Indirect comparison of efficacy of zanubrutinib vs ibrutinib for the treatment of relapsed/refractory Mantle Cell Lymphoma

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Introduction: Mantle cell lymphoma (MCL) is an aggressive and rare form of non-Hodgkin lymphoma, with nearly all patients eventually relapsing after initial treatment. Covalent Bruton tyrosine kinase (BTK) inhibitors, including the first-generation inhibitor ibrutinib, the second-generation inhibitor acalabrutinib and the next-generation inhibitor zanubrutinib, are monotherapy treatment options for relapsed/refractory (R/R) MCL. Zanubrutinib is increasingly being adopted in clinical practice and has recently received a recommendation by the National Institute for Health and Care Excellence in the United Kingdom as an option for R/R MCL after 1 prior line of therapy. While BTK inhibitors have extended progression-free survival (PFS) in these patients, no head-to-head trials of zanubrutinib vs ibrutinib in R/R MCL have been conducted. This study assessed the comparative efficacy of zanubrutinib vs ibrutinib in R/R MCL using a matching-adjusted indirect comparison (MAIC).

Methods: Clinical trials of zanubrutinib and ibrutinib were identified through a systematic literature review. Two relevant single-arm trials in R/R MCL were identified for zanubrutinib: BGB-3111-AU003 (NCT02343120), a phase 1/2 trial in adult patients with B-cell malignancies including 32 patients with previously treated MCL following ≥1 prior therapy, and BGB-3111-206 (NCT03206970), a phase 2 trial in 86 patients with previously treated MCL following ≥1 prior therapy. To increase the sample size for zanubrutinib for the analyses, individual patient data from both trials were pooled (n=118; AU003-206). Four studies were identified for ibrutinib; the most feasible source for inclusion in the analysis was a pooled ibrutinib study (n=370) that included patients from a randomized controlled trial (NCT01646021) and 2 single-arm studies (NCT01236391 and NCT01599949). As both zanubrutinib trials were single arm, an unanchored MAIC was performed. The covariates for matching included age, gender, Eastern Cooperative Oncology group performance status (0 vs ≥1), bulky disease, blastoid variant, extranodal disease, number of prior lines of therapy (<2 vs ≥2) and prior lenalidomide use. Outcomes assessed included PFS and overall survival (OS). Sensitivity analyses using alternative data cuts, subgroups and matching variables were also explored.

Results: After matching for selected covariates, the treatment arms were well balanced; the effective sample size (ESS) of AU003-206 was reduced by 41% (from n=118 to ESS=74). For PFS, a statistically significant difference was observed with zanubrutinib compared with ibrutinib both before (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.40-0.72, *P*<.0001) and after (HR, 0.63; 95% CI, 0.46-0.87, *P*=.0044) matching.

Similar findings were observed for OS: a statistically significant difference was observed with zanubrutinib vs ibrutinib both before (HR, 0.42; 95% CI, 0.29-0.62, *P*<.0001) and after (HR, 0.46; 95% CI, 0.30-0.71, *P*=.0005) matching. Across all sensitivity analyses, results were consistent with the base case showing statistically significantly improved PFS and benefit in OS with zanubrutinib vs ibrutinib.

Conclusions: This MAIC reported that treatment with zanubrutinib significantly improved PFS and OS compared with ibrutinib, suggesting that zanubrutinib may be more effective at delaying disease progression and death in patients with R/R MCL. However, these findings should be interpreted with considerations of inherent MAIC assumptions.