The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

905.OUTCOMES RESEARCH-LYMPHOID MALIGNANCIES

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 exhibit a generally unfavorable prognosis, particularly following failure of cBTKi therapy. Therapies such as chimeric antigen receptor (CAR) T-cell therapies and non-covalent BTKi therapies have shown promise in improving outcomes. Brexu-cel (formerly known as KTE-X19) is the only CAR T-cell therapy approved in the 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. Pirtobrutinib, a highly selective, 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 BTKi, based on ongoing results from a multicenter phase 1/2 study (BRUIN; NCT03740529). In the absence of a direct head-to-head trial comparing brexu-cel and pirtobrutinib, we performed an unanchored MAIC to estimate the relative treatment effects of these therapies in the post-BTKi setting for R/R MCL.

Methods: Individual patient-level data were available for ZUMA-2 (N=68; 35.8 months median follow-up as of July 24, 2021 data cut-off) whereas study-level data were available for BRUIN (N=90 in the BTKi pre-treated cohort; 23.5 months median follow-up as of July 29, 2022 data cut-off). Longer-term overall survival (OS) data for ZUMA-2 from the July 23, 2022 data cut-off (46.1 months median follow-up) were available and used. Logistic propensity score models were used to weight the brexu-cel infused population from ZUMA-2 to match the aggregate baseline characteristics of the BTKi pre-treated cohort in BRUIN. These baseline characteristics represented clinically relevant prognostic factors which were pre-specified based on input from clinical experts and data availability. The base-case model incorporated the top five most pertinent factors, which were reported in at least 50% of patients in both trials: blastoid morphology, MCL International Prognostic Index, number of prior lines of therapy, disease stage, and prior autologous stem cell transplantation. A sensitivity analysis additionally incorporated TP53 mutation (missing in >50% of patients in ZUMA-2 and BRUIN) and Ki-67 proliferation index (missing in >50% of patients in BRUIN). Several prognostic factors (response to prior BTKi therapy, response to last therapy, and duration on prior BTKi therapy) could not be considered due to not being reported for BRUIN. The effective sample size was calculated as a measure of the degree of precision after weighting, reflecting the extent of overlap in the distribution of covariates between the trial populations. Relative treatment effects were expressed as odds ratios or hazard ratios with 95% confidence intervals. Outcomes included objective response (ORR), complete response (CR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: In the base-case MAIC, a significant difference in the odds of ORR and CR in favor of brexu-cel versus pirtobrutinib was observed (Table 1). Similarly, brexu-cel demonstrated a significant improvement in PFS (Table 2). OS and DOR point estimates were in favor of brexu-cel when compared to pirtobrutinib, although not statistically significant. These findings were consistent with unadjusted naïve analyses as well as the sensitivity analyses including adjustment for TP53 mutation and Ki-67 proliferation index.

Conclusions: While acknowledging the inherent limitations of an unanchored indirect comparison, our findings 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. Both treatments were not statistically different in terms of OS and DOR

although the estimated hazard ratios indicated a favorable trend for brexu-cel; however, given the relatively shorter follow-up and the high degree of censoring in BRUIN, an updated analysis incorporating longer follow-up data with more events from BRUIN could provide more reliable results. Although efforts were made to ensure a robust approach to the selection of prognostic factors for inclusion in the model, the possibility of some residual confounding variables cannot be completely ruled out. Nevertheless, these results provide valuable insights that may help inform treatment decisions for this population.

Disclosures Chen: *PRECISIONheor:* Current Employment, Other: PRECISIONheor is a consultancy firm which received funding for this study from Kite, a Gilead Company. **Zhang:** *PRECISIONheor:* Current Employment, Other: PRECISIONheor is a consultancy firm which received funding for this study from Kite, a Gilead Company. **Wu:** *Gilead Sciences:* Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Divested equity in a private or publicly-traded company in the past 24 months, Other; *Abbott:* Current holder of *stock options* in a privately-held company, Other; *AbbVie:* Current holder of *stock options* in a privately-held company, Other; *Amgen:* Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Divested equity in a private or publicly-traded company in the past 24 months, Other; *Avid:* Current holder of *stock options* in a privately-held company, Other; *Curis:* Current holder of *stock options* in a privately-held company, Other; *Viracta:* Current holder of *stock options* in a privately-held company, Other. **Wade:** *Kite, a Gilead Company:* Consultancy; *Abbvie:* Consultancy. **Nunes:** *Amgen:* Current holder of *stock options* in a privately-held company; *Gilead Sciences Europe Ltd:* Current Employment, Current holder of *stock options* in a privately-held company, Honoraria. **Peng:** *Gilead Sciences:* Current Employment, Current equity holder in publicly-traded company. **Snider:** *Kite/Gilead Sciences:* Current Employment, Current equity holder in publicly-traded company. **Maciel:** *PRECISIONheor:* Current Employment, Other: PRECISIONheor is a consultancy firm which received funding for this study from Kite, a Gilead Company. **Chan:** *PRECISIONheor:* Current Employment, Other: PRECISIONheor is a consultancy firm which received funding for this study from Kite, a Gilead Company. **Keeping:** *PRECISIONheor:* Current Employment, Other: PRECISIONheor is a consultancy firm which received funding for this study from Kite, a Gilead Company. **Shah:** *Moffitt Cancer Center:* Current Employment; *DSMC, Pepromene Bio:* Membership on an entity's Board of Directors or advisory committees; *Pharmacyclics/Janssen, Spectrum/Acrotech, BeiGene, Gilead Sciences:* Honoraria; *Incyte, Jazz Pharmaceuticals, Kite/Gilead, SERVIER:* Research Funding; *Celgene, Novartis, Pfizer, Janssen, Seattle Genetics, AstraZeneca, Stemline Therapeutics, Kite/Gilead:* Other: Travel, Accommodations, Expenses; *Takeda, AstraZeneca, Adaptive Biotechnologies, BMS/Celgene, Novartis, Pfizer, Amgen, Precision Biosciences, Kite/Gilead, Jazz Pharmaceuticals, Century Therapeutics, Deciphera, Autolus Therapeutics, Lilly, Pepromene:* Consultancy.

Table 1: Comparison of ORR and CR between brexu-cel (ZUMA-2) and pirtobrutinib (BRUIN)

Outcome	Brexu-cel		Pirtobrutinib		Brexu-cel vs pirtobrutinib	
	N or ESS	Event (%)	N	Event (%)	Odds ratio (95% CI)	*P* value
Unadjusted (naïve) comparison						
ORR	68	62 (91.2)	90	51 (56.7)	**7.90 (3.10, 20.15)**	<0.01
CR	68	46 (67.6)	90	17 (18.9)	**8.98 (4.32, 18.68)**	<0.01
MAIC: Base case model with 5 variables						
ORR	41.7	38.5 (92.4)	90	51 (56.7)	**9.29 (2.75, 31.44)**	<0.01
CR	41.7	28.7 (68.8)	90	17 (18.9)	**9.47 (4.08, 21.96)**	<0.01
MAIC: Sensitivity analysis model with 7 variables						
ORR	17.0	16.3 (96.0)	90	51 (56.7)	**18.35 (1.57, 215.12)**	0.02
CR	17.0	13.1 (76.9)	90	17 (18.9)	**14.33 (4.12, 49.81)**	<0.01

Notes: All bolded odds ratio values are statistically meaningful at the 0.05 significance level. **Abbreviations:** *CI, confidence interval; CR, complete response; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; N, sample size; ORR, objective response.*

Table 2: Comparison of OS, PFS, and DOR between brexu-cel (ZUMA-2) and pirtobrutinib (BRUIN)

Outcome	Brexu-cel		Pirtobrutinib		Brexu-cel vs pirtobrutinib	
	N or ESS	Median (months)	N	Median (months)	Hazard ratio (95% CI)	*P* value
Unadjusted (naïve) comparison						
OS	68	46.4	90	23.5	0.68 (0.41-1.12)	0.13
PFS	68	25.8	90	6.9	**0.48 (0.31-0.75)**	<0.01
DOR	62	28.2	51	17.6	0.67 (0.38-1.17)	0.16
MAIC: Base case model with 5 variables						
OS	41.7	46.6	90	23.5	0.65 (0.37-1.14)	0.13
PFS	41.7	29.3	90	6.9	**0.45 (0.27-0.77)**	<0.01
DOR	37.7	36.5	51	17.6	0.62 (0.33-1.19)	0.15
MAIC: Sensitivity analysis model with 7 variables						
OS	17.0	58.5	90	23.5	0.54 (0.25-1.18)	0.12
PFS	17.0	29.3	90	6.9	**0.43 (0.21-0.87)**	0.02
DOR	15.8	28.2	51	17.6	0.62 (0.27-1.43)	0.26

Notes: All bolded hazard ratio values are statistically meaningful at the 0.05 significance level. **Abbreviations:** *CI, confidence interval; DOR, duration of response; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; N, sample size; OS, overall survival; PFS, progression-free survival.*

Figure 1

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