Matching-Adjusted Indirect Comparison of the Efficacy of Zanubrutinib Versus Ibrutinib for the Treatment of Relapsed/Refractory Mantle Cell Lymphoma

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CONCLUSIONS

- This MAIC demonstrated that treatment with zanubrutinib significantly improved INV-PFS and OS compared with ibrutinib in patients with R/R MCL
- These data suggest that zanubrutinib may be more effective than ibrutinib at delaying disease progression and death in patients with R/R MCL

INTRODUCTION

- Mantle cell lymphoma (MCL) is an aggressive and rare form of non-Hodgkin lymphoma, with most patients eventually relapsing after initial treatment[1]
- Covalent Bruton tyrosine kinase inhibitors (cBTKis), including first-generation ibrutinib and next-generation zanubrutinib, are monotherapy treatment options for relapsed/refractory (R/R) MCL[2]
- Zanubrutinib is increasingly being adopted in clinical practice and was recently recommended by the National Institute for Health and Care Excellence (NICE) as an option for R/R MCL after one prior line of therapy (LOT)[3]
- Both ibrutinib and zanubrutinib have improved clinical outcomes in R/R MCL.[1,4] However, the relative efficacy of these options has not been explored, as no head-to-head trials have been conducted

Aim

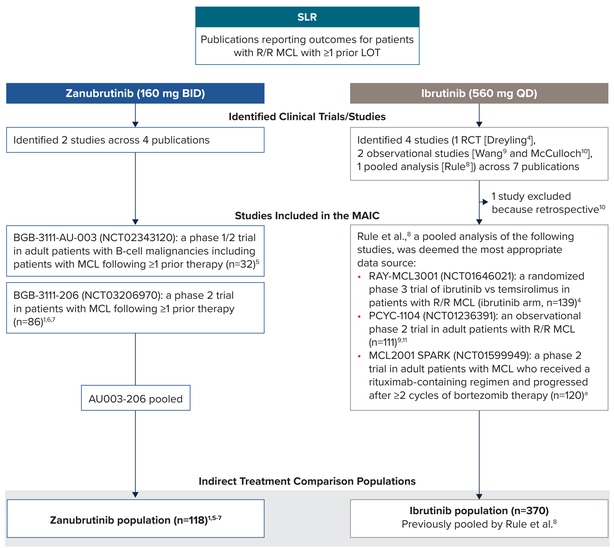
- To assess the comparative efficacy of zanubrutinib versus ibrutinib in patients with R/R MCL through a matching-adjusted indirect comparison (MAIC)

METHODS

Data Source and Study Design

- A systematic literature review (SLR) was conducted to identify clinical trials of zanubrutinib and ibrutinib (latest search date of July 2024; **Figure 1**)
  - The zanubrutinib studies (BGB-3111-AU-003 and BGB-3111-206) were pooled (AU003-206) to increase the sample size for the MAIC[1,5-7]
  - Rule et al. 2017[8] is a pooled analysis of three ibrutinib studies and was deemed the most appropriate data source for this MAIC, based on the patient population and the large dataset

Figure 1. SLR and Identified Studies Extracted for the MAIC



[a]MCL2001 SPARK was not identified in the SLR, but was included via the Rule et al. 2017[8] pooled analysis.
BID, twice daily; QD, once daily; RCT, randomized controlled trial.

Statistical Analysis

- As the included zanubrutinib studies were single-arm studies, an unanchored MAIC was performed to assess the relative efficacy of zanubrutinib versus ibrutinib in R/R MCL
  - Individual patient data (IPD) from the BGB-3111-206 and BGB-3111-AU-003 trials were used (n=118)
  - Balancing weights for the zanubrutinib pooled population were derived using a logistic regression model and were used to estimate the relative treatment effect of zanubrutinib versus ibrutinib in the target population
- Outcomes included investigator-assessed progression-free survival (INV-PFS) and overall survival (OS)
- Covariates included for matching were validated by clinical experts, and included age ≥65 years, male sex, Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs ≥1), bulky disease ≥5 cm, blastoid variant (yes, no), extranodal disease (yes, no), number of prior LOTs (<2 vs ≥2, as the median number of prior LOTs across all studies was 2), and prior lenalidomide treatment (yes, no)
- A Cox proportional hazard regression model was used to derive estimates of relative effect before and after population matching; hazard ratios (HRs) and 95% confidence intervals (CIs) were reported for weighted and unweighted models
- Sensitivity analyses removing one matching covariate at a time ("leave-one-out") were conducted to test consistency with the base case
- Although prior rituximab therapy was received by nearly all patients in the pooled ibrutinib population,[8] a scenario analysis explored the clinical effectiveness among rituximab-naïve patients

RESULTS

Population Covariate Matching and Baseline Characteristics

- Median follow-up times were 35-39 months in the pooled zanubrutinib population[1,5-7] and 24-25 months in the pooled ibrutinib population[8]
- Patients in the zanubrutinib studies were slightly younger, less frail (based on ECOG PS), less heavily pretreated, and had smaller tumor mass (**Table 1**)

Table 1. Baseline Characteristics for Pooled Ibrutinib Population and Pooled Zanubrutinib Population Before and After Matching

Patient characteristic	Zanubrutinib before matching (n=118)[1,5-7]	Zanubrutinib after matching (ESS=74)	Ibrutinib (n=370)[a,8]
Age			
Mean (SD), years	61.9 (10.0)	-	66.8 (9.1)
≥65 years, n (%)	**46 (39.0)**	**(62.4)**	**(62.4)**
Sex, n (%)			
Male	**89 (75.4)**	**(78.0)**	**(78.0)**
Race, n (%)			
Asian	89 (75.4)	-	NR
White	25 (21.2)	-	NR
Other[b]	4 (3.4)	-	NR
ECOG PS, n (%)			
0	**75 (63.6)**	**(43.0)**	**(43.0)**
≥1	43 (36.4)	-	(57.0)
Bulky disease, n (%)			
LDi <5 cm	70 (59.3)	-	(51.0)
LDi ≥5 cm	**46 (39.0)**	**(49.0)**	**(49.0)**
Missing	2 (1.7)	-	NR
Blastoid variant, n (%)			
Yes	**14 (11.9)**	**(12.0)**	**(12.0)**
No	96 (81.3)	-	(88.0)
Unknown	8 (6.8)	-	NR
Extranodal disease at study entry, n (%)[c]			
Yes	**86 (72.9)**	**(58.0)**	**(58.0)**
No	32 (27.1)	-	(42.0)
sMIPI, n (%)[d]			
Low risk	57 (48.3)	-	(24.0)
Intermediate risk	43 (36.4)	-	(45.0)
High risk	18 (15.3)	-	(32.0)
Number of prior systemic therapies			
Median (range)	2.0 (1-4)	-	2.0 (1-9)
1 prior therapy, n (%)	43 (36.4)	-	(26.8)
≥2 prior therapies, n (%)	**75 (63.6)**	**(73.2)**	**(73.2)**
Prior lenalidomide, n (%)	**12 (10.2)**	**(16.0)**	**(16.0)**
Prior systemic rituximab or rituximab-containing regimen, n (%)	94 (79.7)	-	(96.8)[e]

Bold font in Table 1 indicates covariates used in matching. Matching was not performed for race and prior systemic rituximab as these covariates were not reported for the pooled ibrutinib population. [a]Only percentages were reported in Rule et al. 2017.[8] [b]Includes 1 Black or African American and 3 Other/Multiple. [c]Extranodal disease was defined as biopsy or radiographic evidence of bone marrow or gastrointestinal disease. [d]sMIPI score was calculated with cutoffs as low (1-3), intermediate (4-5), and high risk (6-11). [e]Value calculated from individual trials' sources.
ESS, effective sample size; LDi, longest transverse diameter of a lesion; NR, not reported; SD, standard deviation; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index.

- After matching for selected covariates, the treatment arms were well balanced
  - The ESS of the pooled zanubrutinib population was reduced by 41% (from n=118 to ESS=74)
  - MIPI was not matched because there were differences in the definition used across studies

Comparative Efficacy

- The zanubrutinib weighted Kaplan-Meier curves shifted downwards from the unweighted curves for both INV-PFS and OS, driven primarily by adjustments for age, ECOG PS, level of pretreatment, and bulky disease
- For INV-PFS, a statistically significant difference was observed with zanubrutinib versus ibrutinib both before (HR=0.54; 95% CI: 0.40-0.72; *P*<.0001) and after (HR=0.63; 95% CI: 0.46-0.87; *P*=.0044) matching (**Figure 2**)
- A statistically significant difference was also observed with zanubrutinib versus ibrutinib for OS 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 (**Figure 3**)

Figure 2. INV-PFS Before and After Matching

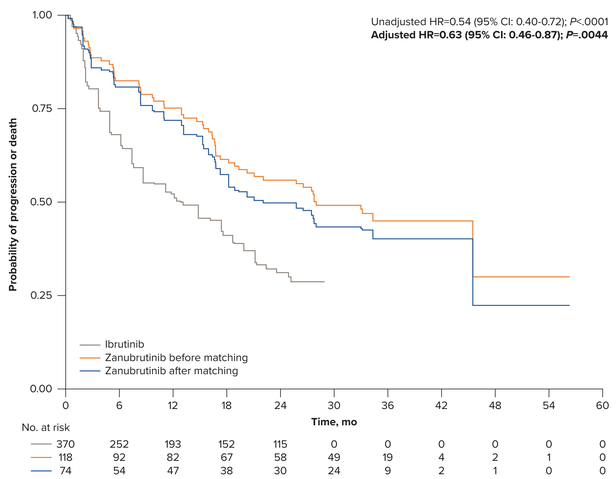
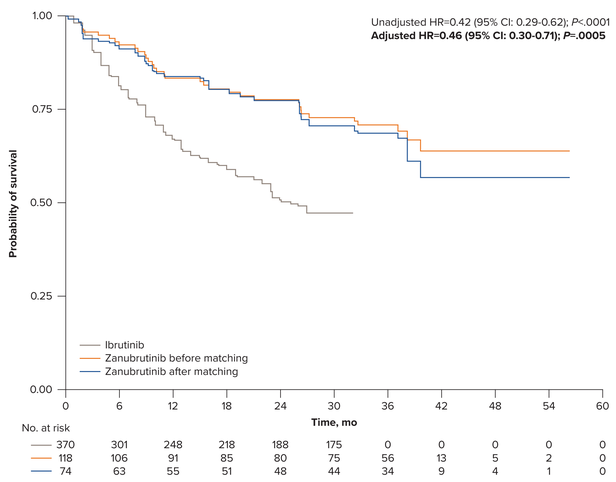


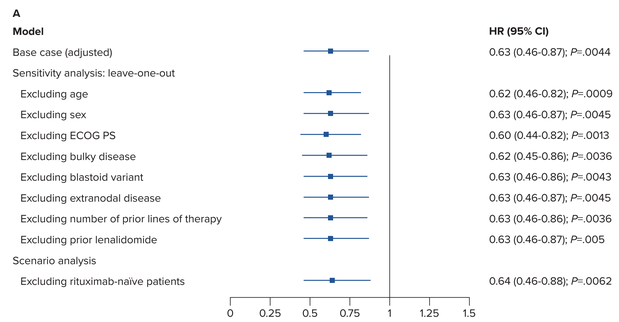
Figure 3. OS Before and After Matching



Sensitivity and Scenario Analyses

- Leave-one-out sensitivity analyses as well as a scenario analysis excluding rituximab-naïve patients were consistent with the base-case analysis, showing a statistically significant improvement in INV-PFS and OS with zanubrutinib versus ibrutinib (**Figures 4A and 4B**)

Figure 4. INV-PFS (A) and OS (B) in Sensitivity and Scenario Analyses



DISCUSSION

- This analysis made the best use of the data available and was aligned with the NICE Decision Support Unit guidelines[3] for population-adjusted comparisons
- These results are consistent with real-world evidence of zanubrutinib and ibrutinib with respect to time-to-next treatment and OS outcomes in the second-line or later setting[12]

Limitations

- These findings should be interpreted within the context of the limitations of MAICs
  - A lack of events may introduce uncertainty into the analysis; however, clinical outcomes from both zanubrutinib trials supported a durable and sustained treatment effect
  - Results of the MAIC are limited by the availability of published baseline characteristics and may not be generalizable to real-world populations

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ACKNOWLEDGMENTS

This study was sponsored by BeOne Medicines Ltd. Medical writing and editorial support was provided by David M. Jensen, PhD, of Amiculum, and supported by BeOne Medicines Ltd.

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Presented at the 67th Annual Meeting and Exposition of the American Society of Hematology; December 6-9, 2025; Orlando, FL, USA