

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

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**Introduction:** 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 (PSM) was used to estimate weights for patients in the ZANU trials so that weighted mean baseline characteristics matched those in PCYC-1121. Number of prior lines of therapy, MZL subtype, response to prior therapy, and age were identified as key prognostic factors and included in the base case PSM. A sensitivity analysis was conducted including additional characteristics (B symptoms, time since last therapy, prior anti-CD20 therapy, bulky disease [ $>5\text{cm}$ ], 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% confidence intervals (CIs).

**Results:** After applying weights estimated from the base case PSM, the effective sample size (ESS) for ZANU was 68 (Table). Compared with IBRU, ZANU significantly reduced the risk of progression (HR 0.38; 95% CI: 0.21, 0.69;  $p=0.001$ ) and was associated with a higher ORR (OR 2.37; 95% CI: 1.13, 4.96;  $p=0.022$ ). OS was comparable for ZANU and IBRU, which is consistent with expected survival for indolent lymphomas. The sensitivity analysis accounting for additional prognostic factors suggested the 2 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

<b>Covariates, %</b>	<b>IBRU (n=60)</b>	<b>ZANU unweighted (n=86)</b>	<b>ZANU weighted (ESS=68)</b>
2 prior lines	30.0	30.2	30.0
≥3 prior lines	33.3	25.6	33.3
Nodal MZL	28.3	36.6	28.3
Splenic MZL	21.7	22.0	21.7
Refractory to last therapy	22.2	30.1	22.2
Aged ≥65 years	60.0	65.1	60.0
<b>Results ZANU vs IBRU (95% CI)</b>			
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)