Matching-Adjusted Indirect Comparison (MAIC) of Zanubrutinib vs Ibrutinib in Relapsed/Refractory Marginal Zone Lymphoma (R/R MZL)

Catherine Thieblemont,[1] Kaijun Wang,[2] Sam Keeping,[3] Ina Zhang,[3] Keri Yang,[2] Boxiong Tang,[2] Leyla Mohseninejad[2]

[1]Hôpital Saint-Louis, Paris, France; [2]BeiGene USA, Inc, San Mateo, CA, USA, and BeiGene Switzerland GmbH, Basel, Switzerland; [3]PRECISIONheor, Vancouver, BC, Canada

INTRODUCTION

- Limited effective and tolerable treatment options are available for patients with MZL who have experienced relapse after or whose lymphoma was refractory to prior standard chemoimmunotherapy with anti-CD20 monoclonal antibodies
- Bruton tyrosine kinase inhibitors (BTKi) have shown deep and durable responses in non-Hodgkin lymphoma subtypes, including Waldenstrom macroglobulinemia, chronic lymphocytic leukemia, and mantle cell lymphoma
- Zanubrutinib, a second-generation BTKi, and ibrutinib, a first-generation BTKi, have been assessed in single-arm clinical trials in MZL
- In the absence of head-to-head randomized controlled trials, comparative efficacy estimates must come from unanchored between-trial comparisons of reported treatment effects

OBJECTIVE

- To assess the comparative efficacy of zanubrutinib vs ibrutinib for the treatment of R/R MZL

METHODS

Data Sources

- Zanubrutinib has been evaluated in 2 single-arm trials in R/R MZL (phase 2 MAGNOLIA trial [NCT03846427]; phase 1/2 BGB-3111-AU-003 trial [NCT02343120])[1,2]
- Ibrutinib has also been evaluated in R/R MZL in a phase 2, single-arm trial (PCYC-1121 [NCT01980628])[3,4]

Statistical Analysis

- Propensity score models were used to match baseline characteristics in MAGNOLIA and BGB-3111-AU-003 to those observed in PCYC-1121
- Prognostic factors were ranked by clinical experts (presented in order of importance in **Table 1**)
- In the base-case model, matched variables included number of prior lines of therapy, MZL subtype, response to prior therapy, and age
- In the sensitivity analysis, the following additional variables were considered: lactate dehydrogenase above normal, bulky disease (>5 cm), prior anti-CD20 therapy, time since last therapy, B symptoms, bone marrow involvement, and Eastern Cooperative Oncology Group (ECOG) performance status
- The impact of each covariate in the base-case and scenario models were explored via a leave-one-out analysis
- Logistic regression models for binary outcomes (objective response rate [ORR]) and Cox proportional hazards models for time-to-event outcomes (overall survival [OS], progression-free survival [PFS]) were used to estimate relative treatment effects for zanubrutinib vs ibrutinib

RESULTS

Patient Demographics and Disease Characteristics

- MAIC convergence was achieved using the full set of base-case covariates, and baseline characteristics were balanced between the 2 treatment groups after matching (**Table 1**)
- 2 factors, bone marrow involvement and ECOG performance status, were removed to achieve convergence in the sensitivity analysis model

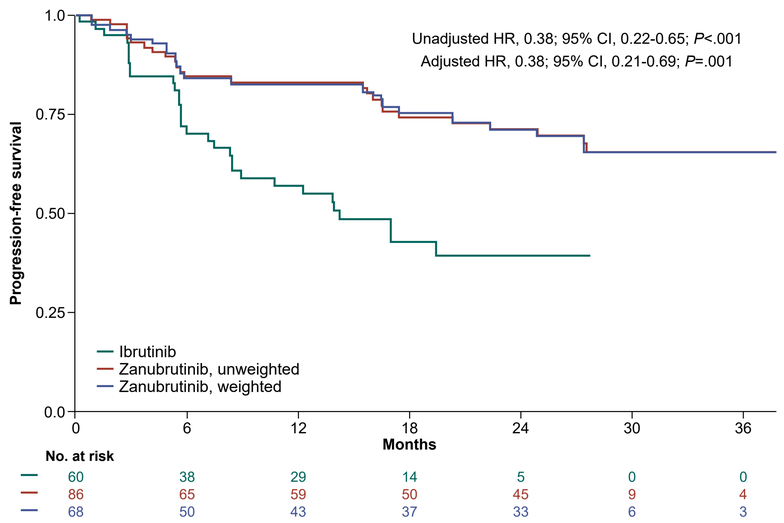
Table 1. Baseline Characteristics in Zanubrutinib Treatment Group Before and After Matching to Ibrutinib Treatment Group

Covariate	Zanubrutinib			Ibrutinib (N=60)
	Observed (N=86)	Weighted base-case model (ESS=68)	Weighted sensitivity model (ESS=24)	
2 prior treatment lines, %	30.2	30.0	30.0	30.0
≥3 prior treatment lines, %	25.6	33.3	33.3	33.3
MZL subtype: nodal, %	36.6	28.3	28.3	28.3
MZL subtype: splenic, %	22.0	21.7	21.7	21.7
Refractory to last therapy, %	30.1	22.2	22.2	22.2
Age ≥65 years, %	65.1	60.0	60.0	60.0
LDH above normal, %	27.9	N/A	19.0	19.0
Bulky disease >5 cm, %	35.4	N/A	22.2	22.2
Prior anti-CD20 therapy, %	98.9	N/A	100	100
Time since last therapy, median, months	29	N/A	45	45
B symptoms, %	19.8	N/A	23.8	23.8
Bone marrow involvement, %	50.0	N/A	N/A	33.3
ECOG 0-1, %	91.9	N/A	N/A	92.1

Matching-Adjusted Indirect Comparison Results

- Results from the MAIC are reported in **Table 2**, with unadjusted comparisons presented for informative purposes only
- Compared with ibrutinib, zanubrutinib significantly reduced the risk of progression (**Figure 1**) and was associated with a significantly higher ORR
- OS was comparable with zanubrutinib and ibrutinib, which is consistent with expectations for indolent lymphomas, although point estimates were in favor of zanubrutinib (**Figure 2**)
- The sensitivity analysis accounting for additional prognostic factors suggested that the 2 treatments were comparable across all outcomes, owing in part to the low effective sample size (ESS) for zanubrutinib in the expanded models, although point estimates were in favor of zanubrutinib
- A leave-one-out analysis showed significantly improved PFS for zanubrutinib when excluding B symptoms, time since last therapy, or bulky disease from the expanded model

Figure 1. MAIC of Zanubrutinib and Ibrutinib in Base-Case PFS Analysis (Cox Proportional Hazards Model)



CONCLUSIONS

- This MAIC demonstrated ORR and PFS benefits for zanubrutinib in comparison to ibrutinib in R/R MZL
- The main limitation of the analysis was that only those patient characteristics reported in both studies could be adjusted for; however, data were available for the main prognostic factors in R/R MZL as specified by clinical experts
- Another limitation of the analysis lies in the uncertainty in long-term survival outcomes due to the indolent nature of MZL; an update of analyses once longer-term data become available is recommended

Figure 2. MAIC of Zanubrutinib and Ibrutinib in Base-Case OS Analysis (Cox Proportional Hazards Model)

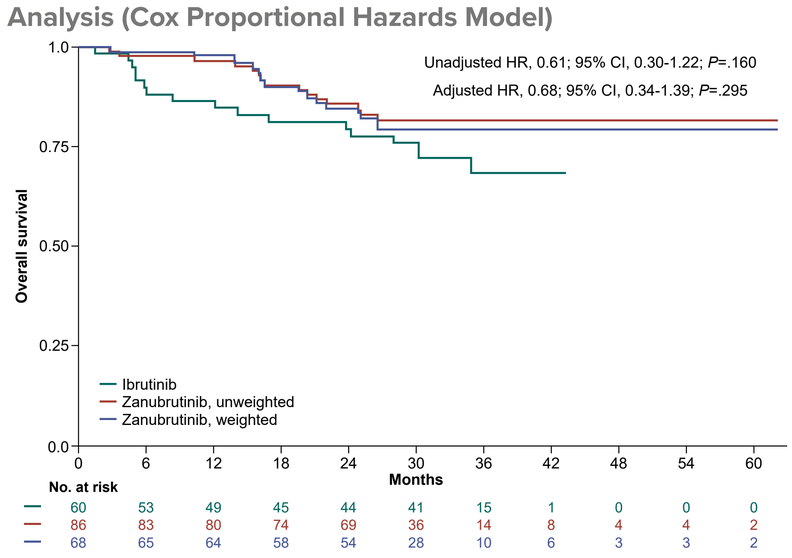


Table 2. Relative Treatment Effect Estimates of Zanubrutinib vs Ibrutinib

Model	Zanubrutinib ESS	ORR OR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
Unadjusted	86	**2.64 (1.32-5.28)** ***P*<.01**	**0.38 (0.22-0.65)** ***P*<.01**	0.61 (0.30-1.22) *P*=.16
Base-case (all covariates)	68	**2.37 (1.13-4.96)** ***P*<.01**	**0.38 (0.21-0.69)** ***P*<.01**	0.68 (0.34-1.39) *P*=.30
Base-case (excluding age)	71	**2.58 (1.25-5.35)** ***P*=.01**	**0.35 (0.20-0.63)** ***P*<.01**	0.68 (0.34-1.38) *P*=.29
Base-case (excluding response to last therapy)	73	**2.31 (1.12-4.77)** ***P*=.02**	**0.41 (0.23-0.71)** ***P*<.01**	0.62 (0.31-1.26) *P*=.19
Base-case (excluding MZL subtype)	74	**2.51 (1.22-5.15)** ***P*=.01**	**0.40 (0.22-0.70)** ***P*<.01**	0.70 (0.35-1.40) *P*=.31
Base-case (excluding number of prior lines)	73	**2.63 (1.27-5.44)** ***P*<.01**	**0.34 (0.19-0.63)** ***P*<.01**	0.59 (0.29-1.20) *P*=.14
Sensitivity analysis (all covariates)	24	1.78 (0.65-4.92) *P*=.26	0.48 (0.22-1.04) *P*=.06	0.88 (0.35-2.20) *P*=.78
Sensitivity analysis (excluding B symptoms)	24	1.99 (0.72-5.48) *P*=.18	**0.44 (0.22-0.90)** ***P*=.02**	0.79 (0.33-1.90) *P*=.60
Sensitivity analysis (excluding time since last therapy)	54	**2.34 (1.07-5.12)** ***P*=.03**	**0.33 (0.18-0.62)** ***P*<.01**	0.49 (0.23-1.06) *P*=.07
Sensitivity analysis (excluding prior anti-CD20 therapy)	24	1.78 (0.65-4.92) *P*=.26	0.48 (0.22-1.04) *P*=.06	0.88 (0.35-2.20) *P*=.78
Sensitivity analysis (excluding bulky disease)	33	1.97 (0.80-4.82) *P*=.14	**0.45 (0.22-0.93)** ***P*=.03**	0.86 (0.38-1.94) *P*=.72
Sensitivity analysis (excluding LDH above normal)	24	1.74 (0.64-4.78) *P*=.28	0.51 (0.23-1.12) *P*=.09	0.95 (0.39-2.32) *P*=.90

All bolded values are statistically significant at the 0.05 significance level.

REFERENCES

1. Opat S, et al. *Clin Cancer Res.* 2021;27(23):6323-6332.
2. Phillips T, et al. *Blood Adv.* 2022;6(11):3472-3479.
3. Noy A, et al. *Blood.* 2017;129(16):2224-2232.
4. Noy A, et al. *Blood Adv.* 2020;4(22):5773-5784.

DISCLOSURES

CT: Consulting or advisory role: Roche, AbbVie, Genmab, Kite Gilead, Takeda, Novartis, Incyte, Celgene, BMS; Research funding: Roche; Travel, accommodations, and expenses: Novartis, Gilead, BMS. **KW:** no disclosures. **SK:** Employment: PRECISIONheor; Research funding: BeiGene. **IZ:** Employment: PRECISIONheor; Research funding: BeiGene. **KY:** Employment: BeiGene; Leadership: BeiGene; Stock or other ownership: BeiGene; Research funding: BeiGene; Travel, accommodations, and expenses: BeiGene. **BT:** Employment: BeiGene; Stock or other ownership: BeiGene. **LM:** Employment: BeiGene.

CORRESPONDENCE

Leyla Mohseninejad
leyla.mohseninejad@beigene.com

ACKNOWLEDGMENTS

The authors thank the patients who participated in the MAGNOLIA, BGB-3111-AU-003, and PCYC-1121 clinical trials. Editorial assistance was provided, under the direction of the authors, by Mary Ann Honors, PhD, MPH, of Articulate Science, LLC, and supported by BeiGene.

Presented at the 17th International Conference on Malignant Lymphoma (ICML); June 13-17, 2023; Lugano, Switzerland

Data originally presented at the EHA 2023 Hybrid Congress; June 8-15, 2023; Frankfurt, Germany; Abstract 1093