Poster 386

Matching-Adjusted Indirect Comparisons of Axi-cel to Mosunetuzumab for the Treatment of Relapsed/Refractory Follicular Lymphoma

M. D. Ray[1] , S. Kanters[2], S. Beygi[1], T. Best[1], J. Wulff[1], E. H. Limbrick-Oldfield[2], A. R. Patel[1], O. O. Oluwole[3]

1 Kite, A Gilead Company, Santa Monica, CA, United States of America; 2 RainCity Analytics, Vancouver, Canada; 3 Vanderbilt University Medical Center, Nashville, TN, United States of America

INTRODUCTION

- Follicular lymphoma (FL) is an indolent form of non-Hodgkin's lymphoma; however, patients with relapsed/refractory (R/R) FL tend to have shorter remission with each subsequent line of treatment (LoT).[1]
- For R/R FL patients, axicabtagene ciloleucel (axi-cel) was the first chimeric antigen receptor (CAR) T-cell therapeutic approved by the Food and Drug Administration and other regulatory agencies, whilst more recently mosunetuzumab became the first approved bispecific monoclonal antibody.
- Both treatments have been studied using non-comparative trials thus far, and as such there lacks any head-to-head evidence.

OBJECTIVES

- To conduct a matching-adjusted indirect comparison (MAIC) of the efficacy and safety of axi-cel relative to mosunetuzumab for the treatment of R/R FL patients with ≥2 prior lines of systemic therapy.

METHODS

- The evidence base consisted of individual patient data (IPD) from the ZUMA-5 trial (NCT03105336) for axi-cel and published aggregate data from the GO29781 trial (NCT02500407) for mosunetuzumab. Published Kaplan-Meier curves were extracted for mosunetuzumab, and pseudo-IPD were derived using the Guyot algorithm.[2] The specific data cuts and sources are presented in **Table 1**.

Table 1. Data sources used in MAIC

Trial	Source	Data cut (Cut-off date)	Median follow-up	Sample size	Analysis set	Outcomes analyzed
ZUMA-5 (axi-cel)	Clinical trial data	36 month (March 31, 2022)	41.7 months*	127	Enrolled	PFS, DOR and Response (each IRC and IA), and safety
GO29781 (mosunet-uzumab)	Budde et al	18 month (Aug 27, 2021)	18.3 months	90	Enrolled	IRC Response, PFS and DOR
	Bartlett et al	24 month (July 8, 2022)	28.3 months	90	Enrolled	IA Response, PFS and DOR, and safety

*IRC was conducted up to *the 24-month data cut. DOR: Duration of response IRC: Independent review committee; IA: Investigator assessed; PFS: Progression-free survival*

- Unanchored MAICs were used to align prognostic factors and effect-modifiers from ZUMA-5 to those of the GO29781 trial (**Table 2**). This is a weight-based analytical method akin to propensity score analyses. Number of prior lines in ZUMA-5 did not include anti-CD20 monotherapy, so we re-derived it to align with the GO29781 definition. Similarly, POD24 was re-defined to allow for any frontline therapy.
- For each outcome, weights were determined on the basis of prognostic factors and effect modifiers identified *a priori* based on input from clinical experts and blinded numerical analyses.

Table 2. Variables included in MAICs

Outcome		Adjusted Variables: Age	Sex	Race	Disease Stage	ECOG	FLIPI	POD24	Double Refractory	Refractory	Prior SCT	N prior lines	Bulky disease	ESS (n = 127)
Efficacy	Progression-free survival					✓	✓	✓	✓	✓	✓	✓	✓	109.1
Efficacy	Duration of response						✓	✓	✓	✓	✓	✓	✓	109.9
Efficacy	Response (ORR and CR)	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	99.2
Safety	CRS (Any grade and grade ≥ 3)	✓				✓	✓	✓	✓	✓	✓	✓	✓	109.1
Safety	NE (Any grade and grade ≥ 3)	✓				✓	✓	✓	✓	✓	✓	✓	✓	109.1
Safety	Treatment related AE (Grade ≥ 3)	✓				✓	✓	✓	✓	✓	✓	✓	✓	109.1
Sensitivity analyses														
	All outcomes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	83.6

CR: Complete response; CRS: Cytokine release syndrome; ECOG: Eastern Cooperative Oncology Group; ESS: Effective sample size; FLIPI: Follicular Lymphoma International Prognostic Index; NE: Neurological events; ORR: Objective response rate; POD24: Progression of disease within 24 months; SCT: Stem cell transplant.

- Hazard ratios (HRs) from Cox regression were used to compare time-to-event outcomes, and the remaining outcomes were compared using odds ratios (ORs).
- Overall survival was immature for the GO29781 trial and not included in the latest publication, therefore was not included in the analysis.
- The primary analyses used the intention-to-treat (ITT) population of ZUMA-5 and the independent review committee (IRC) response assessment. Sensitivity analyses included restricting ZUMA-5 to infused patients and using Investigator assessment (IA).
- In ZUMA-5, responses were assessed using Lugano 2014;[5] while the G029781 trial used the International working group (IWG) classification.[6]

RESULTS

- Patient characteristics are presented in **Table 3** and were generally well-aligned between trials leading to large effective-sample sizes for ZUMA-5, ranging from 99.2 to 109.9 (**Table 2**).

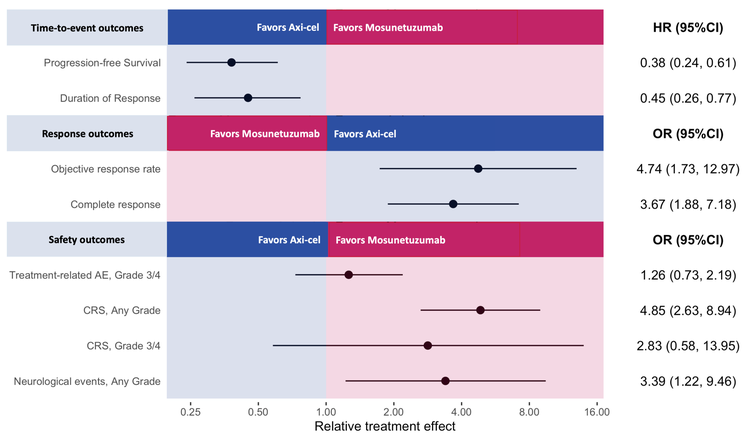
Table 3. Baseline Characteristics

Variable	ZUMA-5 FAS (n = 127)	GO29781 (n = 90)	p-value
Age, median (IQR)	60 (53 – 67)	60 (53 – 67)	--
Age ≥ 65 years, n (%)	40 (31.5)	30 (33.3)	0.775
Male, n (%)	75 (59.1)	55 (61.1)	0.761
Caucasian, n (%)	117 (92.1)	74 (82.2)	0.031
Number of prior LoTs ≥ 3, n (%)	80 (69.3)	56 (62)	0.908
Prior ASCT, n (%)	30 (23.6)	19 (21.1)	0.663
Refractory to prior line, n (%)	86 (68)	62 (69)	0.855
ECOG PS 1, n (%)	48 (37.8)	37 (41.1)	0.622
Disease stage III/IV, n (%)	109 (85.8)	69 (76.7)	0.086
Bulky disease, n %	65 (51.2)	31 (34.4)	0.015
FLIPI Score – High/ ≥3, n (%)	56 (44.1)	40 (44.4)	0.959
POD24, n (%)	83 (65.3)	47 (52)	0.053
Double refractory, n (%)	74 (58.3)	48 (53)	0.471

ASCT: Autologous stem cell transplant; ECOG: Eastern Cooperative Oncology Group; FAS: Full analysis set; FLIPI: Follicular Lymphoma International Prognostic Index; LoT: Line of therapy; PS: Performance status; POD24: Progression of disease within 24 months

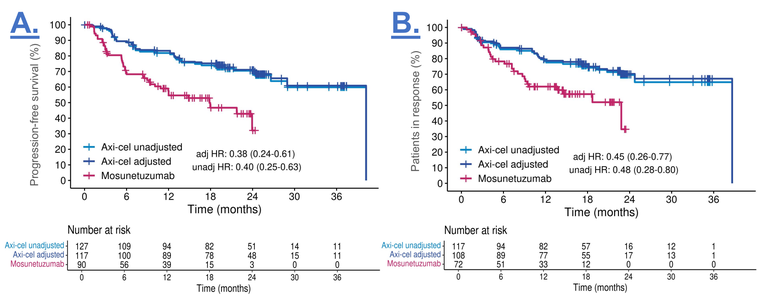
- An overview of the primary analyses for each outcome is presented in **Figure 1**. Comparisons to mosunetuzumab (n = 90) led to improved PFS (HR: 0.38; 95% CI: 0.23 – 0.61) and DOR (HR: 0.45; 95% CI: 0.26 – 0.77) with axi-cel. Results were also favourable for axi-cel for response outcomes.
- **Figure 2** presents the Kaplan-Meier plots for the time-to-event outcomes. Axi-cel led to statistically and clinically meaningful improvements in both PFS and DOR.

Figure 1. MAIC-adjusted treatment effects for axi-cel vs mosunetuzumab; IRC assessment



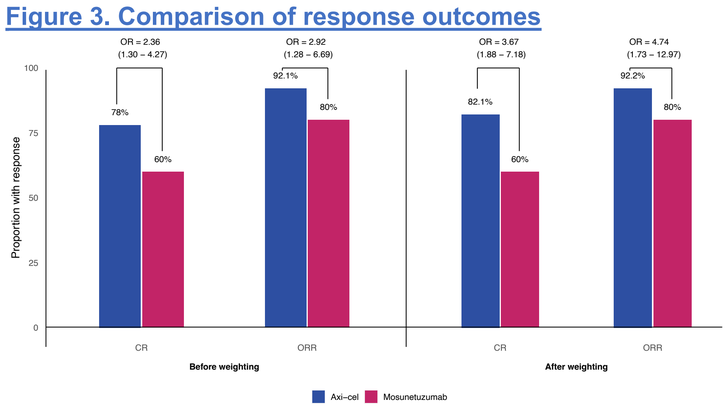
Axi-cel: Axicabtagene ciloleucel; CRS: Cytokine release syndrome; HR: Hazard ratio; OR: Odds ratio

Figure 2. Weighted and unweighted KM curves; FAS population; (A) PFS by IRC; (B) DoR by IRC



DoR: Duration of response; FAS: Full analysis set; HR: Hazard ratio; IRC: Independent review committee; KM: Kaplan-Meier; PFS: Progression-free survival

Figure 3. Comparison of response outcomes



CR: Complete response rate; OR: Odds ratio; ORR: Objective response rate

- Results for the responses outcomes are presented in **Figure 3**. The odds ratio for ORR was 4.74 (95% CI: 1.73 – 12.97), and for CR it was 3.67 (95% CI: 1.88 – 7.18) for the IRC analyses.
- In addition to these analyses, the sensitivity analyses using investigator assessed response/progression showed improved PFS (HR: 0.61; 95% CI: 0.39-0.95) with axi-cel, while DOR favoured axi-cel but was not statistically significant (HR: 0.65; 95% CI: 0.39-1.06).
- In both cases, the adjusted estimates were similar to the naïve estimates, underscoring the fact that the populations were reasonably similar prior to matching.
- Sensitivity analyses using infusion date as index date and adjusting for more patient characteristics led to similar results (not shown).
- Safety outcomes were examined using the safety analysis set (SAS) consisting of only infused patients (n = 124), and axi-cel patients experienced all-grade cytokine release syndrome (CRS) and neurological events (NEs) at a greater rate than mosunetuzumab patients (**Table 4**).
- When restricting to only grade 3 or 4, the OR for severe CRS was reduced to 2.83 and the 95% CI (0.58 – 13.95) showed that this was no longer statistically significant.

Table 4. ORs for adverse events based on MAIC weighting

Adverse event	Any Grade, n (%) ZUMA-5 SAS (n = 124)	Any Grade, n (%) GO29781 (n = 90)	Grade 3-4, n (%) ZUMA-5 SAS (n = 124)	Grade 3-4, n (%) GO29781 (n = 90)	Any Grade Odds ratio (95% CI)	Grade 3-4 Odds ratio (95% CI)
Cytokine release syndrome	97 (78)	40 (44)	8 (6)	2 (2)	4.85 (2.63 - 8.94)	2.83 (0.58 - 13.95)
Neurological events	70 (56)	5 (5)	19 (15)	0 (0)	3.39 (1.22 - 9.46)	--
Treatment related AEs	--	83 (92)	74 (58)	46 (51)	--	1.26 (0.73 - 2.19)

AEs: Adverse events; CI: Confidence interval; SAS: Safety analysis set

CONCLUSIONS

- This is the first study to provide comparative effectiveness and safety of axi-cel and mosunetuzumab.
- This MAIC of ZUMA-5 and GO29781 shows improved effectiveness and more durable response with axi-cel for the treatment of 3L+ r/r FL. This study also shows increased odds of all-grade CRS and NE, but not G3+ CRS and treatment-related adverse events (TRAEs).
- A strength of this study was the high effective sample size, which increases confidence that the adjustments are not overemphasizing spurious relationships. Another strength is that both POD24 and prior LoT were re-defined to align with the definitions used by GO29781 (i.e., there was no alignment of variables with differing definitions).
- The most important limitation to this study was the unanchored design and having some prognostic factors unavailable for alignment, namely, time from last treatment, elevated LDH and baseline metabolic tumour volume (MTV). This is a limitation shared with other similar studies in this space.
- Another notable limitation is the need for more mature OS data for mosunetuzumab. Similarly, the latest data cut for GO29781 only reported on IA data, with IRC only available in an earlier data cut. Both outcomes were analysed.

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DISCLOSURES

MDR, SB, TB, JW, and ARP: Employment or leadership position - Kite, A Gilead company; Stock ownership - Kite, A Gilead company. **SK and EHLO**: Employment or Leadership position: RainCity Analytics; Research funding: RainCity Analytics has received funds from for-profit healthcare companies for research. **OOO**: Consultant or advisory role: Pfizer, Gilead/Kite, AbbVie, Janssen, TGR Therapeutics, ADC, Novartis, Epizyme, Curio Science, Nektar, Syncopation. Honoraria: Pfizer, Gilead.

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