Indirect comparison of efficacy of zanubrutinib versus acalabrutinib in the treatment of relapsed/refractory mantle cell lymphoma

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Background: Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin lymphoma characterized by its aggressive nature and poor prognosis. The treatment landscape for relapsed/refractory (R/R) MCL has evolved significantly with the introduction of targeted therapies, offering new hope for patients. Zanubrutinib and acalabrutinib are second-generation Bruton tyrosine kinase inhibitors (BTKis) that have demonstrated improved safety profiles vs first-generation BTKi ibrutinib in clinical trials. Zanubrutinib and acalabrutinib have demonstrated clinical benefits in separate single-arm trials in patients with R/R MCL and are approved therapies for R/R MCL. However, there is a lack of evidence on their comparative efficacy.

Aims: To assess the comparative efficacy of zanubrutinib vs acalabrutinib in patients with R/R MCL, in the absence of head-to-head clinical trials, using simulated treatment comparison (STC).

Methods: The clinical trials of zanubrutinib and acalabrutinib were identified through the literature review and comprised BGB-3111-206 (NCT03206970), BGB-3111-AU-003 (NCT02343120), and ACE-LY-004 (NCT02213926). These trials were reviewed thoroughly for the population, study design, intervention, and outcomes to assess the comparability for indirect treatment comparison (ITC). The efficacy of zanubrutinib was informed by the pooled individual patient-level data (n=123) from BGB-3111-206 and BGB-3111-AU-003 trials, and the efficacy of acalabrutinib was informed by the published aggregated data of ACE-LY-004 (n=124). As these trials do not have a common comparator, an unanchored ITC was conducted using STC method. A Cox regression model was used to adjust the population for potential prognostic factors or effect modifiers, which were identified from literature and validated with clinical experts. These covariates included prior lines of therapy and prior auto stem cell transplantation, lactate dehydrogenase concentration, Eastern Cooperative Oncology Group performance status ≥2, simplified Mantle Cell Lymphoma International Prognostic Index, age and sex, tumor bulk, race, bone marrow involvement, disease stage, and extranodal disease. The efficacy outcomes of interest included investigator-assessed progression-free survival (PFS), overall survival (OS), and overall response rate (ORR). Hazard ratio (HR) for PFS and OS, and odds ratio (OR) for ORR were estimated with 95% confidence intervals (CIs). All covariates were adjusted in the base case analysis. Sensitivity analyses were performed using a subset of all covariates.

Results: The results of the base case analysis showed that treatment with zanubrutinib was associated with significantly greater PFS (HR, 0.57 [95% CI, 0.35-0.94]; *P*=0.0272) and OS (HR, 0.43 [95% CI, 0.23-0.82]; *P*=0.0105) compared with acalabrutinib in patients with R/R MCL (Table 1). Similarly, the ORR was observed to be higher with zanubrutinib vs acalabrutinib (OR, 2.05 [95% CI, 0.72-5.84]; *P*=0.1798) but did not achieve the significance level. The results of sensitivity analyses (models without race and without age) yielded consistent results.

Summary/Conclusion: The results of this simulated treatment comparison demonstrated that zanubrutinib had significantly better PFS and OS compared with acalabrutinib in the treatment of patients with R/R MCL after adjusting for a large set of covariates. In the absence of a head-to-head

comparison trial, this study provides important insights about the comparative efficacy of zanubrutinib and acalabrutinib in the R/R MCL setting.

Table 1: Results of STC comparing zanubrutinib vs acalabrutinib for efficacy outcomes

Base case and sensitivity analyses	PFS HR (95% CI, *P*-value)	OS HR (95% CI, *P*-value)	ORR OR (95% CI, *P*-value)
Base case analysis (adjusted* for all covariates / Model 1)	**0.57** (0.35-0.94, *P*=0.0272)	**0.43** (0.23-0.82, *P*=0.0105)	2.05 (0.72-5.84, *P*=0.1798)
Sensitivity analysis 1 (Model 1 without race)	**0.62** (0.39-0.98, *P*=0.0418)	**0.42** (0.25-0.70, *P*=0.0009)	1.48 (0.57-3.82, *P*=0.4165)
Sensitivity analysis 2 (Model 1 without age)	**0.58** (0.35-0.97, *P*=0.0388)	**0.48** (0.25-0.94, *P*=0.0335)	2.19 (0.73-6.52, *P*=0.1606)

*Population adjusted for covariates including age, sex, race, ECOG performance status, sMIPI, LDH concentration, tumor bulk, bone marrow involvement, disease stage, extranodal disease, prior lines of therapy / prior auto SCT.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; SCT, stem cell transplantation; STC, simulated treatment comparison.