Treatment Patterns and Outcomes Among Patients Treated With Second-Generation BTK Inhibitors in CLL

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CONCLUSIONS

- In this real-world study from a diverse patient population treated with next-generation BTKis at UCSF, we demonstrated that more patients with ZANU had high-risk features and more comorbidities
- Patients treated with ZANU had a lower risk of starting next treatment and a trend of improved survival versus ACA
- These findings provide additional insights to inform clinical decision-making for CLL treatment in real-world settings

INTRODUCTION

- The introduction of innovative therapeutic classes, such as Bruton tyrosine kinase inhibitors (BTKis), has led to a notable improvement in the outlook for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1-4]
- Next-generation covalent BTKis, including zanubrutinib (ZANU) and acalabrutinib (ACA), are established standards of care for CLL. However, there is limited evidence on how patient characteristics may affect clinical outcomes between the next-generation BTKis
- Patient populations receiving care may also differ across institutes and regions. The University of California, San Francisco (UCSF) Health system serves a large and diverse patient population in the Bay Area. This offers a unique opportunity to evaluate social and demographic characteristics, real-world treatment patterns, and outcomes among patients treated with BTKis for CLL

METHODS

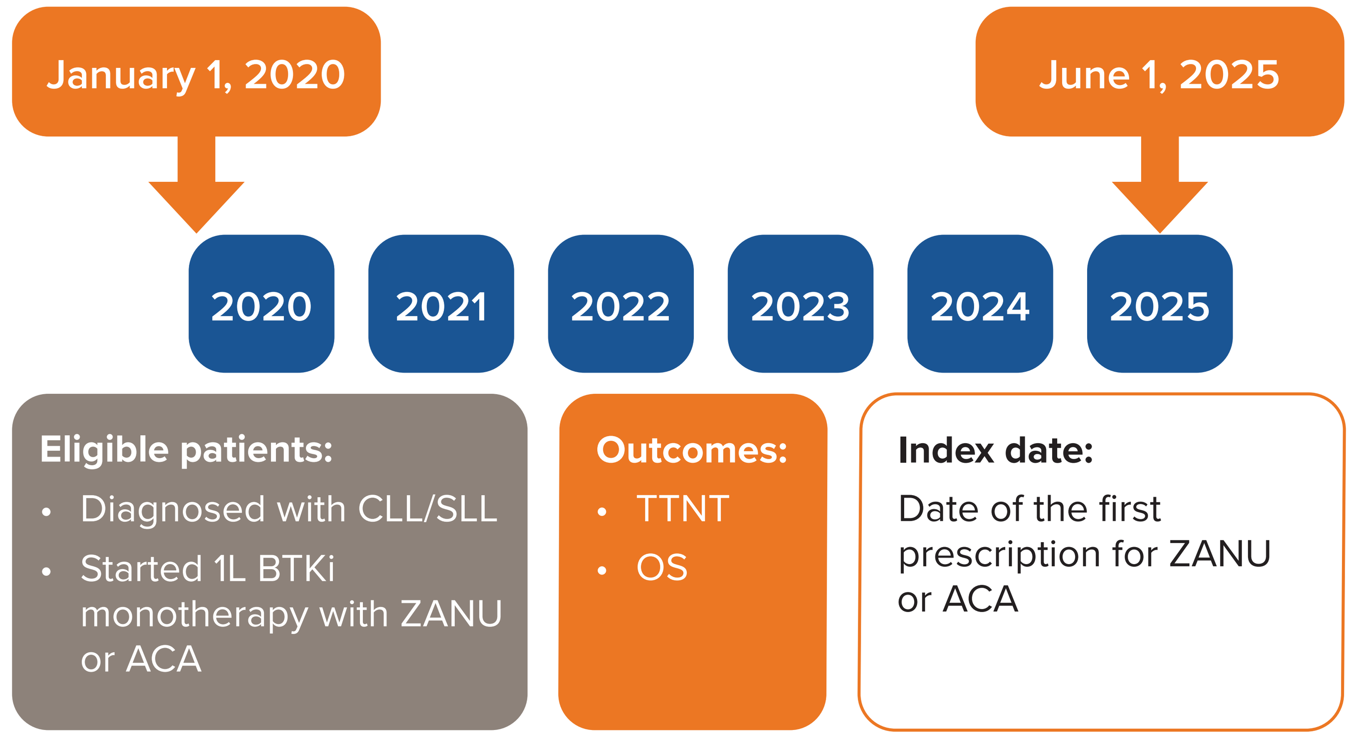
Data Source and Study Population

- This real-world retrospective observational study included adult patients with CLL/SLL receiving ZANU or ACA between January 1, 2020 and June 1, 2025 at the UCSF Health system (**Figure 1**)
- The index date was defined as the date of the first prescription for ZANU or ACA, and patients were followed up until death, their last encounter, or study end (June 1, 2025)
- Patients were excluded from the study if they had experienced <3 months of follow-up after starting ZANU or ACA (except for cases resulting in death), received ZANU or ACA as part of a combination therapy, had no subsequent visit after index date, or if they participated in an interventional clinical trial after the index date

Study Design

- Demographic, social, and clinical characteristics, as well as treatment patterns were extracted from structured data from UCSF Clinical Data Warehouse
- Mutation status and adverse events (AEs) during treatment were extracted from clinical notes using a large language model (LLM; GPT-4o)
- Outcomes included real-world time to next treatment (TTNT; defined as time to next line of therapy or death) and overall survival (OS) from index date.[1] Patients were censored at last activity

Figure 1. Study Design



Abbreviations: 1L, first-line; ACA, acalabrutinib; BTKi, Bruton tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; OS, overall survival; TTNT, time to next treatment; ZANU, zanubrutinib.

Statistical Analysis

- Descriptive statistics were used to summarize baseline characteristics and treatment patterns by treatment groups
- Outcomes were assessed using Kaplan-Meier methods and multivariate Cox proportional hazard models with inverse probability of treatment weighting (IPTW) for balancing covariates between groups, including age, sex, race, comorbidities, driving distance, area deprivation index, line of therapy, and prior BTKi use. Landmark probabilities at 12 months, and adjusted hazard ratios (HR) were reported for each outcome

RESULTS

Patient Characteristics

- The study population included 175 patients with CLL/SLL, with an average age of 72 years (**Table 1**)
  - Among them, 126 patients received ZANU and 49 received ACA, with a median follow-up time of 18 months (interquartile range [IQR]: 8-32 months; ZANU: 16 [7-23]; ACA: 31 [13-40])
- Most patients were male (60%), and the largest ethnic group was White (70%), followed by Asian (10%), Hispanic (5%), and Black or African American (2%). Demographics and characteristics were mostly similar between the ZANU and ACA groups. The median Area Deprivation Index was 2 (IQR: 1-5) and average driving distance from home to clinic was 24 miles (IQR: 12-63)
- Most patients were treatment-naïve (74%) and BTKi-naïve prior to the index date (85%). Compared to patients in the ACA group, more patients in the ZANU group had received medications for hypertension (19% vs 12%) and anticoagulants (28% vs 10%) at baseline. Patients in the ZANU group had a higher median Charlson Comorbidity Index (CCI) score than those in the ACA group (1 vs 0)
- Among patients with extractable clinical notes (n=145; 109 ZANU and 35 ACA), *TP53* mutation was reported in 12% (14% ZANU, 6% ACA), 17p deletion in 13% (15% ZANU, 8% ACA), and 11q deletion in 12% of patients (9% ZANU, 19% ACA)

Comparative Effectiveness

- The median TTNT was 59 (95% confidence interval [CI]: 20 - not reached [NR]) months for ACA and NR months (NR-NR) for ZANU (**Figure 2**)
- The 12-month probabilities of not starting next treatment were 78% (95% CI: 64-88%) for ACA and 83% (95% CI: 74-89%) for ZANU. The 12-month survival probabilities were 89% (95% CI: 76-95%) for ACA, and 91% (95% CI: 84 -95%) for ZANU

Table 1. Baseline Characteristics With Zanubrutinib vs Acalabrutinib in CLL/SLL

	Overall (n=175)	ZANU (n=126)	ACA (n=49)	*P*-value
Age, mean (SD)	72.3 (10.3)	72.1 (10.4)	72.6 (9.9)	0.782
Gender, n (%)				0.514
Female	70 (40.0)	48 (38.1)	22 (44.9)	
Male	105 (60.0)	78 (61.9)	27 (55.1)	
Race, n (%)				0.600
White	122 (69.7%)	85 (67.5%)	37 (75.5%)	
Asian	18 (10.3%)	14 (11.1%)	4 (8.2%)	
Black or African American	4 (2.3%)	2 (1.6%)	2 (4.1%)	
Hispanic or Latino	8 (4.6%)	8 (6.3%)	0 (0.0%)	
Other/Unknown	23 (13.1%)	17 (13.5%)	6 (12.2%)	
ADI, median [Q1, Q3]	2 [1, 5]	2 [2, 4]	2 [1, 5]	0.513
Missing, n	10			
CCI, median [Q1, Q3]	0 [0, 2]	1 [0, 2]	0 [0, 1]	0.108
Lines of therapy group, n (%)				1.000
1	129 (73.7)	93 (73.8)	36 (73.5)	
2+	46 (26.3)	33 (26.2)	13 (26.5)	
BTKi-naïve, n (%)				0.046
Naïve	149 (85.1)	112 (88.9)	37 (75.5)	
Not naïve	26 (14.9)	14 (11.1)	12 (24.5)	
Anti-HTN, n (%)				0.396
Yes	30 (17.1)	24 (19.0)	6 (12.2)	
Anticoagulant, n (%)				0.022
Yes	40 (22.9)	35 (27.8)	5 (10.2)	
Antiplatelet, n (%)				0.324
Yes	5 (2.9)	0 (0.0)	5 (4.0)	
***TP53* mutation, n (%)**				0.241
Positive	17 (11.7)	15 (13.8)	2 (5.6)	
Negative/unknown	128 (88.3)	94 (86.2)	34 (94.4)	
Missing	30	17	13	
17p deletion, n (%)				0.406
Positive	19 (13.1)	16 (14.7)	3 (8.3)	
Negative/unknown	126 (86.9)	93 (85.3)	33 (91.7)	
Missing	30	17	13	
11q deletion, n (%)				0.132
Positive	17 (11.7)	10 (9.2)	7 (19.4)	
Negative/unknown	128 (88.3)	99 (90.8)	29 (80.6)	
Missing	30	17	13	

Abbreviations: ACA, acalabrutinib; ADI, Area Deprivation Index; BTKi, Bruton tyrosine kinase inhibitor; CCI, Charlson Comorbidity Index; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; HTN, hypertensive medications; Q1, lower quartile; Q3, upper quartile; SD, standard deviation; ZANU, zanubrutinib.

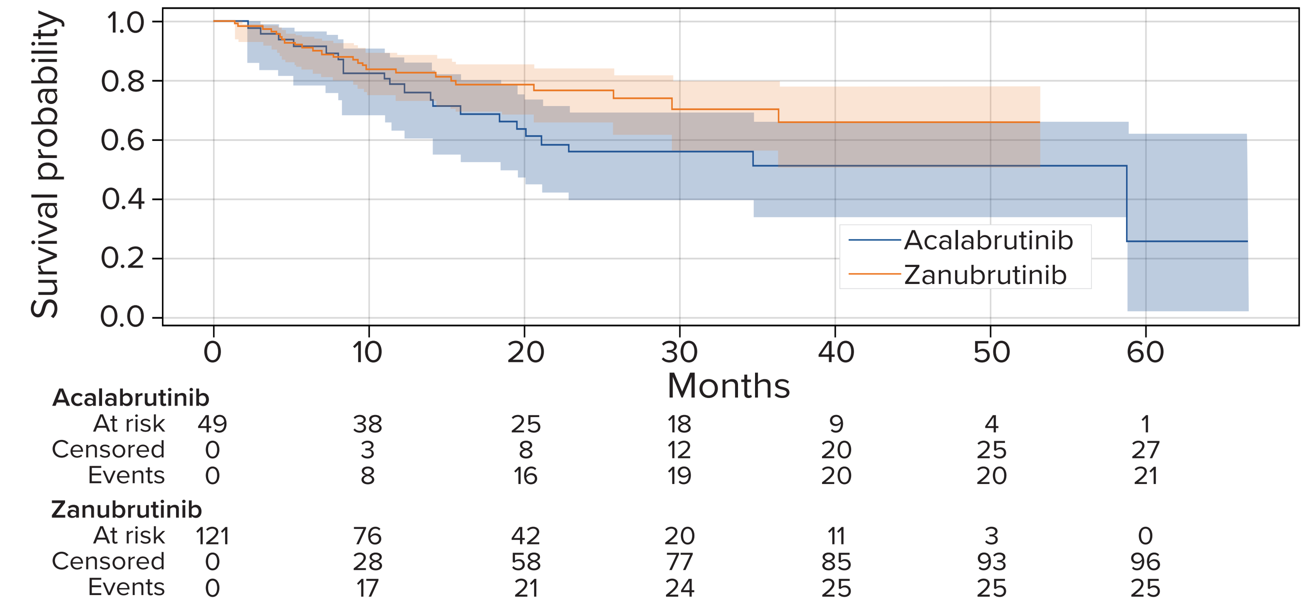
- After IPTW adjustment for baseline factors, patients with ZANU were 47% less likely to receive the next line of therapy or experience death than those with ACA (HR: 0.53; 95% CI: 0.32-0.89; *P*=0.015). Patients with ZANU also had numerically higher probability of survival than those with ACA, although this was not statistically significant (HR: 0.55; 95% CI: 0.29-1.01; *P*=0.054) (**Table 2**)
- In addition, a higher CCI score was associated with worse outcomes for TTNT (HR: 1.20; 95% CI: 1.01-1.42) and OS (HR: 1.24; 95% CI: 1.03-1.50)

Exploring Adverse Events Using a LLM

- Among patients with extractable notes for LLM, 97% of overall patient cohorts had at least one documented AE (grade unspecified) during treatment. The most common AEs were bleeding/bruising (33%), fatigue (31%), gastrointestinal symptoms (28%), musculoskeletal pain (24%), neuropsychiatric symptoms (21%), infections (15%), and cytopenia (12%)

Figure 2. Kaplan-Meier Curves for Outcomes With Zanubrutinib vs Acalabrutinib

A) Time to Next Treatment



B) Overall Survival

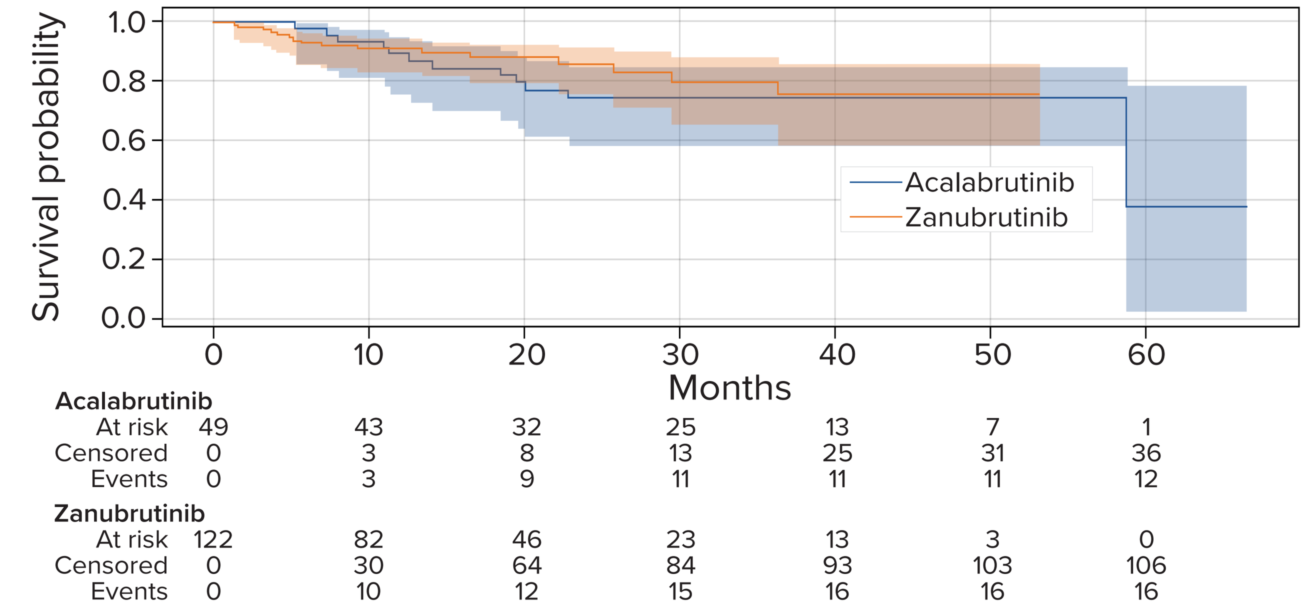


Table 2. IPTW-Adjusted Hazard Ratios for Zanubrutinib vs Acalabrutinib

Outcomes	HR (95% CI)	*P*-Value
TTNT	0.53 (0.32-0.89)	0.015
OS	0.55 (0.29-1.01)	0.054

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; TTNT, time to next treatment.

DISCUSSION

- The results of this study revealed differences in clinical outcomes for patients with CLL/SLL receiving BTKi treatments and based on baseline characteristics
- This study also demonstrated the use of LLM to extract critical information, such as biomarker status and AEs
- Future studies can further explore reasons for treatment discontinuation with clinician validation of the LLM

Study Limitations

- The sample size is limited for additional stratification, such as line of therapy
- Differences in median follow-up time for patients on ZANU (16 months) and ACA (31 months) may have influenced outcomes
- Although LLM has shown great potential to extract clinical notes efficiently, it is limited to patients with sufficient extractable notes
- Information that is poorly documented in routine care (eg, grade of AEs) or outside the UCSF Health system is not available

REFERENCES

1. Burger JA. *N Engl J Med.* 2020;383;460-463.
2. Brown JR, et al. *N Engl J Med.* 2023;388:319-332.
3. Jurczak W, et al. *Clin Lymphoma Myeloma Leuk.* 2022;22:S269-S270.
4. Al-Sawaf O, et al. *Lancet Oncol.* 2020;21:1188-1200.

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