Indirect Comparison of Efficacy of Zanubrutinib Versus Acalabrutinib in the Treatment of Patients With Relapsed or Refractory Mantle Cell Lymphoma

Bijal Shah,[1] Swetha Challagulla,[2] Sheng Xu,[3] Rhys Williams,[2] Shijie Ren,[4,5] Tushar Srivastava,[4] Raju Gautam,[4] Keri Yang[2]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]BeiGene, San Mateo, CA, USA; [3]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [4]ConnectHEOR Ltd, London, UK; [5]SCHARR, University of Sheffield, Sheffield, UK

INTRODUCTION

- Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin lymphoma, which originates due to malignant transformation of B cells in the mantle zone of the lymph follicle
- Zanubrutinib and acalabrutinib are second-generation Bruton tyrosine kinase inhibitors (BTKis) with improved safety profiles compared with first-generation BTKi ibrutinib in clinical trials[1,2]
- Zanubrutinib and acalabrutinib have demonstrated clinical benefits in separate single-arm trials in patients with relapsed/refractory (R/R) MCL. However, the evidence on the comparative effectiveness of zanubrutinib and acalabrutinib is lacking in the literature

OBJECTIVE

- 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 population-adjusted indirect treatment comparison (ITC) via simulated treatment comparison (STC) approach

METHODS

Data Source and Study Design

- A targeted literature review was conducted in PubMed database and clinical trials identifier (clinicaltrials.gov) to identify relevant clinical trial evidence
- Data source for the efficacy of zanubrutinib was informed by the pooled individual patient-level data (IPD) from two clinical trials: BGB-3111-206 (NCT03206970)[3,4] and BGB-3111-AU-003 (NCT02343120)[5]
- The efficacy of acalabrutinib was informed by the published aggregated data of the ACE-LY-004 trial (NCT02213926)[6,7]
- A key difference among these trials was BGB-3111-206 had a Chinese population, and BGB-3111-AU-003 had a White population, whereas ACE-LY-004 was a global study
- The efficacy outcomes of interest are progression-free survival (PFS), overall survival (OS), and overall response rate (ORR). The relative treatment effect were quantified using hazard ratio (HR) for PFS and OS, and odds ratio (OR) for ORR
- STC, an outcome regression-based approach to adjust for cross-trial differences in patient characteristics, was used to estimate the relative efficacy of zanubrutinib vs acalabrutinib, following guidance by National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 18 (NICE DSU TSD18) (**Figure 1**)[8]
- The potential prognostic variables and effect modifiers were identified from the previously published ITCs in MCL and were further validated with clinical experts (**Table 1**)
- In the base case analysis, all covariates for which the data were available in the included trials of zanubrutinib and acalabrutinib were adjusted
- Covariates included age, race, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1-2, simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) intermediate and high risk, bulky disease, Ann Arbor disease stage III-IV, extranodal disease, lactate dehydrogenase, prior lines of treatment, bone marrow involvement, and prior autologous stem cell transplantation (SCT)
- Sensitivity analyses were conducted by excluding the covariates (race and age) that were imbalanced largely across trials of zanubrutinib and acalabrutinib

Figure 1. Study Design

Step 1

Fitting a regression model (Cox regression for time-to-event outcome and logistic regression for binary) to the IPD including all prognostic variables and effect modifiers

Step 2

Predicting the outcome according to the comparator study population using the mean baseline characteristics

Step 3

Deriving the estimate of ITC using the predicted estimate from step 2 and the reported estimate from the comparator study

RESULTS

Baseline Characteristics

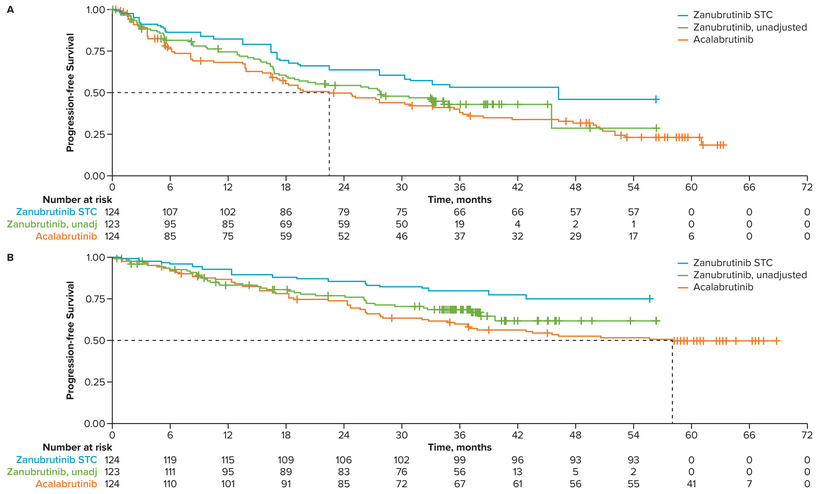
- Noticeable differences were observed in multiple baseline characteristics between the zanubrutinib and acalabrutinib treatment cohorts

Table 1. Summary of Key Baseline Patient Characteristics Identified as Prognostic Variables and Effect Modifiers

Baseline Characteristics (Proportion of Patients)	Acalabrutinib: ACE-LY-004 (n=124)	Zanubrutinib: BGB-3111-206 + AU-003 (n=123)
Age ≥65 years	64.5%	39.8%
Race: White	74.2%	24.4%
Sex: Male	79.8%	74.8%
ECOG PS 1-2 (vs 0)	42.7%	35.8%
sMIPI intermediate risk (vs low)	43.9%	37.4%
sMIPI high risk (vs low)	17.1%	15.4%
Bulky disease (LD ≥5 cm)	37.1%	38.8%
Ann Arbor stage III-IV	75.0%	90.2%
Extranodal disease	72.6%	57.7%
Lactate dehydrogenase, high	26.6%	38.2%
Prior lines of treatment >2	22.6%	32.5%
Bone marrow involvement	50.8%	49.6%
Prior autologous SCT	17.7%	8.9%

LD, longest diameter.

Figure 2. Kaplan-Meier Curve for (A) PFS and (B) OS



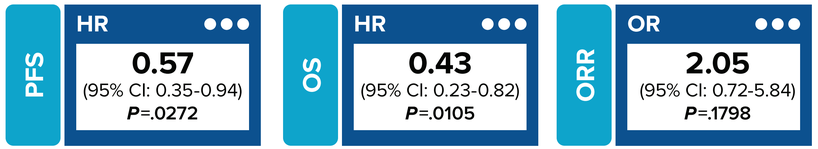
CONCLUSIONS

- The results of this population-adjusted ITC revealed that treatment with zanubrutinib was associated with significantly greater PFS and OS vs acalabrutinib. Patients treated with zanubrutinib were also shown to be achieving numerically higher ORR than patients treated with acalabrutinib. The study provides evidence to support the superiority of zanubrutinib over acalabrutinib in R/R MCL

Base Case Analysis

- The results of STC showed that treatment with zanubrutinib was associated with a beneficial treatment effect in PFS, OS, and ORR (**Figure 2**, **Figure 3**)
  - Zanubrutinib had statistically significantly longer PFS than acalabrutinib with an HR of 0.57 (95% CI: 0.35-0.94; *P*=.0272) (**Figure 2**, **Figure 3**)
  - Likewise, zanubrutinib had statistically significantly longer OS than acalabrutinib with an HR of 0.43 (95% CI: 0.23-0.82; *P*=.0105) (**Figure 2**, **Figure 3**)
  - For the ORR, the results of STC showed that odds of achieving ORR were higher for patients treated with zanubrutinib than those treated with acalabrutinib (OR, 2.05 [95% CI: 0.72-5.84]; *P*=.1798), but the difference did not reach a statistical significance (**Figure 3**)
- The proportion of patients with high LDH and >2 prior lines of treatment were found to be significantly predictive of survival outcomes in the regression models

Figure 3. The Results of STC Comparing Zanubrutinib vs Acalabrutinib for Efficacy Outcomes in the Base Case Analysis



Sensitivity Analysis

- The sensitivity analyses, without adjusting for race and age, provided results consistent with base case analysis, demonstrating the robustness of the ITC analysis using STC (**Table 2**)

Table 2. Sensitivity Analyses Results of STC Comparing Zanubrutinib vs Acalabrutinib for Efficacy Outcomes

Sensitivity Analyses	PFS HR (95% CI, *P* value)	OS HR (95% CI, *P* value)	ORR OR (95% CI, *P* value)
Sensitivity analysis 1 (base case without race)	0.62 (0.39-0.98, *P*=.0418)	0.42 (0.25-0.70, *P*=.0009)	1.48 (0.57-3.82, *P*=.4165)
Sensitivity analysis 2 (base case without age)	0.58 (0.35-0.97, *P*=.0388)	0.48 (0.25-0.94, *P*=.0335)	2.19 (0.73-6.52, *P*=.1606)

DISCUSSION

- The strength of the present ITC study includes (i) the analysis was conducted per standards documented in the NICE DSU TSD 18, with rigorous statistical methods to provide reliable estimates; (ii) a large set of covariates, which in the opinion of clinical experts could influence treatment outcomes, were adjusted in the analysis
- Despite the thorough nature of the analysis, this study has certain limitations. The study has restricted granularity and specificity due to reliance on the aggregated data for comparator. The differences in designs, patient populations, or treatment regimens across the studies being compared can introduce heterogeneity, potentially affecting the validity of indirect comparisons

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DISCLOSURES

BS: Employment: Moffitt Cancer Center. Research Funding: Jazz Pharmaceuticals, Servier, Kite. Travel accommodations for Kite. Other relationships with DSMB, Peprromene Bio. **SC, SX, RW, KY:** Employment and may hold stock: BeiGene. **SR, TS, RG:** Employment: ConnectHEOR.

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CORRESPONDENCE: Bijal Shah, bijal.shah@moffitt.org

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