Matching-adjusted indirect comparison (MAIC) of zanubrutinib (ZANU) versus ibrutinib (IBRU) in relapsed/refractory marginal zone lymphoma (R/R MZL)

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Background: ZANU is a Bruton tyrosine kinase inhibitor (BTKi) that has been evaluated for the treatment of R/R MZL in two phase 2, single-arm trials (MAGNOLIA, n=66, NCT03846427; BGB-3111-AU-003, n=20, NCT02343120). At 28 and 35 months of study follow-up in MAGNOLIA and BGB-3111-AU-003, respectively, median progression-free survival (PFS) and overall survival (OS) were not reached. IBRU, a first-generation BTKi, has also been evaluated for R/R MZL in a phase 2, single-arm trial (PCYC-1121, n=60 [Noy et al., *Blood* 2017; Noy et al., *Blood Adv* 2020]). Here, we conducted an unanchored MAIC to estimate the comparative efficacy of ZANU vs IBRU in R/R MZL.

Methods: The MAIC utilized study-level data from PCYC-1121 and pooled individual patient-level data from MAGNOLIA and BGB-3111-AU-003. A logistic propensity score model was used to estimate weights for patients in the ZANU trials so that weighted mean baseline characteristics matched those in PCYC-1121. The following characteristics were identified as key prognostic factors and included in the base case propensity score model: number of prior lines of therapy, MZL subtype, response to prior therapy, and age. A sensitivity analysis was conducted including additional characteristics (B symptoms, time since last therapy, prior anti-CD20 therapy, bulky disease [>5cm], and lactate dehydrogenase above normal). Comparisons were conducted for OS, PFS, and objective response rate (ORR) by independent review committee using weighted statistical models with relative treatment effects presented as hazard ratios (HRs), odds ratios (ORs), and 95% CIs.

Results: After applying weights estimated from the base case propensity score model, the effective sample size (ESS) for ZANU was 68 (Table). Compared with IBRU, ZANU reduced the risk of progression (HR 0.38; 95% CI 0.21-0.69) and was associated with a higher ORR (OR 2.37; 95% CI: 1.13-4.96). OS was comparable for ZANU and IBRU, which is consistent with expectations for indolent lymphomas. The sensitivity analysis accounting for additional prognostic factors suggested the two treatments were comparable across all outcomes, owing in part to the low ESS (24) for ZANU associated with the expanded model. A leave-one-out analysis showed improved PFS (HR 0.33–0.45) for ZANU when excluding B symptoms, time since last therapy, or bulky disease from the expanded model.

Conclusions: This MAIC demonstrated ORR and PFS benefits for ZANU vs IBRU in R/R MZL.

Table: Efficacy outcomes

Covariates, %	IBRU (n=60)	ZANU unweighted (n=86)	ZANU weighted (ESS=68)
2 prior lines; ≥3 prior lines	30.0; 33.3	30.2; 25.6	30.0; 33.3
Nodal MZL; Splenic MZL	28.3; 21.7	36.6; 22.0	28.3; 21.7
Refractory to last therapy	22.2	30.1	22.2
Aged ≥65 years	60.0	65.1	60.0
Results ZANU vs IBRU (95% CI)			
ORR OR		2.64 (1.32, 5.28)	2.37 (1.13, 4.96)
PFS HR		0.38 (0.22, 0.65)	0.38 (0.21, 0.69)
OS HR		0.61 (0.30, 1.22)	0.68 (0.34, 1.39)