A Meta-Analysis Investigating Response Rates of Continuous Bruton Tyrosine Kinase Inhibitor Monotherapies in the Treatment of B-Cell Lymphoma

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CONCLUSIONS

- Zanubrutinib demonstrated significantly higher CR and ORRs compared with acalabrutinib and ibrutinib across BCL indications
- Within each BCL indication, zanubrutinib demonstrated either similar, numerically higher, or statistically significantly higher response rates
- These findings suggest that zanubrutinib may offer a more effective treatment option for patients across BCL indications

INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitor (zanubrutinib, acalabrutinib, and ibrutinib) monotherapy has led to improved outcomes in patients with B-cell lymphomas (BCLs), including chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia, marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), and Richter transformation[1,2]
- While the efficacy of each BTK inhibitor is understood within each individual BCL indication, this meta-analysis aims to compare response rates associated with BTK inhibitor monotherapy across BCL indications at the treatment naive (TN) and/or relapsed/refractory (R/R) stage

METHODS

- A systematic literature review was performed to identify clinical trials reporting complete response (CR) rates or overall response rates (ORRs) in patients with at least one type of BCL treated with zanubrutinib, acalabrutinib, or ibrutinib monotherapies
- Response rates, at similar follow-up time points (with a maximum difference of 12 months) and longest available follow-up time points, were extracted from each study and pooled across all applicable studies reporting data for zanubrutinib, acalabrutinib, or ibrutinib; investigator-assessed (INV) response rates were prioritized when available

Statistical Methods

- Results were presented as odds ratios (OR) with corresponding 95% confidence intervals; ORs >1 favor zanubrutinib over comparator BTK inhibitors
- ORs were estimated for zanubrutinib vs each comparator BTK inhibitor (acalabrutinib or ibrutinib) for each response outcome in each BCL indication
- The ORs were then meta-analyzed across BCL indications using a random-effects model to account for variability between studies
- Between-study heterogeneity was assessed using I^2, the *P* value from the Q test, and τ (the standard deviation of underlying effects across studies)

RESULTS

- In total, 22 trials assessing 3599 patients were included for analysis across 4 BCL indications (**Table 1**)[3-27]
  - Fifteen trials (17 treatment arms) assessed patients with R/R disease or those who had been previously treated,[3-16, 26] while 4 trials (5 treatment arms) assessed TN patients,[17-23] and 3 trials (4 treatment arms) included a mixed population[24,25,27]
  - Sixteen trials reported INV response outcomes and 3 only reported independent-review committee outcomes for the matching follow-up periods

Table 1. Characteristics of Trials Included in the Analysis by BCL Indication

Trials, n	22
Patients, n	3599
Treatment arms, n (%)	26
Zanubrutinib monotherapy	8 (31)
Ibrutinib monotherapy	11 (42)
Acalabrutinib monotherapy	7 (27)
Treatment status, n (%)	
Treatment naive	5 (19)
Relapsed/refractory	17 (65)
Mixed	4 (16)
Tumor type, n (%)	
CLL/SLL	11 (42)
MCL	6 (23)
MZL	4 (16)
WM	5 (19)

Abbreviations: BCL, B-cell lymphoma; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

- The meta-analysis showed that zanubrutinib was associated with statistically significant improvements in both CR and ORR compared with acalabrutinib and ibrutinib across different BCL indications
- **CR rates** (**Figure 1**):
  - The pooled estimates of the OR (95% CI) for CR rates were 1.80 (1.03-3.13) for zanubrutinib vs acalabrutinib and 2.85 (1.16-7.04) for zanubrutinib vs ibrutinib
  - In R/R MCL, zanubrutinib demonstrated statistically superior efficacy over both acalabrutinib and ibrutinib for CR, with OR (95% CI) of 3.33 (1.91-5.81) and 9.53 (5.45-16.66), respectively; in R/R MZL, zanubrutinib showed superior efficacy over ibrutinib for CR, with an OR (95% CI) of 3.32 (1.28-8.61)
- **ORR** (**Figure 2**):
  - The pooled estimates of the OR (95% CI) for ORR were 1.59 (1.0003-2.53) for zanubrutinib vs acalabrutinib and 2.25 (1.40-3.61) for zanubrutinib vs ibrutinib
  - In R/R MCL and R/R MZL, zanubrutinib showed superior ORR over ibrutinib, with OR (95% CI) of 2.23 (1.21-4.12) and 2.39 (1.18-4.85), respectively

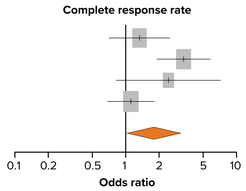
Statistical Heterogeneity

- Moderate to high statistical heterogeneity was observed in the meta-analyses
- The I^2 values, which represent the percentage of variance due to heterogeneity, were:
  - CR rates: 68.5% for zanubrutinib vs acalabrutinib and 85.6% for zanubrutinib vs ibrutinib
  - ORR: 51.5% for zanubrutinib vs acalabrutinib and 49.2% for zanubrutinib vs ibrutinib

Figure 1. Odds Ratios for Complete Response Comparisons Across BCL Indications

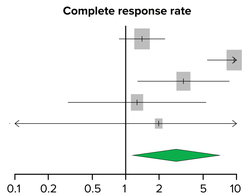
Zanubrutinib vs acalabrutinib

Indication	N	zanu CR (95% CI)	aca CR (95% CI)	Odds ratio (95% CI)
R/R CLL	3	10.70 (7.78, 14.54)	8.25 (5.04, 13.23)	1.33 (0.71, 2.51)
R/R MCL	3	68.60 (58.08, 77.50)	39.62 (32.29, 47.44)	3.33 (1.91, 5.81)
R/R MZL	2	25.80 (16.80, 37.45)	12.50 (5.30, 26.72)	2.43 (0.82, 7.19)
TN CLL	3	20.70 (16.05, 26.28)	19.00 (13.90, 25.42)	1.11 (0.68, 1.81)
			Pooled odds ratio	**1.80 (1.03, 3.13)**



Zanubrutinib vs ibrutinib

Indication	N	zanu CR (95% CI)	ibr CR (95% CI)	Odds ratio (95% CI)
R/R CLL	4	10.70 (7.78, 14.54)	7.86 (5.83, 10.52)	1.40 (0.87, 2.26)
R/R MCL	2	77.90 (67.93, 85.44)	27.00 (22.72, 31.75)	9.53 (5.45, 16.66)
R/R MZL	3	26.95 (18.60, 37.33)	10.00 (4.65, 20.20)	3.32 (1.28, 8.61)
TN CLL	2	16.54 (13.00, 20.81)	13.54 (3.70, 38.95)	1.27 (0.30, 5.30)
WM	3	0.99 (0.20, 4.70)	0.50 (0.03, 7.48)	1.98 (0.08, 48.95)
			Pooled odds ratio	**2.85 (1.16, 7.04)**

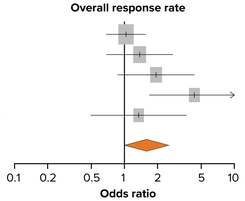


Abbreviations: aca, acalabrutinib; BCL, B-cell lymphoma; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; ibr, ibrutinib; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; N, number of trials or cohorts pooled; R/R, relapsed/refractory; TN, treatment naive; WM: Waldenström macroglobulinemia; zanu, zanubrutinib.

Figure 2. Odds Ratios for Overall Response Comparisons Across BCL Indications

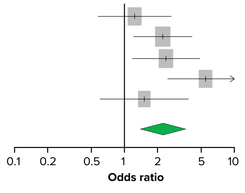
Zanubrutinib vs acalabrutinib

Indication	N	zanu ORR (95% CI)	aca ORR (95% CI)	Odds ratio (95% CI)
R/R CLL	2	85.60 (81.36, 89.00)	85.20 (81.45, 88.30)	1.03 (0.69, 1.56)
R/R MCL	3	84.00 (74.68, 90.33)	79.24 (72.17, 84.89)	1.38 (0.69, 2.75)
R/R MZL	2	68.20 (56.28, 78.13)	52.50 (37.27, 67.28)	1.94 (0.87, 4.33)
TN CLL	3	97.50 (94.56, 98.87)	90.00 (84.67, 93.62)	4.33 (1.68, 11.15)
WM	3	94.71 (90.18, 97.21)	93.00 (86.30, 96.55)	1.35 (0.50, 3.67)
			Pooled odds ratio	**1.59 (1.0003, 2.53)**



Zanubrutinib vs ibrutinib

Indication	N	zanu ORR (95% CI)	ibr ORR (95% CI)	Odds ratio (95% CI)
R/R CLL	4	85.60 (81.36, 89.00)	82.77 (70.44, 90.64)	1.24 (0.58, 2.66)
R/R MCL	2	83.70 (74.34, 90.10)	69.70 (64.82, 74.17)	2.23 (1.21, 4.12)
R/R MZL	3	76.73 (66.64, 84.47)	58.00 (45.57, 69.49)	2.39 (1.18, 4.85)
TN CLL	2	97.11 (94.71, 98.44)	86.00 (79.10, 90.88)	5.47 (2.47, 12.12)
WM	4	94.71 (90.18, 97.21)	92.19 (86.11, 95.75)	1.52 (0.60, 3.83)
			Pooled odds ratio	**2.25 (1.40, 3.61)**



Abbreviations: aca, acalabrutinib; BCL, B-cell lymphoma; CI, confidence interval; CLL, chronic lymphocytic leukemia; ibr, ibrutinib; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; N, number of trials or cohorts pooled; ORR, overall response rate; R/R, relapsed/refractory; TN, treatment naive; WM: Waldenström macroglobulinemia; zanu, zanubrutinib.

DISCUSSION

- This analysis indicates that zanubrutinib is associated with higher response rates across BCL indications compared with acalabrutinib and ibrutinib
- Within each indication, zanubrutinib consistently demonstrated either numerically higher or statistically superior response rates; these findings suggest that zanubrutinib offers a more effective treatment option for patients with BCL
- The observed heterogeneity is likely driven by differences in key study characteristics across trials, including patient populations, mutation status, indication, line of therapy, and follow-up duration
- This variability suggests that the relative efficacy of zanubrutinib compared with other BTK inhibitors may differ by indication; nonetheless, zanubrutinib generally demonstrated superior efficacy and was favored in the majority of indications assessed

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DISCLOSURES

PLZ: Advisory board: Sobi, Kite Pharma/Gilead, Janssen, BMS, MSD, AstraZeneca, Takeda, Roche, Recordati, Kyowa Kirin, Novartis, ADC Therap., Incyte, BeOne Medicines Ltd; Speakers bureau: Sobi, Kite Pharma/Gilead, Janssen, BMS, MSD, AstraZeneca, Takeda, Roche, Recordati, Kyowa Kirin, Novartis, Incyte, BeOne Medicines Ltd; Consultant: MSD, Takeda, Recordati, Novartis. **RW, MX, LM, KY:** Employment and own stock: BeOne Medicines Ltd. **PZ:** Employment: Evidera. **HB:** Employment and stock: AstraZeneca; Consulting or advisory role: Regeneron. **BN:** No disclosure.

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