Poster
ABCL-411

Matching-adjusted Indirect Comparison of Axicabtagene Ciloleucel vs Odronextamab for the Treatment of Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL) After 2 Prior Lines of Systemic Treatment

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BACKGROUND

- Large B-cell lymphoma (LBCL) is an aggressive and common type of Non-Hodgkin lymphoma (NHL).[1] The majority of patients may respond well to first line therapy. Still, 40% of patients with LBCL progress beyond 1L LBCL[2] and median survival for 3L+ diffuse large B-cell lymphoma (DLBCL) historically was 6.3 months.[3]
- Based on the pivotal ZUMA-1 trial[4], axicabtagene ciloleucel (axi-cel) was the first chimeric antigen receptor (CAR) T-cell therapy approved for adult patients with LBCL who are relapsed/refractory (R/R) to 2+ lines of therapy (LoTs) in the United States (US) and Europe.[5,6] Following the success of the ZUMA-7 trial[7], this indication was expanded to 2L use by both the US Food and Drug Administration and the European Medicines Agency.
- Odronextamab is a CD20xCD3 bispecific antibody under investigation for 3L+ R/R LBCL in the pivotal ELM-2 trial[8], which recently reported positive short-term outcomes.[9,10,11]
- In the absence of head-to-head evidence, we conducted an unanchored matching adjusted indirect treatment comparison (MAIC) to compare axi-cel to odronextamab in 3L+ R/R patients with LBCL.

OBJECTIVES

- To evaluate the comparative efficacy and safety of axi-cel vs odronextamab for the treatment of R/R LBCL in patients with 2+ prior LoTs using a systematic literature review (SLR) and MAIC.

METHODS

- Systematic searches of MEDLINE/EMBASE/CENTRAL and recent conferences of interest were conducted.
- For ZUMA-1[4], 60-month data were used to evaluate overall survival (OS) and adverse events (AEs).
- 24-month ZUMA-1[4] data assessed by an independent review committee were used for response outcomes to match the central review used for response assessment in ELM-2[8]. Median follow-up for ELM-2[8] was 32.8 months.
- Prognostic factors and effect modifiers were identified using a targeted literature review, clinical consultation, and ZUMA-1[4] individual patient data (IPD) analyses.
- Outcomes of interest included: overall survival (OS), progression-free survival (PFS), duration of response (DoR), duration of complete response (DoCR), overall response rate (ORR), complete response (CR), cytokine release syndromes (CRS; any and G3+), any grade ≥3 (G3+) AEs, G5 AEs, thrombocytopenia (any and G3+), and neutropenia (any and G3+).
- A logistic model was used to develop weights for ZUMA-1[4] axi-cel patients to match the ELM-2[8] population using the following covariates: International prognostic index (IPI) score, Eastern Cooperative Oncology Group (ECOG) score, disease stage, refractory to last therapy, prior LoT, primary refractory, transformed disease, and prior auto-SCT (stem-cell transplant). A diagram of this matching process is displayed in **Figure 1**.
- Dichotomous outcomes were modeled using weighted logistic regression models (described using odds ratios [ORs] and 95% confidence intervals [CI]), while time-to-event outcomes used weighted Cox proportional hazards models (hazard ratios [HRs]; 95% CIs), both incorporating robust sandwich estimators for standard errors.
- Tests for proportional hazards were computed for all time-to-event endpoints and restricted mean survival times (RMSTs) were computed in cases of violation.
- Sensitivity analyses included: adding ZUMA-1 cohorts 4[12] and 6[13], using ZUMA-1[4] investigator assessed response, and adding Age 65+ to the matching variables.

METHODS

Figure 1. MAIC weighting of ZUMA-1 to match ELM-2



RESULTS

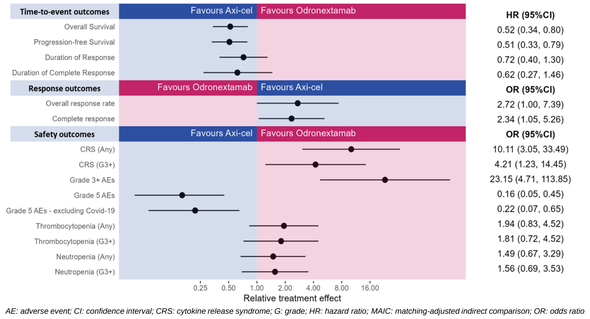
- The SLR yielded 754 total records from which 10 records were included, with 7 contributing to the MAIC relating to ZUMA-1[4] and ELM-2[8]. Most publications were excluded for either study design (observational studies) or publication type. The JapicCTI-183914 axi-cel trial also met the inclusion criteria but given that IPD were available for ZUMA-1[4] only, the analysis set was restricted to ZUMA-1[4] and ELM-2[8].
- The largest initial population differences were IPI score, the number of patients with 3+ prior lines of therapy, primary refractory, and presence of double or triple hit lymphoma (**Table 1**). However, after matching, all characteristics aligned exactly.
- All models converged (no covariates needed to be removed) and effective sample sizes (ESSs) were 34.4 (from 101) for ZUMA-1 cohorts 1 and 2[4] and 58.7 (from 182) for cohorts 1, 2, 4, and 6.[4, 12, 13]

Table 1. Patient characteristics for ZUMA-1 and ELM-2, pre- and post-adjustment for all endpoints in the base case

Variables	ZUMA-1 (Cohorts 1 and 2)		ZUMA-1 (Cohorts 1, 2, 4 and 6)		ELM-2 covariates
	Original IPD	Weighted IPD	Original IPD	Weighted IPD	
IPI score (3-5)	**45.5%**	55.9%	**46.2%**	55.9%	55.9%
ECOG PS (0)	41.6%	32.3%	44.5%	32.3%	32.3%
Disease stage (III-IV)	85.1%	81.1%	77.5%	81.1%	81.1%
Refractory to last therapy	91.1%	86.6%	81.9%	86.6%	86.6%
Prior lines (3+)	**69.3%**	47.2%	**61.0%**	47.2%	47.2%
Primary refractory	**25.7%**	55.1%	**20.9%**	55.1%	55.1%
Double or triple hit	**31.7%**	10.2%	**33.5%**	10.2%	10.2%
Transformed disease	15.8%	18.9%	19.2%	18.9%	18.9%
Prior auto-SCT	24.8%	17.3%	26.9%	17.3%	17.3%

*Values in **bold** indicate large differences in baseline values between axi-cel patients and odronextamab patients. Abbreviations: ECOG = Eastern Cooperative Oncology Group; IPD: individual patient data; IPI: international prognostic index; PS: performance score; SCT: stem cell transplant*

Figure 2. Summary of MAIC-adjusted results

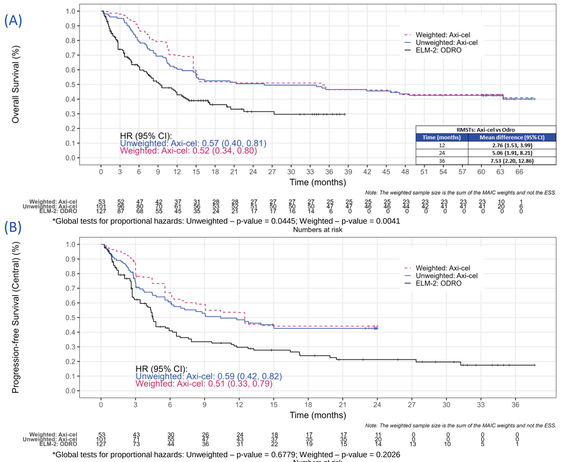


AE: adverse event; CI: confidence interval; CRS: cytokine release syndrome; G: grade; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OR: odds ratio

RESULTS

- **Figure 2** provides an overview of all the analyses. Axi-cel demonstrated statistically significant response, and lower grade 5 AE-incidence when compared to odronextamab.
- Odronextamab was favored for CRS (any grade and G3+) and overall G3+ AEs with all estimates being statistically significant.
- As shown in **Figure 3 (A)** and **(B)**, respectively, axi-cel had OS and PFS superior to odronextamab.
- Axi-cel was favored for DoR and DoCR although results were not statistically significant, while odronextamab was favored for thrombocytopenia and neutropenia with estimates that were also not statistically significant **(Figure 2)**.
- Sensitivity analyses were generally aligned with the base case; exceptions were G3+ CRS and G5 AEs which were no longer significant when adding ZUMA-1 safety cohorts 4[12] and 6[13] (**Table 2**).

Figure 3. MAIC of OS (A) and PFS (B) between axi-cel and odronextamab



Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; ODRO: odronextamab; OS: overall survival; PFS: progression-free survival; RMST: restricted mean survival time

Table 2. Summary of MAIC sensitivity analysis results

Outcome	Measure (Axi-cel vs Odro)	Adjusted Estimates		
		Adding ZUMA-1 Cohorts 4 and 6	ZUMA-1 Investigator Assessed Response	Adding Age 65+ to Matching Variables
OS	HR (95% CI) *<1 favors axi-cel*	**0.54 (0.36, 0.79)**	--	**0.49 (0.30, 0.79)**
PFS*		**0.64 (0.43, 0.96)**	0.68 (0.44, 1.04)	**0.56 (0.33, 0.95)**
DoR*		0.93 (0.57, 1.53)	1.04 (0.60, 1.80)	0.82 (0.42, 1.63)
DoCR*		0.77 (0.35, 1.70)	0.98 (0.43, 2.23)	0.67 (0.26, 1.72)
ORR*	OR (95% CI) *>1 favors axi-cel*	**4.72 (2.20, 10.12)**	**8.00 (3.19, 20.03)**	**4.74 (1.93, 11.63)**
CR*		**2.98 (1.56, 5.71)**	**4.07 (1.88, 8.82)**	**2.88 (1.14, 7.24)**
CRS (Any)	OR (95% CI) *<1 favors axi-cel*	**9.83 (4.31, 22.41)**	--	**12.41 (2.58, 59.69)**
CRS (G3+)		3.26 (0.97, 10.99)	--	4.71 (0.99, 22.33)
Grade 3+ AEs		**19.60 (4.91, 78.32)**	--	6.76 (0.86, 53.35)
Grade 5 AEs		0.49 (0.22, 1.08)	--	**0.20 (0.05, 0.87)**
Thrombocytopenia (Any)		1.99 (0.96, 4.10)	--	2.23 (0.81, 6.13)
Thrombocytopenia (G3+)		1.64 (0.73, 3.69)	--	2.11 (0.69, 6.45)
Neutropenia (Any)		1.72 (0.90, 3.29)	--	1.51 (0.59, 3.83)
Neutropenia (G3+)		**2.00 (1.03, 3.90)**	--	1.55 (0.58, 4.14)

AE: adverse event; CI: confidence interval; CR: complete response; CRS: cytokine release syndrome; DoR: duration of response; DoCR: duration of complete response; G: grade; HR: hazard ratio; Odro: odronextamab; OR: odds ratio; ORR: objective response; OS: overall survival; PFS: progression-free survival
Central review; **Bolded values are statistically significant*

DISCUSSION

- This MAIC suggests that axi-cel has significantly better efficacy vs odronextamab in R/R patients with LBCL with 2+ prior lines in terms of OS, PFS, and response.
- However, aside from grade 5 AEs, odronextamab showed better safety. This differential safety result was partially offset when including ZUMA-1 cohorts 4[12] & 6[13], which reflected updated toxicity management guidelines. In contrast, the ZUMA-1 cohorts 1 & 2[4] safety data reflected practices from 2015 and may not reflect current practices.
- A strength of this analysis is that both trials were conducted in CAR T naïve patient populations.
- Our study had some limitations. First, the analyses assumed that all prognostic factors and effect modifiers were known and adjusted for.
- Second, the trials used different response criteria (IWG response vs. Lugano criteria), and different criteria for AEs (NCI-CTCAE v4.03 and v5.0).
- Third, we aimed to analyze neurotoxicity; however, this outcome is not currently available from a published source of ELM-2[8].
- Finally, differences in safety protocols including prophylactic use of medications may have induced bias which was partially alleviated in the conduct of the sensitivity analysis including ZUMA-1 safety cohorts 4[12] and 6[13].

CONCLUSIONS

- The advent of CAR T-cell therapy have revolutionized the treatment paradigm for R/R 3L+ patients with LBCL, with 43% experiencing long-term survival.
- The evaluation of the comparative efficacy and safety of axi-cel and odronextamab in 3L+ R/R patients with LBCL showcased significant superiority for axi-cel in terms of ORR, CR, PFS and OS in the base case as well as sensitivity analyses.
- Odronextamab had lower rates of all grade and G3+ CRS and G3+ AEs, whereas G5+ AEs favored axi-cel.
- While analyses and results reported were robust, further analyses will be warranted once long-term survival data become available.

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DISCLOSURES

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Disclosure: Consulting or advisory role for Allogene, Amgen, Bluebird Bio, BMS/Celgene, Calibr, Cellular Biomedicine Group, Cowen, ecoR1, Emerging Therapy Solutions Gerson Lehman Group, GammaDelta Therapeutics, Iovance, Janssen, Kite, a Gilead Company, Legend Biotech, Novartis, Umoja, and Wugen; research funding from Allogene, Kite, and BMS; and patents, royalties, other intellectual property in the field of cellular immunotherapy.

Presented at the Society of Hematologic Oncology Conference, Houston, Texas, September 4-7, 2024