Comparative efficacy of zanubrutinib (ZANU) versus rituximab (RTX) in relapsed marginal zone lymphoma (MZL): matching-adjusted indirect comparison (MAIC)

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Background: ZANU is a Bruton tyrosine kinase inhibitor that has been evaluated for relapsed/refractory MZL in two phase 2, single-arm (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. Here, we conducted an unanchored MAIC to estimate relative treatment effects of ZANU vs RTX, a commonly used treatment for patients with relapsed MZL. Note the comparison was restricted to the relapsed population because RTX refractory patients would not be retreated with RTX.

Methods: The MAIC was performed using pooled individual patient-level data from MAGNOLIA and BGB-3111-AU-003. Study level-data of RTX in relapsed patients were used from CHRONOS-3 (Özcan et al., *Ann Oncol* 2021) which was identified as the most suitable comparator study via a systematic literature review. A logistic propensity score model was used to estimate weights for patients in ZANU trials such that their weighted mean baseline characteristics matched those of CHRONOS-3. The following characteristics were identified as key prognostic factors and included in the base case propensity score model: prior lines of therapy, MZL subtype, relapse after prior therapy, and age. Sensitivity analyses incorporating additional characteristics were not possible owing to a lack of reporting from CHRONOS-3, but the impact of each covariate in the base model was explored via a leave-one-out analysis. 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 39. ZANU reduced the risk of progression (HR 0.29; 95% CI 0.13–0.65) and had a higher probability of response (OR 5.09; 95% CI: 1.84–14.08) when compared with RTX (Table). OS was comparable for ZANU and RTX, which is consistent with the survival expectancy for indolent lymphomas. The leave-one-out analysis showed that removing any of the characteristics from the propensity score model yielded comparable results.

Conclusions: MAIC results suggest ZANU is associated with improved PFS and ORR compared with RTX in relapsed MZL.

Table: Efficacy outcomes

Covariates	RTX (n=29)	ZANU unweighted (n=86)	ZANU weighted (ESS=39)
2 prior lines; ≥3 prior lines, %	20.7; 13.8	30.2; 25.6	20.7; 13.8
Nodal MZL; Splenic MZL, %	41.4; 20.7	36.6; 22.0	41.4; 20.7
Relapse to last therapy, %	100	69.9	100
Median age, years	63	68	63
Results ZANU vs RTX (95% CI)			
ORR OR		3.51 (1.46, 8.44)	5.09 (1.84, 14.08)
PFS HR		0.29 (0.15, 0.56)	0.29 (0.13, 0.65)
OS HR		0.79 (0.28, 2.20)	0.73 (0.26, 2.01)