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Title: Real-world treatment and survival outcomes for zanubrutinib (zanu) and acalabrutinib (acala) monotherapy among treatment-naive patients with chronic lymphocytic leukemia (CLL) in the United States

Background: Bruton tyrosine kinase (BTK) inhibitors are central to the management of CLL/SLL (hereafter referred to as CLL). Acala was approved for CLL in the US in 2019, followed by zanu in 2023. Despite their widespread use, real-world evidence comparing therapy effectiveness is limited. This US-based study compared the real-world effectiveness of zanu and acala monotherapy as first-line treatment for patients with CLL based on overall survival (OS) and time to next treatment (TTNT).

Methods: This retrospective analysis utilized the Komodo claims database between January 2015 and August 2025. Eligible patients were adults (aged ≥18 years) in the US with ≥2 diagnoses of CLL or SLL, who were treatment naive for CLL and had an index claim for monotherapy with zanu (January 2023 to August 2025) or acala (November 2019 to August 2025). The index date was defined as the date of the first observed claim for the respective therapy. Patients were required to have continuous enrollment or activities within 1 year prior to and 3 months after the index date. Patients with evidence of clinical trial participation, prior CLL/SLL treatment, or two diagnoses of mantle cell lymphoma between January 2015 and the index date were excluded. Outcomes included OS (measured from index claim to all-cause mortality), and TTNT (measured from index claim to initiation of subsequent therapy or death). If death did not occur, patients were censored at the date of last activity or the enrollment end date. For OS analysis, Komodo data captured the death date, but not the cause of mortality. Survival analyses were conducted using Kaplan-Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was adjusted for age, sex, US region, treatment initiation year, and Charlson Comorbidity Index (CCI).

Results: Among 16,788 patients (zanu, n=5819; acala, n=10,969), median age was higher in zanu (73.3 years) vs acala (71.8 years) cohorts. Most patients were male (acala, 62%; zanu, 59%), non-Hispanic white (acala, 73%; zanu, 72%), and the median CCI was 2 in both cohorts. Median follow-up was 12.8 and 16.4 months for in zanu and acala cohorts, respectively. Median TTNT and OS were not reached for either cohort. With the unadjusted model, zanu had a longer TTNT (unadjusted HR, 0.88; 95% CI, 0.79-0.97; *P*=.009) and OS (HR, 0.72; 95% CI, 0.62-0.82; *P*<.001). After IPTW adjustment, zanu was associated with a significantly improved OS (IPTW-adjusted HR, 0.75; 95% CI, 0.65-0.86; *P*<.001) and TTNT (IPTW-adjusted HR, 0.89; 95% CI, 0.80-0.98; *P*=.02) compared with acala.

Conclusions: In this real-world analysis, zanu monotherapy demonstrated significantly longer TTNT and improved OS compared with acala monotherapy. These findings suggest that zanu may offer superior outcomes in the real-world setting.

Conflict of Interests: 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.