Real-World Treatment and Survival Outcomes for Zanubrutinib and Acalabrutinib Monotherapy Among Treatment-Naïve Patients With Chronic Lymphocytic Leukemia in the United States

7045

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CONCLUSIONS

- In this real-world study of treatment-naïve patients with CLL, patients receiving zanubrutinib demonstrated significantly longer TTNT and improved OS compared with acalabrutinib
- These findings were consistent across unadjusted and IPTW-adjusted analyses, providing robust real-world comparative evidence among a large sample of insured patients in the US on the clinical effectiveness of zanubrutinib in routine practice
- Collectively, these results help inform treatment selection in treatment-naïve CLL patients, where optimizing disease control and tolerability remains an important unmet need

INTRODUCTION

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukemia among adults[1]
- Covalent Bruton tyrosine kinase (BTK) inhibitors have greatly improved treatment outcomes for patients, and these targeted therapies are now considered standard of care
- Second-generation BTK inhibitors, acalabrutinib and zanubrutinib, are the preferred regimen by the National Comprehensive Cancer Network
- However, optimal sequencing and comparative effectiveness of BTK inhibitors remain uncertain, highlighting the need for real-world evidence among larger samples of patients and over a longer follow-up period to guide treatment selection[2,3]

AIM

- Compare the real-world outcomes, including time to next treatment (TTNT) and overall survival (OS) among patients with CLL/SLL treated with zanubrutinib or acalabrutinib

METHODS

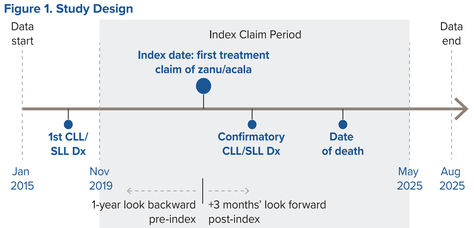
Data Source and Study Design

- A retrospective, observational study included patients identified from the Komodo database, a large US-based administrative claims database capturing longitudinal real-world data, over the period from January 2015 to August 2025 (**Figure 1**)

Study Population

- Adult patients (≥18 years) with confirmed CLL/SLL diagnosis (ICD-10: C91.1X/C83.0X) initiating first-line (1L) zanubrutinib, or acalabrutinib monotherapy
- Index date: Date of first prescription of acalabrutinib (Nov 2019-Aug 2025) or zanubrutinib (Jan 2023-Aug 2025) following a CLL/SLL diagnosis
- Required continuous enrollment for ≥12 months pre-index and ≥3 months post-index
- Excluded patients with history of clinical trial, history of prior CLL/SLL treatment (such as chemotherapy, targeted therapy, stem cell, or cell-based therapy), or diagnosed with MCL between Jan 2015 and first zanubrutinib/acalabrutinib index date

Figure 1. Study Design



Abbreviations: acala, acalabrutinib; CLL, chronic lymphocytic leukemia; Dx, diagnosis; SLL, small lymphocytic lymphoma; zanu, zanubrutinib.

Study Outcomes

- **Baseline characteristics:** Age, sex, race/ethnicity, geographic region, Charlson Comorbidity Index (CCI), and treatment initiation year
- **Time to Next Treatment (TTNT)**: Time from initiation of BTK inhibitor monotherapy to initiation of next treatment or death
- **Overall Survival (OS)**: Time from initiation of BTK inhibitor monotherapy to death
- For all outcomes, patients were followed until they reached their outcome, the study period ends, last confirmed activity date, or end of enrollment, whichever occurred earliest

Statistical Analysis

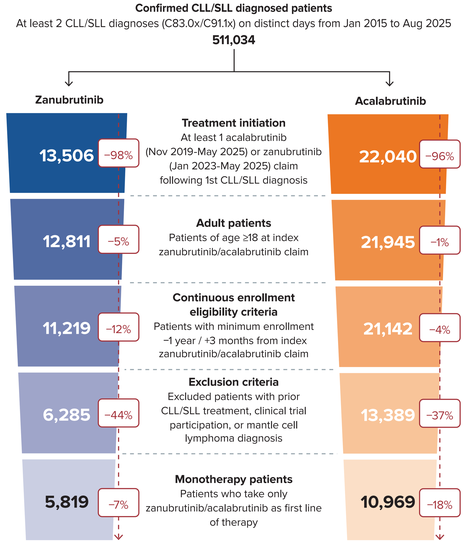
- Kaplan-Meier methods were used to estimate TTNT and OS, with group comparisons assessed using the log-rank test ($P<.05$ considered statistically significant) and Cox proportional hazards models with inverse probability of treatment weighting (IPTW) to adjust for baseline confounders (age, sex, geographic region, CCI, and treatment initiation year)

RESULTS

Patient population and baseline characteristics

- A total of 511,034 patients with CLL/SLL were identified, of whom 5,819 and 10,969 patients comprised the zanubrutinib and acalabrutinib monotherapy cohorts, respectively (**Figure 2**)

Figure 2. CLL Cohorts: Zanubrutinib and Acalabrutinib Monotherapy



Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia.

- Patients had a median age of 74.0 and 73.0 years, and were predominantly male (59% and 62%) in the zanubrutinib and acalabrutinib cohorts respectively
- Geographic distribution was consistent across cohorts, with the South region contributing the highest proportion of patients (35%), moderate comorbidity burden (mean CCI: 2.52 and 2.48), and similar racial distribution (predominantly non-Hispanic, White 72%) in the zanubrutinib and acalabrutinib cohorts, respectively (**Table 1**)

Table 1. Demographics and Clinical Characteristics for CLL

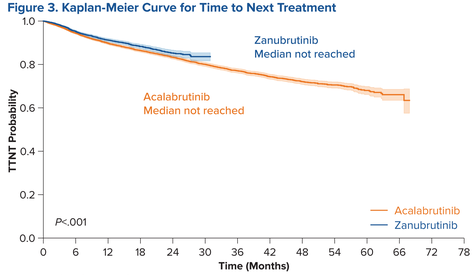
	Zanubrutinib (N=5,819)	Acalabrutinib (N=10,969)
Median age at index date, years	74.0	73.0
Gender, n (%)		
Male	3,460 (59)	6,816 (62)
Female	2,298 (40)	4,037 (37)
Unknown	61 (1)	116 (1)
US region, n (%)		
Northeast	1,261 (22)	2,413 (22)
Midwest	1,471 (25)	2,726 (25)
South	2,047 (35)	3,877 (35)
West	1,037 (18)	1,943 (18)
Other	3 (0)	10 (0)
Charlson Comorbidity Index (CCI)		
Mean (SD)	2.52 (2.6)	2.48 (2.6)
Median	2	2
Race and ethnicity, n (%)		
White	4,189 (72)	7,846 (72)
Black or African American	582 (10)	1,014 (9)
Hispanic or Latino	291 (5)	527 (5)
Asian or Pacific Islander	116 (2)	211 (2)
Unknown	466 (8)	1,036 (9)
Other	175 (3)	335 (3)
Treatment initiation year, n (%)		
2019	0	44 (0)
2020	0	1,098 (10)
2021	0	1,986 (18)
2022	0	2,242 (20)
2023	1,754 (30)	1,903 (17)
2024	3,143 (54)	2,580 (24)
2025	922 (16)	1,116 (10)
Median follow-up months (IQR)	12.8 (7.5-19.1)	16.4 (4.9-35.4)

Abbreviations: CCI, Charlson Comorbidity Index; CLL, chronic lymphocytic leukemia; IQR, interquartile range; SD, standard deviation.

Clinical Outcomes

- **Time to Next Treatment (TTNT)**
  - Median TTNT was not reached for both zanubrutinib and acalabrutinib (**Figure 3**)
  - Kaplan-Meier estimates showed a higher proportion of patients initiating on zanubrutinib had not progressed to their next treatment at 18 months (88% vs 86%), 24 months (85% vs 83%) and 30 months (84% vs 80%) compared with acalabrutinib
- **Overall Survival (OS)**
  - Median OS was not reached for all treatment cohorts (**Figure 4**)
  - Kaplan-Meier estimates showed higher survival probabilities with zanubrutinib at 18 months (94% vs 93%), 24 months (92% vs 91%), and 30 months (91% vs 89%) compared with acalabrutinib

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



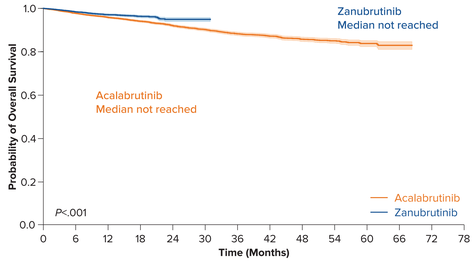
Number of patients at risk, n (%)

	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Acalabrutinib	5,819 (100%)	4,753 (82%)	2,935 (50%)	1,577 (27%)	623 (11%)	49 (1%)	0	0	0	0	0			
Zanubrutinib	10,969 (100%)	9,478 (86%)	7,395 (67%)	5,855 (53%)	4,594 (42%)	3,645 (33%)	2,698 (25%)	1,896 (17%)	1,204 (11%)	652 (6%)	267 (2%)			

Months	Zanubrutinib, % (95% CI)	Acalabrutinib, % (95% CI)
6M	95 (95-96)	94 (94-95)
12M	91 (90-92)	90 (89-90)
18M	88 (87-89)	86 (86-87)
24M	85 (84-87)	83 (82-84)
30M	84 (82-85)	80 (79-81)

Abbreviations: acala, acalabrutinib; CI, confidence interval; KM, Kaplan-Meier; M, months; TTNT; time to next treatment; zanu, zanubrutinib.

Figure 4. Kaplan-Meier Curve for Overall Survival



Number of patients at risk, n (%)

	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Acalabrutinib	5,819 (100%)	4,817 (83%)	3,073 (53%)	1,699 (29%)	682 (12%)	52 (1%)	0	0	0	0	0			
Zanubrutinib	10,969 (100%)	9,524 (87%)	7,680 (70%)	6,214 (57%)	4,955 (45%)	4,005 (37%)	2,979 (27%)	2,145 (20%)	1,385 (13%)	755 (7%)	320 (3%)			

Months	Zanubrutinib, % (95% CI)	Acalabrutinib, % (95% CI)
6M	98 (98-98)	98 (98-98)
12M	96 (95-96)	95 (95-96)
18M	94 (93-95)	93 (93-94)
24M	92 (91-94)	91 (90-92)
30M	91 (90-93)	89 (88-89)

Abbreviations: acala, acalabrutinib; CI, confidence interval; KM, Kaplan-Meier; M, months; OS, overall survival; zanu, zanubrutinib.

- In the unadjusted Cox model, patients receiving zanubrutinib had a longer TTNT (unadjusted hazard ratio [HR], 0.88; $P=.009$) and longer OS (HR, 0.72; $P<.001$)
- After IPTW adjustment, results were consistent and patients receiving zanubrutinib demonstrated significantly improved OS (IPTW-adjusted HR, 0.75; $P<.001$) and TTNT (IPTW-adjusted HR, 0.89; $P=.02$) compared with acalabrutinib

Table 2. Cox Proportional Hazards Analysis Comparing TTNT and OS Between Zanubrutinib vs Acalabrutinib and Zanubrutinib (Unadjusted and IPTW-Adjusted Models)

	Zanubrutinib vs Acalabrutinib	
Outcomes	HR (95% CI)	*P* value
TTNT		
Unadjusted[a]	0.88 (0.79–0.97)	.009
IPTW-adjusted[b]	0.89 (0.80–0.98)	.020
OS		
Unadjusted[a]	0.72 (0.62–0.82)	<.001
IPTW-adjusted[b]	0.75 (0.65–0.86)	<.001

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

LIMITATIONS

- As with claims-based analyses, 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
- Differences in launch timelines of BTK inhibitor resulted in variable follow-up durations across treatment cohorts. However, this study tried to reduce this imbalance by adjusting for treatment initiation year in the adjusted models
- This study included patients with CLL who initiated acalabrutinib between 2020 and 2022, coinciding with the COVID-19 pandemic, while zanubrutinib was not approved for CLL/SLL at the time. However, this study tried to reduce this imbalance by adjusting for treatment initiation year in the adjusted models
- The study faces concerns related to residual confounding and selection bias due to lack of information on key clinical variables for CLL disease aggressiveness, e.g. Cytogenetic tests to detect *TP53*, IGHV mutation, e.g. FISH test

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DISCLOSURES

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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