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Matching-Adjusted Indirect Comparison (MAIC) of Axicabtagene Ciloleucel (axi-cel) and Glofitamab (glofit) in Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL) After at Least Two Prior Systemic Therapies (3L+)

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BACKGROUND

- LBCL is the predominant form of non-Hodgkin lymphoma and current established first-line treatment involves immunochemotherapy whereby an anti-CD20 antibody is combined with cytotoxic agents including cyclophosphamide, doxorubicin, vincristine, and prednisone.[1]
- As approximately 40-50% of patients become refractory to or relapse after treatment, further investigation of treatment options in these settings is therefore warranted.[2]
- Axi-cel is a chimeric antigen receptor T-cell (CAR T) therapy that has received approval by the US Food and Drug Administration (US FDA), based on findings from ZUMA-1, for the treatment of R/R LBCL after two or more lines of systemic therapy, and ZUMA-7, for treatment in second-line. [3-5]
- Glofit is a bispecific antibody evaluated in NP30179 and had also received US FDA approval for the treatment of R/R LBCL after two or greater lines of therapy.[6]
- In the absence of head-to-head randomized controlled trials, relative treatment effects for these two therapies must be estimated from unanchored between-trial comparisons of reported treatment effects.

OBJECTIVES

- To estimate relative treatment effects of axi-cel versus glofit for the treatment of R/R LBCL in the third line or greater setting by means of an MAIC.

METHODS

- A pre-specified logistic propensity score model was used to weigh ZUMA-1 (axi-cel) individual patient-level data to match the mean baseline characteristics in NP30179 (glofit).
- 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), overall survival (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 reported as hazard ratios (HRs) or odds ratios (ORs) for axi-cel versus glofit along with their 95% confidence intervals (CIs).
- For time-to-event outcomes, relative treatment effects were also summarized in terms of the difference in restricted mean survival time (RMST, with 95% CI), which reflects the area under the curve up to the time corresponding to the shortest follow-up of the two 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 63.1 months) and published outcomes for glofit (median follow-up, 12.6 months).
- Scenario analyses for OS and safety included ZUMA-1 additional safety management Cohort 4 (N=41; median follow-up, 24 months) and Cohort 6 (N=40; median follow-up, 26.9 months).
- Matched variables deemed clinically relevant by experts were Eastern Cooperative Oncology Group Performance Status (ECOG PS), disease stage, response to last therapy, prior lines of therapy, lactate dehydrogenase (LDH), primary refractoriness, LBCL subtype, and prior autologous stem cell transplant (auto-SCT) (**Table 1**).

RESULTS

PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS

- Prior to matching, the axi-cel and glofit trial populations differed for most of the included covariates (**Table 1**).
- Refractory disease in ZUMA-1 was recategorized to match NP30179 and defined as patients who had no response, progression, or relapse within 6 months of last therapy.
- Model convergence was achieved using the full set of covariates, and after matching, these baseline characteristics were balanced between the two trial populations.

Table 1. Baseline characteristics in ZUMA-1 before and after matching to NP30179

Variable		Base case analysis: ZUMA-1 Cohorts 1+2		Scenario analysis: ZUMA-1 Cohorts 1+2+4+6		NP30179 (N=155)
		Observed (N=101)	MAIC matched (ESS=31.5)	Observed (N=182)	MAIC matched (ESS=62.7)	
ECOG PS 0		41.6	44.8	44.5	44.8	44.8
Disease stage III-IV		85.1	75.3	77.5	75.3	75.3
Refractory to last therapy		96.0	85.2	91.8	85.2	85.2
≥3 prior therapies		61.4	59.4	54.4	59.4	59.4
Elevated LDH >250 U/L		66.7	61.9	62.6	61.9	61.9
Primary refractory		25.7	58.4	20.9	58.4	58.4
B-cell lymphoma subtypes	HGBCL	24.8	7.1	26.4	7.1	7.1
	DLBCL	51.5	71.0	48.9	71.0	71.0
	TFL	15.8	18.1	19.2	18.1	18.1
Prior auto-SCT		24.8	18.6	26.9	18.6	18.6

Abbreviations: auto-SCT, autologous stem cell transplant; 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; PS, performance status; TFL, transformed follicular lymphoma.

MATCHING-ADJUSTED INDIRECT COMPARISONS

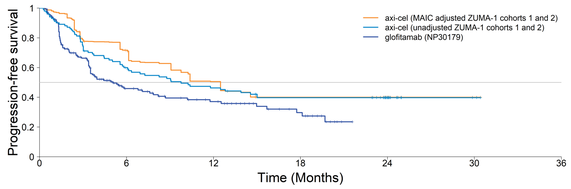
- Results from the MAIC are reported in **Table 2**, with naïve comparisons shown for informative purposes only.
- The effective sample size (ESS) of the axi-cel population after weighting was approximately 31% and 34% of the original sample size for the base-case and scenario analyses, respectively.
- The estimated ORs for objective response favored axi-cel and results were statistically significant.
- Axi-cel was associated with improved PFS compared with glofit (HR: 0.62, 95% CI: 0.40, 0.96); the PFS RMST for the 22-month follow-up was 3.21 months (95% CI: -0.04, 6.47) longer with axi-cel (**Figure 1**).
- In the scenario analysis, axi-cel improved OS (**Figure 2**) compared with glofit (HR: 0.63, 95% CI: 0.42, 0.95) with a difference in RMST of 3.27 months (95% CI: 0.66, 5.88) for the 24-month follow-up.
- Axi-cel was associated with a higher rate of Grade ≥3 CRS and NEs relative to glofit but the differences were reduced in the scenario analyses.
- Results of the leave-one-out sensitivity analysis, whereby covariates were excluded one at a time in the propensity score model, suggested primary refractoriness, LBCL subtype, and response to last therapy had the greatest impact on MAIC weights and, subsequently, results.

Table 2. Naïve and MAIC-weighted relative treatment effect estimates of axi-cel versus glofit

Outcomes	Naïve estimates	MAIC estimates	
		Base case	Scenario
Efficacy outcomes, tumor response – OR (95% CI)			
Objective response	**2.70 (1.57, 4.67)**	**2.32 (1.01, 5.33)**	--
Complete response	**1.84 (1.11, 3.06)**	1.72 (0.80, 3.71)	--
Efficacy outcomes, time-to-event outcomes – HR (95% CI)			
Progression-free survival	**0.69 (0.50, 0.97)**	**0.62 (0.40, 0.96)**	--
Duration of response	0.96 (0.57, 1.61)	0.72 (0.35, 1.48)	--
Overall survival	**0.65 (0.45, 0.94)**	0.70 (0.42, 1.18)	**0.63 (0.42, 0.95)**
Safety outcomes – OR (95% CI)			
CRS, Grade 1-2	3.19 (1.75, 5.83)	2.01 (0.85, 4.74)	3.19 (1.55, 6.57)
CRS, Grade ≥3	3.01 (1.08, 8.43)	4.93 (1.42, 17.08)	2.83 (0.89, 8.97)
NEs, Grade 1-2	0.98 (0.58, 1.66)	0.85 (0.38, 1.94)	1.07 (0.58, 1.97)
NEs, Grade ≥3	13.20 (4.92, 35.39)	22.59 (7.25, 70.36)	15.54 (5.53, 43.63)

Notes: All bolded values are statistically meaningful at the 0.05 significance level. **Abbreviations**: CI, confidence interval; CRS, cytokine release syndrome; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NEs, neurological events; OR, odds ratio.

Figure 1. Progression-free survival of axi-cel and glofitamab

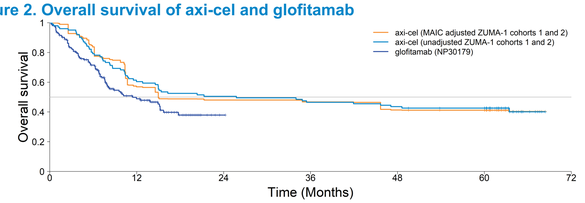


N or ESS at risk over time

axi-cel adjusted	32	25	22	20	16	11	11	11	6	1	1	
axi-cel unadjusted	101	74	58	50	44	37	35	35	19	3	2	
glofitamab	155	92	47	35	29	18	13	1				

Abbreviations: ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

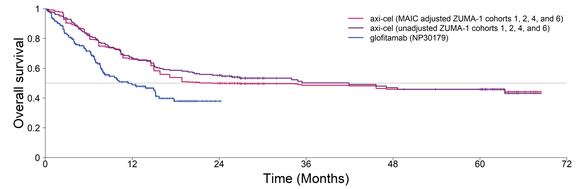
Figure 2. Overall survival of axi-cel and glofitamab



N or ESS at risk over time

axi-cel adjusted	32	29	26	24	18	16	15	15	15	15	15	15	15	15	13	13	13	13	13	7	1		
axi-cel unadjusted	101	96	80	70	61	56	53	52	51	50	50	50	47	47	46	46	44	42	41	41	41	20	6
glofitamab	155	121	97	58	49	33	20	5	1														

Abbreviations: ESS, effective sample size; MAIC, matching-adjusted indirect comparison.



N or ESS at risk over time

axi-cel adjusted	63	57	52	46	41	37	34	31	31	25	21	18	17	17	17	17	16	16	16	16	9	1	
axi-cel unadjusted	182	169	148	134	121	112	106	101	98	72	54	50	47	47	46	46	44	42	41	41	41	20	6
glofitamab	155	121	97	58	49	33	20	5	1														

Abbreviations: ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

LIMITATIONS

- Prognostic characteristics that needed adjustment in the MAIC were determined based on clinical expert recommendation; however, the analysis was limited to data availability as variables had to be reported in both trials for matching; for example, International Prognostic Index score was not feasible to be matched on due to not being reported in NP30179.
- Common to comparisons of single-arm or non-comparative studies, estimates may be susceptible to residual bias given uncertainty regarding any unknown or unmeasured prognostic factors/effect-modifiers not captured in the selected model which may impact the observed outcome of interest.
- A proportion of patients in NP30179 were not eligible for ZUMA-1 (34% received prior CAR T therapy) and this difference could not be accounted for in the MAIC without individual patient level data from NP30179; although it is important to note that the impact of prior CAR T exposure on survival estimates is unclear.
- The toxicity management program was only investigated in ZUMA-1 Cohorts 4+6 (N=81) which has been shown to lower rates of grade 3 or higher CRS.[7]
- Given limited 1-year median follow-up data from NP30179, an update to the current analysis will be important once more mature data becomes available for NP30179.

CONCLUSIONS

- Based on the available evidence, this analysis suggests that axi-cel may be more efficacious in terms of ORR and PFS versus glofit among R/R LBCL patients receiving treatment in the third line or greater setting.
- Axi-cel was associated with improved OS compared to glofit based on both the naïve and MAIC scenario analyses; the OS HR point estimate also favored axi-cel in the base-case MAIC but the difference was not statistically significant.
- Axi-cel was associated with a higher risk of grade 3 or higher CRS and NEs relative to glofit; however, axi-cel's risk-benefit profile has improved over time likely owing to enhanced event management in clinical practice.[7,8]

REFERENCES

1. Tilly H, et al. Ann Oncol. 2015; 26:v116-25. DOI: 10.1093/annonc/mdv304
2. Chaganti S, et al. Br J Haematol. 2016;174(1):43-56. DOI: 10.1111/bjh.14136
3. Neelapu SS, et al. N Engl J Med. 2017;377(26):2531-2544. DOI: 10.1056/NEJMoa1707447
4. Locke FL, et al. Lancet Oncol. 2019;20(1):31-42. DOI: 10.1016/S1470-2045(18)30864-7
5. Locke FL, et al. N Engl J Med. 2021; 386(7):640-654. DOI: 10.1056/NEJMoa2116133
6. Dickinson MJ, et al. N Engl J Med. 2022;387(24):2220-31. DOI: 10.1056/NEJMoa2206913
7. Oluwole OO, et al. Br J Haematol. 2021; 194(4):690-700. DOI: 10.1111/bjh.17527
8. Bachy et al. Nat Med. 2022; 28(10):2145-2154. DOI: 10.1038/s41591-022-01969-y

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DISCLOSURES

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