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Title: Real-world overall survival of patients with chronic lymphocytic leukemia treated with frontline Bruton tyrosine kinase inhibitor monotherapy: an analysis of a large US multi-payer claims database

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Introduction: Covalent Bruton tyrosine kinase inhibitors (cBTKis) have markedly improved clinical outcomes for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Although observational studies comparing cBTKis have emerged, direct comparative estimates of long-term survival remain limited. This study compared real-world overall survival (rwOS) among patients with CLL/SLL initiating cBTKi monotherapy in the first-line (1L) seting, overall and by patient subgroups, leveraging a large multi-payer claims database.

Methods: This retrospective cohort study used PurpleLab CLEAR claims, which include open and closed medical and pharmacy claims across commercial, Medicare, and Medicaid coverage. Eligible adult patients with CLL/SLL (≥ 2 CLL/SLL diagnostic codes on ≥2 distinct dates) who initiated 1L cBTKi monotherapy with zanubrutinib (zanu), acalabrutinib (acala), or ibrutinib (ibru) between January 2020 and February 2026 were included (data cutoff: May 29, 2026). The index date was defined as initiation of 1L therapy. Mortality data were assessed and linked across multiple data sources. Median rwOS and survival probabilities at 24 and 36 months were estimated by the Kaplan-Meier method. Hazard ratios and 95% confidence intervals [CIs] were estimated using crude and inverse probability of treatment weighting (IPTW)-weighted Cox proportional hazards models to compare rwOS for each cBTKi. IPTW used stabilized weights derived from a multinomial propensity score model based on index year, categorical age (< 65, 65-74, ≥ 75 years), sex, Charlson Comorbidity Index (CCI) modified to exclude B-cell malignancies, geographic region, and race/ethnicity. Covariate balance was assessed using standardized mean differences before and after weighting. Pre-specified subgroup analyses were conducted by age, sex, and CCI.

Results: A total of 23,168 patients met eligibility criteria (median age: 75 years; IQR: 69-80), including 5893 treated with zanu (median age: 76 years; IQR: 69-81), 9423 treated with acala (75 years; IQR: 68-80), and 7852 treated with ibru (74 years; IQR: 68-79) in 1L setting. Medicare was the most common payer (55.7%), followed by commercial insurance (35.0%). Most patients were male (60.5%) and Non-Hispanic White (61.5%), with a median CCI of 3. The

most common baseline comorbidities were hypertension (68.6%) and diabetes (29.9%). Median follow-up was 17 months among patients treated with zanu compared with 24 months for patients receiving acala and 36 months for ibru, consistent with regulatory milestones.

During the follow-up, 5200 deaths were recorded, and median rwOS was not reached in any treatment group. Zanu-treated patients had higher probability of survival at 24 months (86.8% [95% CI: 85.5-88.2]) and 36 months (83.1% [95% CI: 81.3-84.9]) compared with acala (83.1% [95% CI: 82.2-83.9] and 77.3% [95% CI: 76.2-78.3]) and ibru (81.3% [95% CI: 80.2-82.5] and 75.0% [95% CI: 73.7-76.3]; all *P*<.0001).

In both crude and IPTW-weighted analyses, zanu was associated with lower all-cause mortality compared with acala (crude hazard ratio [cHR]: 0.81; [95% confidence interval [CI]: 0.74, 0.88], *P*<.0001; IPTW-weighted HR [wHR]: 0.75, [95% CI: 0.67, 0.84], *P*<.0001) and ibru (cHR: 0.67 [95% CI: 0.61, 0.72], *P*<.0001; wHR: 0.68, [95% CI: 0.60, 0.77], *P*<.0001).

Similar results were observed across all subgroups, except for age<65, which was the smallest subgroup and may be underpowered. Zanu was associated with better survival than acala, among patients aged 65-74 (wHR: 0.69 [95% CI: 0.52-0.92]) and ≥ 75 (wHR: 0.74 [95% CI: 0.65-0.84]), with CCI ≤ 3 (wHR: 0.67 [95% CI: 0.55-0.81]) and CCI > 3 (wHR: 0.79 [95% CI: 0.69-0.92]). Similarly, zanu-treated patients had better survival than those treated with ibru, among patients aged 65-74 (wHR: 0.64 [95% CI: 0.48-0.86]), ≥ 75 (wHR: 0.67 [95% CI: 0.59-0.77]), with CCI ≤ 3 (wHR: 0.58 [95% CI: 0.48-0.70]) and CCI > 3 (wHR: 0.74 [95% CI: 0.63-0.86]).

Conclusions: In this large real-world cohort of patients with CLL/SLL initiating 1L cBTKi monotherapy, zanu was associated with significantly improved OS than acala or ibru. These findings were consistent across age, sex, and comorbidity subgroups, supporting the survival benefit of zanu in routine clinical practice. However, the study period overlapped with the COVID-19 pandemic, which may limit the generalizability of these results to other time periods.