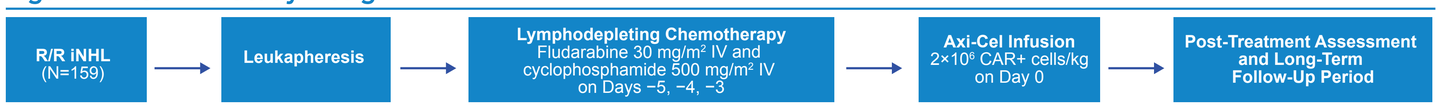
- Axi-cel is a CD19-directed genetically modified autologous T-cell immunotherapy with a CD28 co-stimulatory domain that provides rapid and strong expansion and reprograms T cells to trigger target-specific cytotoxicity of cancer cells[1,2]
- Axi-cel is approved for the treatment of adults with relapsed/refractory (R/R) follicular lymphoma (FL)[1,3]
- ZUMA-5 is a Phase 2, multicenter, single-arm study of axi-cel in patients with R/R indolent non-Hodgkin lymphoma (iNHL), including FL and marginal zone lymphoma (MZL)
  - In the 2-year analysis (N=110; median follow-up was 30.9 months in FL and 23.8 months in MZL), overall response rates (ORR) in patients with FL and MZL were 94% (79% complete response [CR] rate) and 83% (63% CR rate), respectively[4]
  - Median progression-free survival (PFS) in the 2-year analysis was 39.6 months in patients with FL and 17.3 months in those with MZL[4]

OBJECTIVES

- To evaluate updated clinical and pharmacologic outcomes from ZUMA-5 with ≥3 years of follow-up
- To identify pharmacologic covariates of efficacy outcomes

METHODS

Figure 1. ZUMA-5 Study Design[4]



[a] Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible. [b] Single-agent anti-CD20 antibody did not count as line of therapy for eligibility.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

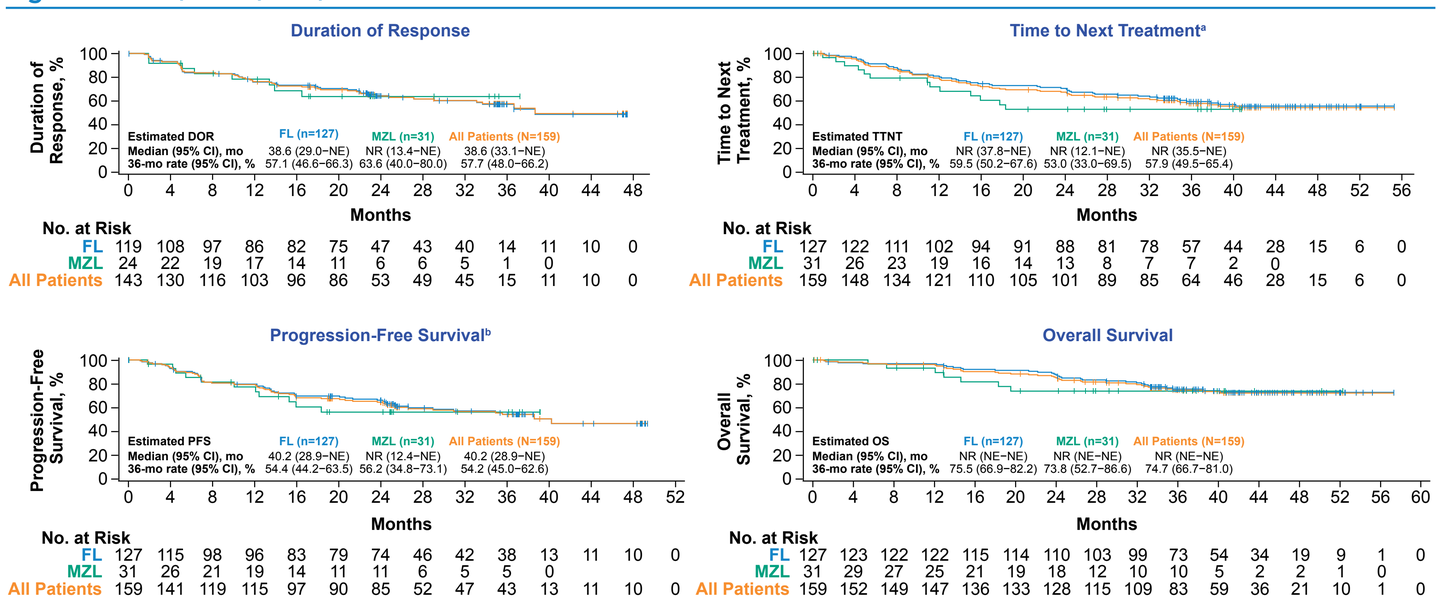
3-Year Analysis

- The updated efficacy analysis occurred when the median follow-up of all enrolled patients was ≥36 months
  - Data cutoff date: March 31, 2022
  - Protocol-specified central review only occurred up to 24 months
- Efficacy outcomes were assessed by investigators and reported for all 159 enrolled patients (intent-to-treat population; 127 with FL; 31 with MZL)
  - One patient was found to have diffuse large B-cell lymphoma after enrollment via pretreatment biopsy. This patient did not receive axi-cel and discontinued the study
  - Exploratory analyses of lymphoma-specific survival were performed, where deaths related to lymphoma (including disease progression [PD]), axi-cel, or lymphodepleting chemotherapy were considered events of interest
- Safety data are reported for the 152 patients treated with axi-cel (124 with FL; 28 with MZL)
- Univariable and multivariable analyses were conducted using random forest analysis to rank the association of pharmacologic covariates with efficacy outcomes in patients with FL who were considered eligible for the primary efficacy analysis (the first 86 treated patients with ≥36 months of follow-up)

RESULTS

- Median follow-up for all enrolled patients with iNHL was 40.5 months (range, 8.3–57.4)
  - Median follow-up was 41.7 months (32.7–57.4) among patients with FL and 31.8 (8.3–52.3) among those with MZL
- Among all enrolled patients with iNHL (N=159), the ORR was 90% (95% CI, 84–94), with a 75% CR rate
  - Patients with FL had an ORR of 94% (79% CR rate) and those with MZL had a 77% ORR (65% CR rate)

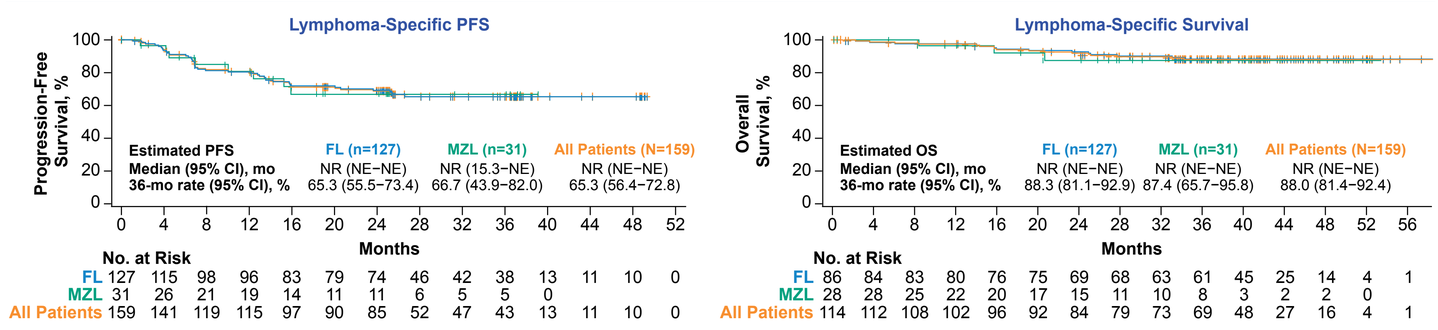
Figure 2. DOR, TTNT, PFS, and OS



[a] Time to next treatment is defined as the time from the leukapheresis date to the start of subsequent anticancer therapy or death from any cause. [b] Progression events were determined by the investigator.
DOR, duration of response; FL, follicular lymphoma; mo, month; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached, OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment.

- At data cutoff, responses were ongoing in 52% of enrolled patients with iNHL (53% in FL; 52% in MZL)
- Median duration of response was not yet reached in enrolled patients with a CR and was 4.9 months in those with a partial response
- With longer follow-up since the prior analysis,[4] medians for PFS increased in enrolled patients with both FL (40.2 months) and MZL (not reached; **Figure 2**)
- Medians of time to next treatment and overall survival (OS) were not yet reached (**Figure 2**)
  - After Month 24, 3 progression events and 10 deaths occurred (1 patient with MZL died due to PD; 4 patients died after subsequent therapy including 2 with FL who received subsequent allogeneic stem cell transplantation)
- Estimated PFS at 36-months was largely consistent in patients with FL regardless of high-risk baseline characteristics
- Median PFS among enrolled patients with FL who had progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy (POD24) was consistent with that of all enrolled patients

Figure 3. Lymphoma-Specific PFS and Lymphoma-Specific Survival[a]



[a] Death related to lymphoma-specific reasons including complications of underlying lymphoma, axi-cel or lymphodepleting chemotherapy were per investigator assessment.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; mo, month; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached, OS, overall survival; PFS, progression-free survival.

- Medians for lymphoma-specific survival endpoints were not yet reached (**Figure 3**)
  - As of data cutoff, a total of 14 deaths in ZUMA-5 were lymphoma-specific (11 due to complications of underlying lymphoma and 3 due to adverse events [AEs] related to study treatment in patients with FL [1 COVID-19 pneumonia, 1 multiple organ dysfunction in the context of cytokine release syndrome, and 1 progressive multifocal leukoencephalopathy])

RESULTS *(Continued)*

Table 1. AEs With Occurrence After the 2-Year Analysis[a]

AE, n (%)	Follicular Lymphoma (n=124)		Marginal Zone Lymphoma (n=28)		All Treated Patients (N=152)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	8 (6)	5 (4)	9 (32)	6 (21)	17 (11)	11 (7)
Serious AE	5 (4)	5 (4)	3 (11)	2 (7)	8 (5)	7 (5)
Cytopenia	0	0	4 (14)	4 (14)	4 (3)	4 (3)
Infection	4 (3)	1 (1)	6 (21)	1 (4)	10 (7)	2 (1)
CRS	0	0	3 (11)	0	3 (2)	0
Neurologic event	0	0	1 (4)	1 (4)	1 (1)	1 (1)

CRS was graded according to Lee et al. *Blood.*[6] NEs were identified using the modified blinatumomab registrational study.[7] The severity of all AEs, including NEs and symptoms of CRS, was graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
[a] Includes all AEs that occurred in treated patients after the data cutoff date of the 2-year analysis (March 31, 2021) and by the data cutoff date of the current analysis (March 31, 2022).
AE, adverse event; CRS, cytokine release syndrome; NE, neurologic event.

- AEs of interest occurring among treated patients since the 2-year analysis were largely in recently enrolled patients with MZL (**Table 1**)
  - No new cases of Grade ≥3 hypogammaglobulinemia occurred after the data cutoff date for the primary analysis (March 12, 2020)
  - No cases of axi-cel–related secondary malignancies, tumor lysis syndrome, or replication competent retrovirus occurred at anytime on study
- Since the 2-year analysis, 10 additional patients died due to progression (n=1), new malignancies (n=3; 1 malignant anorectal and 2 acute myeloid leukemia; none related to axi-cel), and other causes not related to axi-cel (n=6; lung infection, E. coli sepsis, graft-versus-host disease, sepsis, COVID pneumonia, and unknown)
- Chimeric antigen receptor (CAR) T-cell expansion by peak and area under the curve was significantly higher in treated patients who had an ongoing response at 36 months (53.9 cells/µL) than in those who had relapsed (29.6 cells/µL) or nonresponders (22.2 cells/µL; *P*=.0011)
- FL International Prognostic Index (FLIPI) score, along with elevated baseline levels of CCL17, CCL22, TNF-α and IL-16 were the top 5 covariates identified by the multivariate analysis to be associated negatively with PFS in patients with FL
  - Additionally, peak CAR T-cell levels in blood and total number of infused naive and central memory T cells associated positively with ongoing response and PFS in patients with FL, as previously shown[8]

CONCLUSIONS

- After 3 years of follow-up in ZUMA-5, axi-cel demonstrated continued durable responses in patients with R/R iNHL
  - In FL, patients with POD24 benefited from axi-cel, with a PFS similar to that of the overall population
  - In MZL, survival outcomes improved with longer follow-up, with a median PFS not yet reached
  - Late progression or death due to lymphoma or study treatment was uncommon
  - Longer follow-up is needed to determine whether the emergence of plateau in lymphoma-specific PFS will be maintained
- No new safety signals were observed since the previous analysis
- Multivariate analysis of pretreatment and posttreatment characteristics identified FLIPI score and key pretreatment immune counter-regulatory serum biomarkers associated negatively with durable response
- These data further support axi-cel as a highly effective therapeutic approach for patients with R/R iNHL

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- These data were previously presented at the 2022 Annual Meeting of the American Society of Hematology[9]

DISCLOSURES

- SSN: consulting fees or honoraria from Kite, Merck, Bristol Myers Squibb, Novartis, Allogene Therapeutics, Cell Medica/Kuur/Athenex, Incyte, Legend Biotech, Adicet Bio, bluebird bio, Sellas Life *Sciences*, Fosun Kite, Sana Biotechnology, Caribou, Astellas Pharma, MorphoSys, Medscape, Aptitude Health, Bio Ascend, and MJH Life *Sciences*; grants, contracts, or research funding from Kite, Bristol Myers Squibb, Poseida, Cellectis, Unum Therapeutics (Cogent Biosciences), Allogene, Precision Bio*Sciences*, and Adicet Bio; stock options from Longbow *Immunotherapy*; and patents, royalties, or other intellectual property from Takeda Pharmaceuticals, related to cell therapy

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