A Real-World Comparison of Treatment and Survival Outcomes With Zanubrutinib and Acalabrutinib Monotherapy Among Patients With Relapsed or Refractory Mantle Cell Lymphoma in the United States

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CONCLUSIONS

- In this large real-world study of patients receiving 2L+ treatment for MCL, zanubrutinib monotherapy was associated with significantly longer TTNT and OS compared with acalabrutinib monotherapy, supporting its potential clinical benefit in routine care
- These findings provide robust real-world comparative evidence among a large cohort of commercially insured patients in the US on the clinical effectiveness of zanubrutinib and complement emerging real-world data demonstrating clinically meaningful differences among covalent BTKis
- Real-world evidence provides a novel approach to compare clinical outcomes when comparisons do not exist in clinical trials. However, unmeasured confounding factors and lack of randomization should caution interpretation and generalizability to other populations
- Zanubrutinib is an effective treatment option for R/R MCL, where durable disease control and tolerability remain key unmet needs

INTRODUCTION

- Mantle cell lymphoma (MCL) is a rare and clinically heterogeneous subtype of B-cell non-Hodgkin lymphoma (NHL) that represents approximately 5-6% of NHL cases[1,2]
- MCL is characterized by an aggressive clinical course in the majority of patients with repeated relapses and remains incurable with standard therapies[2]
- Second-generation Bruton tyrosine kinase inhibitors (BTKis), zanubrutinib and acalabrutinib, are established therapies for relapsed or refractory (R/R) MCL
- However, comparative effectiveness data between these agents in routine clinical practice are limited[3,4]

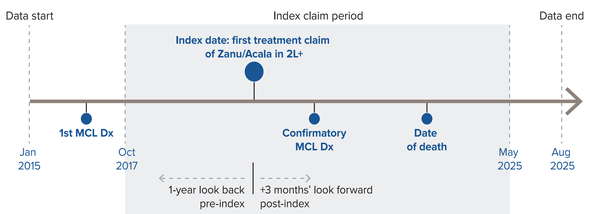
AIM

- To describe baseline characteristics and compare real-world treatment outcomes among patients with R/R MCL receiving zanubrutinib or acalabrutinib

METHODS

- This real-world, retrospective, observational analysis was conducted using claims data from the Komodo database, a large United States (US)-based administrative claims database capturing longitudinal real-world data (**Figure 1**). Eligible patients were adults (aged ≥18 years) in the US, with a diagnosis of MCL, who initiated zanubrutinib or acalabrutinib monotherapy in second-line or later (2L+) from January 2015 through August 2025
  - Required continuous enrollment for or within 1 year prior to and 3 months following the index date
  - Patients were excluded if they participated in clinical trials, had end-stage renal disease or had a prior stem cell transplant
  - If an outcome was not observed, patients were censored at the date of last activity, the enrollment end date, or end of study period

Figure 1. Study Design



Abbreviations: 2L, second line; Acala, acalabrutinib; Dx, diagnosis; MCL, mantle cell lymphoma; Zanu, zanubrutinib.

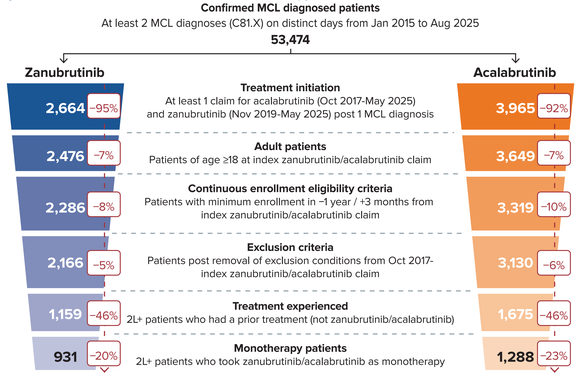
- Descriptive statistics including medians, interquartile range, and percentages were reported for baseline characteristics. Kaplan-Meier estimates and the log-rank test ($P<.05$ was considered statistically significant) were used to estimate time to next treatment (TTNT) and overall survival (OS), and compare survival distributions across treatment groups
  - TTNT was defined as the date of initiation of monotherapy BTKi to the initiation of next treatment or death
  - OS was defined as the date of initiation of a BTKi to death
- For all outcomes, patients were followed until they reached their outcome, or the end of enrollment, or the last confirmed activity date, or end of study period, whichever comes earlier
- Cox proportional hazards regression models were used to generate unadjusted or adjusted hazard ratios (HR) for treatment comparisons with associated 95% CIs and P-values
- Inverse probability of treatment weighting (IPTW) was adjusted for age, sex, US region, treatment initiation year, and Charlson Comorbidity Index (CCI)

RESULTS

Patient Characteristics

- A total of 53,474 patients with an R/R MCL diagnosis were identified in the Komodo database during the study period (**Figure 2**)
  - The final cohort consists of 931 and 1,288 patients who received 2L+ zanubrutinib and acalabrutinib monotherapy, respectively
  - The median age at index was 73.0 and 72.0 years for patients on zanubrutinib and acalabrutinib, respectively
  - Patients receiving zanubrutinib and acalabrutinib were predominantly male (71% and 75%, respectively) and White (73% and 74%, respectively)

Figure 2. Zanubrutinib and Acalabrutinib Monotherapy in 2L+



Abbreviations: 2L, second line; MCL, mantle cell lymphoma.

- Geographic distribution was consistent, with the South US region contributing the highest proportion of patients (37% and 32%, respectively)
  - Patients had largely moderate comorbidity burden (mean CCI: 3.5 and 3.6, respectively)
- Median follow-up was 14.8 and 18.2 months for zanubrutinib and acalabrutinib, respectively (**Table 1**)

Table 1. Patient Characteristics

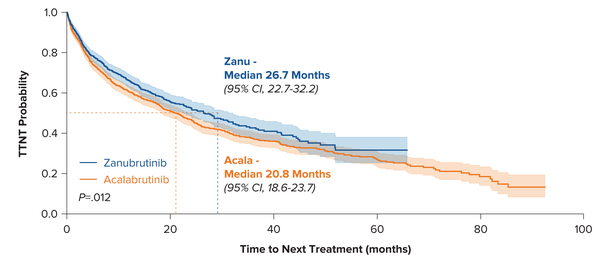
	Zanubrutinib (N=931)	Acalabrutinib (N=1,288)
Median age at index date	73.0	72.0
Male, n (%)	661 (71)	966 (75)
US region, n (%)		
Northeast	205 (22)	245 (19)
Midwest	214 (23)	361 (28)
South	345 (37)	412 (32)
West	168 (18)	270 (21)
Mean Charlson Comorbidity Index (CCI), (SD)	3.5 (3.2)	3.6 (3.1)
Race and ethnicity, n (%)		
White	680 (73)	953 (74)
Hispanic or Latino	75 (8)	103 (8)
Black or African American	46 (5)	64 (5)
Asian or Pacific Islander	27 (3)	26 (2)
Other	28 (3)	39 (3)
Unknown	75 (8)	103 (8)
Duration of follow-up months, median (IQR)	14.8 (7.7-25.5)	18.2 (7.9-38.2)
Treatment initiation year, n (%)		
2017	0	21 (2)
2018	0	157 (12)
2019	0	152 (12)
2020	73 (8)	190 (15)
2021	130 (14)	191 (15)
2022	124 (13)	148 (11)
2023	210 (23)	160 (12)
2024	311 (33)	179 (14)
2025	83 (9)	90 (7)

Abbreviations: 2L, second line; CCI, Charlson Comorbidity Index; IQR, interquartile range; SD, standard deviation; US, United States.

Clinical Outcomes

- Median TTNT was 26.7 months for zanubrutinib and 20.8 months for acalabrutinib ($P=.01$) (**Figure 3**)
  - Patients receiving zanubrutinib had numerically higher probability of not advancing to next treatment at 12 months (66.3% vs 60.6%), 24 months (52.8% vs 46.7%), and 36 months (42.8% vs 37.5%) compared with acalabrutinib across unadjusted (HR: 0.86) and IPTW-adjusted (HR: 0.86) models (**Figure 3**)

Figure 3. Kaplan-Meier Curves for Time to Next Treatment



Number of patients at risk, n (%)

Zanubrutinib	931 (100%)	234 (24%)	68 (8%)	10 (1%)	0
Acalabrutinib	1,288 (100%)	429 (34%)	190 (15%)	77 (6%)	20 (1%)

Kaplan-Meier Estimated Rates

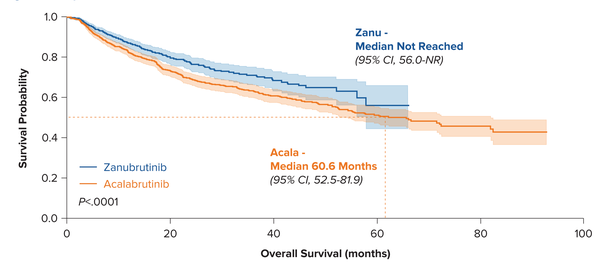
Months	Zanubrutinib % (95% CI)	Acalabrutinib % (95% CI)
12M	66.3 (63.0-69.4)	60.6 (57.8-63.3)
24M	52.8 (48.9-56.6)	46.7 (43.7-49.8)
36M	42.8 (38.0-47.5)	37.5 (34.3-40.7)

Abbreviations: Acala, acalabrutinib; CI, confidence interval; M, months; Zanu, zanubrutinib.

Overall Survival

- Median OS was not reached for the zanubrutinib cohort versus 60.6 months for the acalabrutinib cohort (**Figure 4**)
- Patients receiving zanubrutinib had higher probability of survival at 12 months (86.4% vs 81.6%), 24 months (76.3% vs 68.6%), and 36 months (70.4% vs 62.6%) than those receiving acalabrutinib (**Figure 4**)

Figure 4. Kaplan-Meier Curves for Overall Survival



Number of patients at risk, n (%)

Zanubrutinib	931 (100%)	324 (35%)	97 (10%)	11 (1%)	0
Acalabrutinib	1,288 (100%)	603 (47%)	305 (24%)	132 (10%)	36 (3%)

Kaplan-Meier Estimated Rates

Months	Zanubrutinib % (95% CI)	Acalabrutinib % (95% CI)
12M	86.4 (83.9-88.6)	81.6 (79.3-83.7)
24M	76.3 (72.7-79.6)	68.6 (65.6-71.4)
36M	70.4 (65.8-74.5)	62.6 (59.4-65.7)

Abbreviations: Acala, Acalabrutinib; CI, confidence interval; M, months; NR, not reached; OS, overall survival; Zanu, Zanubrutinib.

Comparative Effectiveness Between Zanubrutinib and Acalabrutinib

- Zanubrutinib showed significantly longer TTNT compared with acalabrutinib across unadjusted (HR: 0.86; $P=.012$) and IPTW-adjusted models (HR: 0.86; $P=.025$) (**Table 2**)
- In the unadjusted and adjusted OS models, patients receiving zanubrutinib had 26% (HR: 0.74; $P<.001$) and 19% lower risk of death (HR: 0.81; $P=.03$) compared with patients receiving acalabrutinib (**Table 2**)

Table 2. Unadjusted and Adjusted Models for TTNT and OS

Outcomes	Zanubrutinib vs Acalabrutinib HR (95% CI)	*P* value
TTNT		
Unadjusted[a]	0.86 (0.76-0.97)	.012
IPTW Adjusted[b]	0.86 (0.76-0.98)	.025
OS		
Unadjusted[a]	0.74 (0.62-0.88)	<.001
IPTW Adjusted[b]	0.81 (0.68-0.98)	.030

[a]Reference treatment was acalabrutinib for zanubrutinib vs acalabrutinib. [b]Covariates included in IPTW-adjusted model are age, sex, region, CCI, treatment initiation year.
Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; rw, real world; TTNT, time to next treatment.

LIMITATIONS

- The follow-up time between zanubrutinib and acalabrutinib groups was imbalanced, reflecting different regulatory milestones, staggered clinical adoption, and enrollment timing. The study analysis tried to reduce this imbalance by adjusting for treatment initiation year in the adjusted models
- As with claims-based analyses, the potential for miscoding or delayed coding may lead to under-identification or misclassification of clinical events and procedures
- Mortality data were derived from multiple linked sources, and delays in capture or misreporting may impact OS estimates
- The study faces concerns related to residual confounding and selection bias due to lack of information on key clinical variables for disease aggressiveness, e.g. TP53 mutation, Ki-67 index, and physician treatment selection pattern, etc.

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DISCLOSURES

YW: Research: AbbVie, AstraZeneca, BeOne Medicines, Ltd, Bristol Myers Squibb, Eli Lilly, Genentech, Genmab, Incyte, InnoCare, Loxo Oncology, Merck, MorphoSys, Novartis. Consulting or advisory role: AbbVie, AstraZeneca, BeOne Medicines, Ltd, Eli Lilly, Genmab, Incyte, InnoCare, Janssen, Kite, Loxo Oncology, TG Therapeutics. Honorarium: Kite. **RJ:** Honoraria: SecuraBio; Consulting or advisory role: AbbVie, AstraZeneca, Genentech, BeOne Medicines, Ltd, Genmab, Lilly; Speakers' bureau and travel, accommodations, expenses: AbbVie, Adaptive, BeOne Medicines, Ltd, AstraZeneca. **GAM:** Employment: BeOne Medicines, Ltd; Stock or other ownership: BeOne Medicines, Ltd, Gilead, Amgen, CRISPR Therapeutics; Consulting or advisory role: CRISPR Therapeutics, BeOne Medicines, Ltd; Travel, accommodations, expenses: BeOne Medicines, Ltd, CRISPR Therapeutics. **QF:** Employment and may own stock: BeOne Medicines, Ltd, AbbVie. **DN, NJ, VG:** Employee of ZS Associates and serve as paid consultants for BeOne Medicines, Ltd. **DAE:** Honoraria: BeOne Medicines, Ltd; Consulting or advisory role: BeOne Medicines, Ltd, ADC Therapeutics; Speakers' bureau: Incyte, AstraZeneca. **MS, RW:** Employment and may own stock: BeOne Medicines, Ltd.

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