Treatment patterns and outcomes among patients treated with second-generation BTK inhibitors in CLL

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Background

Next-generation covalent Bruton tyrosine kinase inhibitors (BTKi), including zanubrutinib (ZANU) and acalabrutinib (ACA), are established standards of care for chronic lymphocytic leukemia (CLL). However, there is limited evidence on how patient characteristics may affect clinical outcomes between the next-generation BTKi.

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 BTKi for CLL.

Methods

This real-world retrospective observational study included adult patients receiving ZANU or ACA between 01 Jan 2020 and 01 Jun 2025 at the UCSF Health system. 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 (01 Jun 2025). Descriptive statistics of demographic, social, and clinical characteristics and treatment patterns were summarized by treatment groups using structured data from UCSF Clinical Data Warehouse (CDW). Mutation status and adverse events (AEs) during treatment were extracted from clinical notes using a large language model (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. 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

This study included 175 patients (126 ZANU and 49 ACA) with a median follow-up time of 18 months (interquartile range [IQR]: 8–32 months; ZANU: 16 [7-23]; ACA: 31 [13-40]). The mean age of the overall patient cohort was 72 years (SD: 10), with 60% male, 67% White, 11% Asian, 5% Hispanic, and 2% Black. Median Area Deprivation Index (ADI) 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 ACA patients, more ZANU patients had received medications for hypertension (19% vs 12%) and anticoagulants (28% vs 10%) at baseline. 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).

The median TTNT was 59 (95% CI: 20-not reached [NR]) months for ACA and NR for ZANU. The median OS was 59 (95% CI: 59-NR) months for ACA and NR for ZANU. 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, respectively. After IPTW adjustment for baseline factors, patients with ZANU were 47% less likely to receive the next line of therapy or death than those with ACA (HR: 0.53; 95% CI: 0.32-0.89; *P*=0.015). Patients with ZANU also had better survival than those with ACA, although this was not statistically significant (HR: 0.55; 95% CI: 0.29-1.01; *P*=0.054). In addition, a higher Charlson Comorbidity Index 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).

Among patients with extractable notes, 97% 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%).

Conclusion

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