



Matching-Adjusted Indirect Comparison (MAIC) of Axicabtagene Ciloleucel (axi-cel) and Lisocabtagene Maraleucel (liso-cel) in Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL) After Two or More Prior Lines of Therapy

Olalekan O Oluwole¹, Jenny MH Chen², Keith Chan², Anik R Patel³, Jeroen P Jansen⁴, Sam Keeping², Zahid Bashir³, Yan Zheng³, Julia T Snider³, Frederick L Locke⁵

VANDERBILT-INGRAM CANCER CENTER

¹Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; ²PRECISIONheor, Vancouver, BC, Canada; ³Kite, a Gilead Company, Santa Monica, CA, USA; ⁴PRECISIONheor, Oakland, CA, USA; ⁵Moffitt Cancer Center, Tampa, FL, USA

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Background

- Despite an overall good prognosis for patients with diffuse LBCL in the first-line setting, about 10-15% of patients will have primary refractory disease and a further 20-30% will relapse, requiring further intervention.¹
- Prior to CAR T therapy, prognosis was extremely poor for patients who relapse early or are refractory to treatment, with a median overall survival (OS) of 6.3 months and an objective response rate (ORR) of 26% reported in a retrospective analysis of 636 patients with refractory diffuse LBCL.²
- Axi-cel and liso-cel are autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapies approved by the US Food and Drug Administration for the treatment of R/R LBCL after two or more lines of systemic therapy.
- Approvals were based on results of single-arm registrational trials: ZUMA-1^{3,4} (NCT02348216, phase 1/2 trial) evaluated axi-cel and TRANSCEND-NHL-001⁵ (NCT02631044; phase 1) evaluated liso-cel.
- Both have demonstrated high and durable responses in single-arm trials, but comparative evidence is lacking.

Objective

- To estimate relative treatment effects of axi-cel versus liso-cel for the treatment of R/R LBCL using matching-adjusted indirect comparison (MAIC).

Materials & Methods

- A pre-specified logistic propensity score model was used to estimate weights for the individual patient data in ZUMA-1^{3,4} (axi-cel) to match the mean baseline characteristics observed in TRANSCEND-NHL-001⁵ (liso-cel).
- Outcomes were then compared across matched populations using weighted statistical tests: logistic regression models for binary outcomes and Cox proportional hazards models for time-to-event outcomes.
- The efficacy outcomes of interest were response rates as assessed by independent review committee (IRC), OS, progression-free survival (PFS, by IRC), and duration of response (DOR, by IRC); relevant safety outcomes were cytokine release syndrome (CRS) and neurological events (NEs).
- Relative treatment effects were expressed in terms of hazard ratios (HRs) or odds ratios (ORs) for axi-cel versus liso-cel along with their 95% confidence intervals (CIs).
- Additionally, for time-to-event outcomes, relative treatment effects were summarized in terms of the difference in restricted mean survival time (RMST, with 95% CI) which reflects the area under the curve up to a specific time-point reflecting the shortest follow-up of both trials.
- Base-case analyses were conducted using ZUMA-1 pivotal Cohorts 1 and 2 (N=101; median follow-up, 27.1 months for all outcomes except OS, where median follow-up was 51.1 months) and published outcomes for liso-cel (median OS follow-up, 17.5 months; median PFS follow-up, 12.3 months).
- Scenario analyses for OS and safety included ZUMA-1 additional safety management Cohort 4 (N=41; median follow-up, 14.8 months) and Cohort 6 (N=40; median follow-up, 8.9 months).
- Licensed liso-cel doses were used where possible: the analysis of tumor response and AEs included liso-cel dose levels 1, 1D, and 2 (50–100 X 10⁶ CAR-T cells) whereas the analysis of OS, PFS, and DOR was based on all liso-cel doses (50–150 X 10⁶ CAR-T cells) from TRANSCEND-NHL-001.
- Matched variables were Eastern Cooperative Oncology Group (ECOG) performance status, best response of CR to last therapy, LBCL subtype, # of prior lines of therapy, prior autologous stem cell transplantation, tumor burden by sum of product diameter, age, and lactate dehydrogenase; additionally, use of bridging therapy was included as a matching variable for the scenario analyses (**Table 1**)

Patient demographics and disease characteristics

- Prior to matching, the axi-cel and liso-cel populations differed for most of the included covariates.
- MAIC convergence was achieved using the full set of covariates, and after matching, these baseline characteristics were balanced between the two trial populations (see **Table 1**).

Table 1: Baseline characteristics in ZUMA-1 before and after matching to TRANSCEND-NHL-001 for the analysis of overall survival

Variable		ZUMA-1 Cohorts 1+2		ZUMA-1 Cohorts 1+2+4+6		TRANSCEND -NHL-001 (N=256)
		Observed (N=101)	MAIC matched (ESS=44.8)	Observed (N=182)	MAIC matched (ESS=89.8)	
ECOG PS (%)	0	41.6	41.0	44.5	41.0	41.0
	≥ 1	58.4	59.0	55.5	59.0	59.0
Best response to last tx (%)	CR	8.9	20.7	12.1	20.7	20.7
	Non-CR	91.1	79.3	87.9	79.3	79.3
Bridging therapy (%)*	Yes	0	0	26.9	58.6	58.6
	No	0	0	73.1	41.4	41.4
B-cell lymphoma subtypes (%)	DLBCL	51.5	51.2	48.9	51.2	51.2
	HGBCL (DH/TH)	24.8	12.9	26.4	12.9	12.9
	TFL	15.8	22.3	19.2	22.3	22.3
	Other	7.9	13.6	5.5	13.6	13.6
No. of prior therapies (%)	2	27.7	45.0	36.3	45.0	45.0
	3	28.7	25.0	30.8	25.0	25.0
	≥4	40.6	26.0	30.2	26.0	26.0
	Yes	24.8	33.0	26.9	33.0	33.0
Prior auto-SCT (%)	No	75.2	67.0	73.1	67.0	67.0
	<50 cm ²	61.4	71.7	67.6	71.7	71.7
Tumor burden by SPD (%)	≥50 cm ²	38.6	28.3	32.4	28.3	28.3
	<65 years	76.2	57.8	68.7	57.8	57.8
Age (%)	≥65 years	23.8	42.2	31.3	42.2	42.2
	<500 U/L	67.7	77.7	74.7	77.7	77.7
LDH (%)	≥500 U/L	32.3	22.3	25.3	22.3	22.3

Abbreviations: auto-SCT, autologous stem cell transplant; CR, complete response; DH/TH, double hit/triple hit; ECOG, Eastern Cooperative Oncology Group; DLBCL, diffuse large B-cell lymphoma; ESS, effective sample size; HGBCL, high-grade B-cell lymphoma; LDH, lactate dehydrogenase; MAIC, matching-adjusted indirect comparison; OS, overall survival; PS, performance score; SPD, sum of product diameter; TFL, transformed follicular lymphoma; tx, treatment

*Only included in the propensity score model for the scenario analysis with ZUMA-1 Cohorts 1+2+4+6

Matching-adjusted indirect comparisons

- Results from the MAIC is described below and those from the naïve comparisons are presented in **Table 2** for informative purposes only.
- The effective sample size (ESS) of the axi-cel population after weighting was approximately 50% of the original sample size for the base-case and scenario analyses.
- The estimated ORs for objective response (2.18 [0.96–4.98]) and complete response (1.84 [0.97–3.50]) favored axi-cel, but these differences were not statistically significant (**Table 2**).
- Axi-cel was associated with a statistically significant improvement in OS (HR: 0.53 [0.34–0.83]) in the base-case (**Figure 1**); the OS RMST for the 36-month follow-up was 6.4 months (95% CI: 3.4–8.2) months longer for axi-cel than for liso-cel. The upward shift in the weighted axi-cel KM curve is a reflection of the axi-cel population having a higher risk profile prior to matching and is largely driven by the number of prior therapies and b-cell lymphoma subtypes.
- Axi-cel was also associated with improved PFS compared with liso-cel (HR: 0.61 [0.40–0.93]); the PFS RMST for the 30-month follow-up was 3.6 months (95% CI: 1.8–4.7) longer with axi-cel.

Results

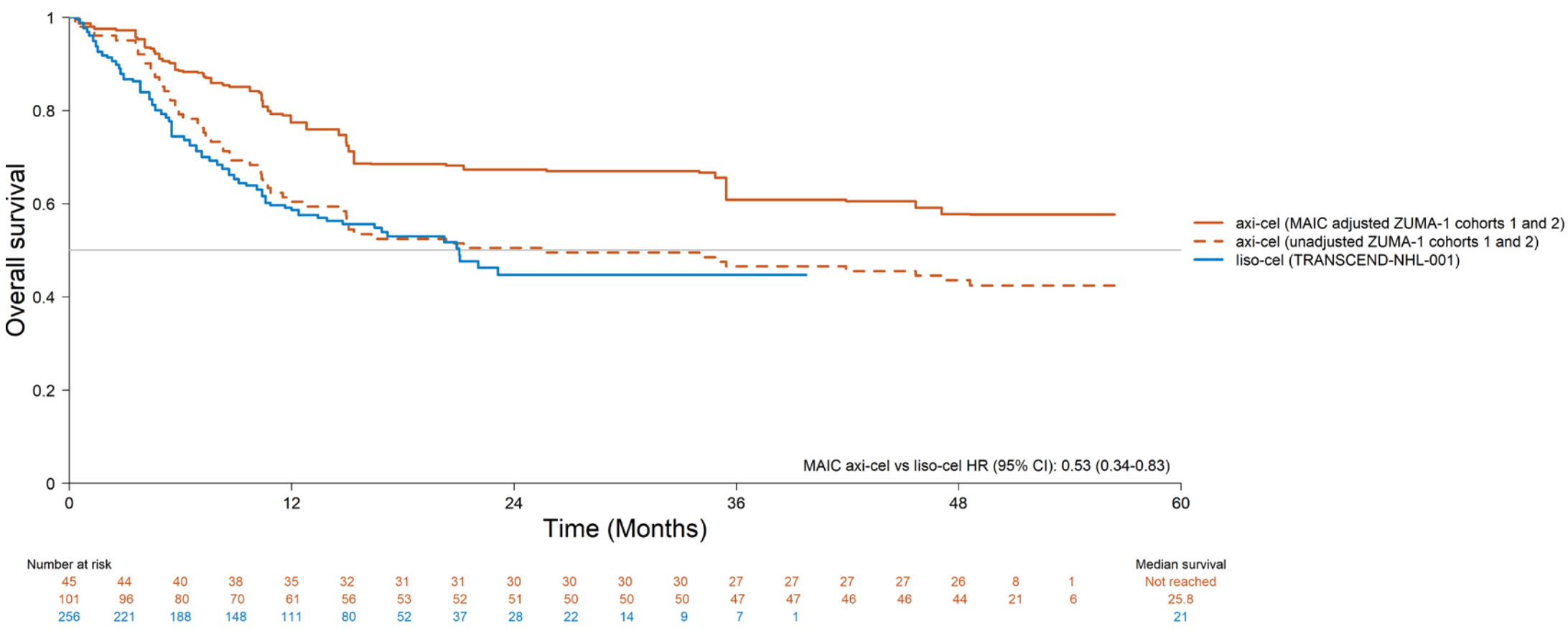
- DOR results were in favor of axi-cel, although not statistically significant (HR: 0.63 [0.37–1.06]); the DOR RMST for the 30-month follow-up was 1.4 months (95% CI: 0.5–2.0) longer with axi-cel.
- Compared to liso-cel, axi-cel was associated with a higher rate of grade ≥3 CRS (OR: 3.64 [1.04–12.76]) and grade ≥3 NEs (OR: 3.45 [1.65–7.19]).
- The estimated differences in grade ≥3 CRS and grade ≥3 NEs were smaller in the scenario analyses including the expanded safety management cohorts (OR: 1.71 [0.47–6.19] and 2.90 [1.54–5.47], respectively); notably, differences in grade ≥3 CRS were not statistically significant.
- Differences in OS did not reach statistical significance in the scenario analysis (HR: 0.76 [0.52–1.10]) but RMST was 2.8 months (95% CI: 1.2–4.0) longer with axi-cel compared to liso-cel.

Table 2: Naïve and MAIC-weighted relative treatment effect estimates of axi-cel versus liso-cel

Analyses	Outcomes	Naïve estimates	MAIC estimates
Efficacy outcomes – OS/PFS/DOR		HR (95% CI)	HR (95% CI)
Base-case	OS	0.90 (0.65–1.25)	0.53 (0.34–0.83)
Scenario	OS	0.79 (0.59–1.06)	0.76 (0.52–1.10)
Base-case	PFS	0.91 (0.67–1.24)	0.61 (0.40–0.93)
Base-case	DOR	0.82 (0.54–1.24)	0.63 (0.37–1.06)
Efficacy outcomes – Tumor response		OR (95% CI)	OR (95% CI)
Base-case	ORR	1.09 (0.64–1.87)	2.18 (0.96–4.98)
Base-case	CR	1.04 (0.65–1.67)	1.84 (0.97–3.50)
Safety outcomes – CRS and NEs		OR (95% CI)	OR (95% CI)
Base-case	Grade 1-2 CRS	8.37 (4.70–14.91)	7.95 (3.75–16.87)
Base-case	Grade ≥3 CRS	4.52 (1.62–12.60)	3.64 (1.04–12.76)
Base-case	Grade 1-2 NEs	2.49 (1.46–4.25)	2.15 (1.09–4.24)
Base-case	Grade ≥3 NEs	3.76 (2.07–6.85)	3.45 (1.65–7.19)
Scenario	Grade 1-2 CRS	9.20 (5.71–14.81)	7.16 (4.02–12.77)
Scenario	Grade ≥3 CRS	2.61 (0.96–7.10)	1.71 (0.47–6.19)
Scenario	Grade 1-2 NEs	3.01 (1.91–4.73)	2.94 (1.71–5.06)
Scenario	Grade ≥3 NEs	2.63 (1.53–4.53)	2.90 (1.54–5.47)

Notes: All bolded values are statistically meaningful at the 0.05 significance level. **Abbreviations:** CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; HR, hazard ratio; NE, neurological event; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Figure 1: Matching-adjusted indirect comparison of axi-cel (ZUMA-1 Cohorts 1+2) and liso-cel regarding overall survival; Cox proportional hazards model



Limitations

- As with any analysis of single-arm or non-comparative studies, there will always be uncertainty regarding any unknown or unmeasured prognostic factors/effect-modifiers not captured in the chosen model which may have influenced the outcome of interest; estimates are therefore subject to unknown amounts of residual bias.
- Potential prognostic characteristics and effect modifiers to be adjusted for in the MAIC were based on recommendations from clinical experts but limited by data availability (must be reported for both trials).
- This current analysis did not factor in the pre-infusion time starting from the time of leukapheresis, and it was assumed that the hazard rates were comparable between both trial populations during this period:
 - A higher proportion of leukapheresed patients did not receive CAR T-cell infusion in TRANSCEND-NHL-001 (50/344 [14.5%]) compared to ZUMA-1 (10/111 [9.0%]) in Cohorts 1+2 and 17/199 [8.5%] in Cohorts 1+2+4+6; most notably, more patients did not receive infusion due to death in TRANSCEND-NHL-001 (33/344 [9.6%]) compared to ZUMA-1 (2/111 [1.8%]) in Cohorts 1+2 and 4/199 [2.0%] in Cohorts 1+2+4+6).
 - The median times from leukapheresis to infusion were 23–29 days to axi-cel infusion and 37 days to liso-cel infusion, and the current MAIC assumed that this 1–2 weeks difference did not have a significant impact on OS and PFS estimates.
- A small proportion of patients in TRANSCEND-NHL-001 were not eligible for ZUMA-1 (3% prior allogeneic SCT, 3% secondary central nervous system lymphoma, 1% ECOG PS 2, and 23% reduced renal and cardiac function) and this difference could not be adjusted for in the MAIC without IPD for TRANSCEND-NHL-001; although the impact of these variables on survival estimates is unclear, outcomes in patients receiving standard-of-care axi-cel in the real-world setting were shown to closely resemble those reported in the ZUMA-1.⁶

Conclusion

- Based on the available evidence, this analysis suggests that axi-cel demonstrated comparable response rates and more favorable OS and PFS versus liso-cel among R/R LBCL patients who received two or more lines of prior therapy.
- Axi-cel was associated with a higher risk of CRS and NEs, although the risk-benefit of axi-cel has improved over time with improved management of such events in clinical practice.

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Contact information

Corresponding author: O Oluwole, olalekan.oluwole@vumc.org