Matching-Adjusted Indirect Comparison (MAIC) of Zanubrutinib Versus Real-World Chemoimmunotherapy (CIT) or Chemotherapy (Chemo) in Relapsed/Refractory Marginal Zone Lymphoma (R/R MZL)

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Background: MZL is a rare indolent form of non-Hodgkin lymphoma, with high morbidity and decreased quality of life associated with relapsed disease. Zanubrutinib is a next generation Bruton tyrosine kinase inhibitor that has been approved for the treatment of R/R MZL in the EU and UK based on 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. While no standard of care currently exists for patients with R/R MZL, a repetition of rituximab-based CIT or chemo is recommended by clinical guidelines. To better understand the relative treatment effects of zanubrutinib and CIT or chemo, a cohort representative of the patients included in the zanubrutinib trials was identified from a United Kingdom (UK) registry, the Haematological Malignancy Research Network (HMRN).

Aims: An unanchored MAIC was conducted to estimate the comparative effectiveness of zanubrutinib versus CIT or chemo in R/R MZL.

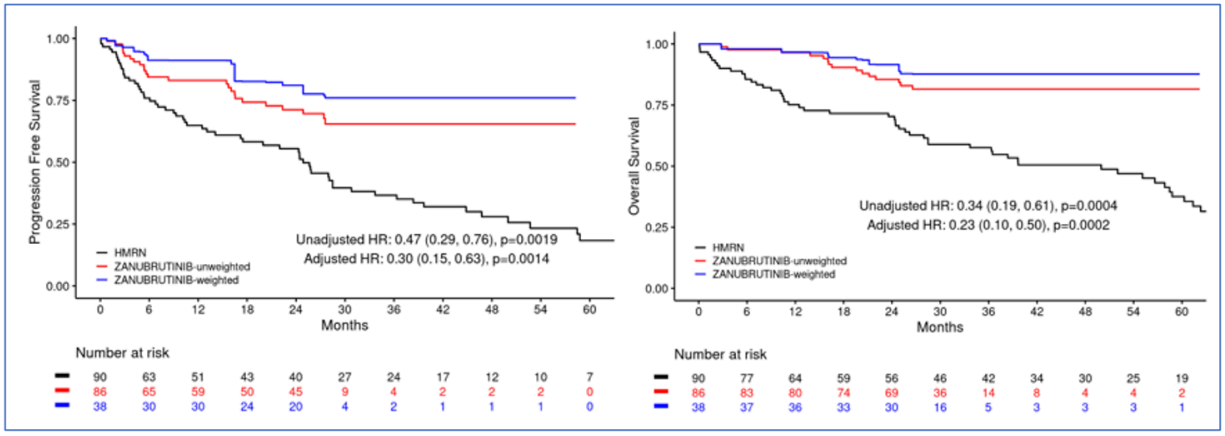
Methods: The MAIC utilized aggregate data from HMRN and pooled individual patient-level data from MAGNOLIA and BGB-3111-AU-003 (MAGNOLIA-003 hereafter). Real-world evidence on the effectiveness of CIT or chemo was based on a cohort of the HMRN registry constructed to resemble the patients included in MAGNOLIA-003. Overall, the HMRN cohort selected for analysis consisted of 90 patients who were enrolled from 2014 onwards, with an ECOG performance status ≤2 at this time, and who received CIT or chemo after having previously received at least one anti-CD20-based therapy. A logistic propensity score model was applied to estimate weights for patients in MAGNOLIA-003 such that weighted mean baseline characteristics matched those in the HMRN dataset. The following characteristics were pre-specified as key prognostic factors and considered for adjustment in the base case model: number of prior lines of therapy, refractory to prior therapy, age, progression of disease within 24 months of initiation of systemic therapy, and median time since diagnosis. Comparisons were conducted for PFS and OS. Relative treatment effects were estimated from Cox models and presented as hazard ratios (HRs) and 95% confidence intervals (CIs). A sensitivity analysis focused on old/frail patients receiving CIT only was also performed. Leave-one-out analyses were performed, whereby one covariate was omitted from the model at a time to explore the impact of each covariate on the model results.

Results: After applying weights estimated from the base case model, the effective sample size (ESS) for MAGNOLIA-003 was 38. Compared with CIT or chemo, zanubrutinib significantly reduced the risk of progression (HR 0.30; 95% CI 0.15–0.63, p=0.001) and death (HR 0.23; 95% CI 0.10–0.50, p<0.001) (Figure). The sensitivity analysis comparison of zanubrutinib (ESS=40) to CIT also demonstrated significantly reduced risk of progression (HR: 0.28; 95% CI 0.14-0.57, p<0.001) and death (HR: 0.23, 95%

CI 0.10-0.49, p<0.001). The leave-one-out analyses demonstrated comparable point estimates and similar patterns of significance in relative effect estimates to the base case model.

Summary/Conclusion: This MAIC demonstrated significant PFS and OS benefits for zanubrutinib over CIT or chemo in R/R MZL.

Figure. PFS and OS Kaplan-Meier results in comparison of MAGNOLIA/BGB-3111-AU-003 (zanubrutinib) and HMRN (CIT or chemo)



Note: CIT or chemo included the following regimen in order of most to least common: bendamustine/rituximab (30%), single agent rituximab (13%), cyclophosphamide/rituximab+/-steroid (13%), R-CVP (11%), chlorambucil (8%), R-CHOP (4%), FCR (2%), other rituximab (7%), and other non-rituximab (11%).

CI, confidence interval; FCR + fludarabine + cyclophosphamide + rituximab; HMRN, Haematological Malignancy Research Network; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisone.