Matching-adjusted indirect comparison (MAIC) of brexucabtagene autoleucel (brexu-cel) and pirtobrutinib in patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) previously treated with a covalent bruton tyrosine kinase inhibitor (cBTKI)

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INTRODUCTION

- Patients with MCL often require multiple lines of therapy and have a poor prognosis, particularly after failure of BTKi therapy.
- Brexu-cel is the only CAR T-cell therapy approved in the United States (US) for R/R MCL based on results from a phase 2 multicenter, single-arm trial (ZUMA-2; NCT02601313) in patients with R/R MCL who had 1–5 prior therapies, including a BTKi.[1,2]
- Pirtobrutinib, a non-covalent BTKi, was recently approved in the US for treatment of R/R MCL after at least two lines of systemic therapy including a cBTKi, based on results of the ongoing multicenter phase 1/2 study (BRUIN; NCT03740529).[3-5]
- Brexu-cel and pirtobrutinib have not been compared in a head-to-head randomized controlled trial.

AIM

- To estimate the relative treatment effects of brexu-cel versus pirtobrutinib for R/R MCL in the post-cBTKi setting via an unanchored MAIC.

METHODS

- Logistic propensity score models were used to weigh ZUMA-2 individual patient-level data (N=68 modified intention-to-treat [mITT] set) so that the mean baseline characteristics matched those observed in BRUIN (N=90 in the cBTKi pre-treated cohort).
- Clinically relevant prognostic factors were pre-specified based on input from clinical experts and data availability (see **Table 1**).
- The base-case model included the top five most pertinent factors reported in at least 50% of patients in both trials: 1) blastoid morphology, 2) MCL International Prognostic Index, 3) number of prior lines of therapy, 4) disease stage, and 5) prior autologous stem cell transplantation; the sensitivity analysis model additionally incorporated 6) TP53 mutation (>50% missing data in both trials) and 7) Ki-67 proliferation index (>50% missing data in BRUIN).
- The estimated effective sample size (ESS) measured the degree of precision after weighting, reflecting the extent of overlap in the distribution of covariates between trial populations.
- Outcomes were then compared across matched populations using logistic regression models for binary outcomes and Cox proportional hazards models for time-to-event outcomes.
- Outcomes of interest were objective response rate (ORR) as assessed by independent review committee (IRC), complete response (CR by IRC), duration of response (DOR by IRC), progression-free survival (PFS by IRC), and overall survival (OS).
- Median follow-up times were 35.6 months for ZUMA-2 and 23.5 months for BRUIN; longer-term OS data for ZUMA-2 (46.1 months median follow-up) were available and used.
- Relative treatment effects were expressed in terms of hazard ratios (HRs) or odds ratios (ORs) for brexu-cel versus pirtobrutinib along with their 95% confidence intervals (CIs).

RESULTS

PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS

- Prior to matching, the brexu-cel and pirtobrutinib trial populations differed for most included covariates (**Table 1**).
- 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-2 before and after matching to BRUIN

Characteristic		Observed ZUMA-2 mITT N=68	BRUIN N=90	Adjusted ZUMA-2 mITT	
				Base-case ESS=39.1	Sensitivity analysis ESS=16.5
Blastoid		25	9	9	9
MIPI	High risk	14	22	22	22
	Intermediate risk	44	56	56	56
>3 prior lines		37	34	34	34
Stage IV		85	78	78	78
Prior auto-SCT		43	19	19	19
TP53 mutation		17	47	18	47
Ki-67 index ≥30%		83	74	82	74
Bulky disease ≥10 cm		10	3	11	18
Bone marrow involvement		55	51	59	70
Extranodal disease		56	39	56	65
Prior BTKi	Any BTKi	100	100	100	100
	Ibrutinib	85	66	90	91
Male		84	80	84	89

Notes: *All values reported in percentages. Variables shaded in grey were not included in the indicated model.* ***Abbreviations****: auto-SCT, autologous stem cell transplant; BTKi, Bruton's tyrosine kinase inhibitor; ESS, effective sample size; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MIPI, MCL International Prognostic Index; mITT, modified intention-to-treat.*

MATCHING-ADJUSTED INDIRECT COMPARISONS

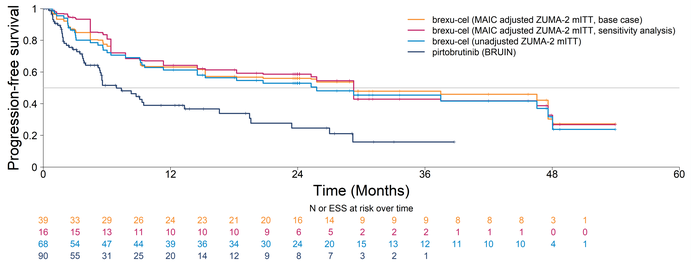
- Results from the MAIC are summarized in **Table 2** with those from the unadjusted (naïve) comparisons (latter presented for informative purposes only).
- The brexu-cel population ESS after weighting was reduced by approximately 43% and 76% of the original sample size for the base-case and sensitivity analyses, respectively.
- Brexu-cel was associated with statistically significant improvement in ORR (OR: 10.39, 95% CI: 2.81, 38.46) and CR (OR: 10.11, 95% CI: 4.26, 24.00) compared to pirtobrutinib.
- Brexu-cel was also associated with statistically significant improvement in PFS compared with pirtobrutinib in the base case (HR: 0.44, 95% CI: 0.25, 0.75) and sensitivity analysis (HR: 0.41, 95% CI: 0.20, 0.85; **Figure 1**).
- HR point estimates for OS (**Figure 2**) and DOR (**Figure 3**) favored brexu-cel over pirtobrutinib, but the confidence intervals crossed the bounds for statistical significance.

Table 2. Naïve and MAIC-weighted relative treatment effect estimates

Outcomes	Brexu-cel vs pirtobrutinib		
	Unadjusted	MAIC, base-case	MAIC, sensitivity analysis
Efficacy outcomes, tumor response – OR (95% CI)			
Objective response	7.90 (3.10, 20.15)	10.39 (2.81, 38.46)	18.95 (1.50, 238.71)
Complete response	8.98 (4.32, 18.68)	10.11 (4.26, 24.00)	15.01 (4.20, 53.70)
Efficacy outcomes, time-to-event outcomes – HR (95% CI)			
Progression-free survival	0.48 (0.31, 0.75)	0.44 (0.25, 0.75)	0.41 (0.20, 0.85)
Overall survival	0.68 (0.41, 1.12)	0.61 (0.34, 1.10)	0.50 (0.23, 1.11)
Duration of response	0.67 (0.38, 1.17)	0.60 (0.31, 1.17)	0.59 (0.25, 1.39)

Abbreviations*: CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OR, odds ratio.*

Figure 1. Progression-free survival of brexu-cel and pirtobrutinib



For ZUMA-2, the Kaplan-Meier curve was based on individual patient data whereas for BRUIN, the published Kaplan-Meier curve was digitized from Shah et al. 2022[5] (data cut-off: July 29, 2022). ***Abbreviations****: ESS, effective sample size; MAIC, matching-adjusted indirect comparison; mITT, modified intention-to-treat; N, sample size.*

Figure 2. Overall survival of brexu-cel and pirtobrutinib

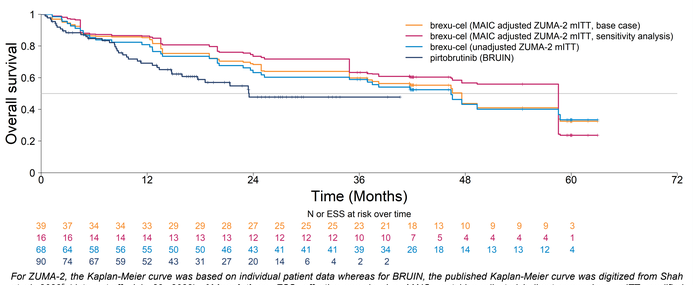


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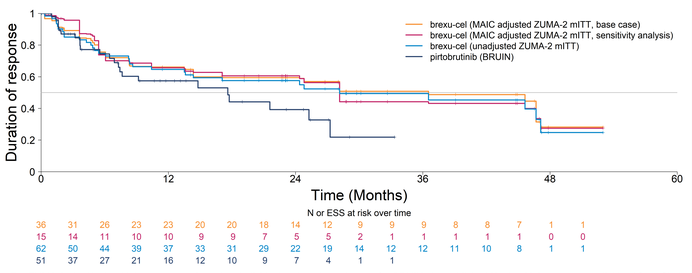
Figure 3. Duration of response of brexu-cel and pirtobrutinib



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STRENGTHS/LIMITATIONS

- Results were consistent across the adjusted (both base-case and sensitivity analyses) and unadjusted comparisons, suggesting that the results were not sensitive to adjustment for different covariates.
- Despite efforts to ensure a robust approach to the selection of prognostic factors for inclusion in the model, the possibility of residual confounding cannot be completely ruled out, which is an inherent limitation of the MAIC method.
  - Several potentially relevant prognostic factors (response to prior BTKi therapy, response to last therapy, and duration on prior BTKi therapy) could not be considered as they were not reported for BRUIN.
  - In BRUIN, patients discontinued their prior BTKi due to disease progression (82.2%), intolerance/toxicity (13.3%), or other reasons (4.4%) whereas all patients in ZUMA-2 had previously discontinued BTKi due to disease progression; while reason for prior BTKi discontinuation could not be adjusted for, it is important to highlight that patients who discontinued due to intolerance may have better prognosis.
- Differences between brexu-cel and pirtobrutinib for OS and DOR crossed the bounds for statistical significance although point estimates favored brexu-cel.
  - Note, MAICs cannot be considered equivalent to a randomized controlled trial; therefore, the ability to detect statistically significant differences for outcomes with small numbers of events is limited, particularly when the starting sample sizes for the included non-randomized studies are low.
  - Given the relatively shorter follow-up and the high degree of censoring in BRUIN, an updated analysis incorporating more mature BRUIN data (with more events) may provide more definitive OS results.
  - Differences in subsequent therapy between the two trials may also have impacted the OS results; of note, 17 (18.9%) of patients in BRUIN went on to receive subsequent CAR T-cell therapy after pirtobrutinib.

CONCLUSIONS

- Results from this MAIC suggest that brexu-cel offers clinically and statistically significant efficacy benefits in terms of ORR, CR, and PFS compared to pirtobrutinib in patients with R/R MCL after prior cBTKi therapy.
- Study findings suggest that brexu-cel remains an important treatment option and may be the preferred therapy for patients with R/R MCL who have previously received cBTKi therapy.

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