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Title: Real-world comparative outcomes of zanubrutinib, acalabrutinib, and ibrutinib in chronic lymphocytic leukemia/small lymphocytic lymphoma: an AI-assisted systematic literature Review and meta-analysis

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Background: Covalent Bruton tyrosine kinase inhibitors (cBTKis), including zanubrutinib (zanu), acalabrutinib (acala), and ibrutinib (ibru), are established treatments for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Head-to-head randomized clinical trials remain limited to relapsed/refractory (R/R) patients (pts), while real-world evidence has emerged recently to address this gap in evidence. We assessed real-world effectiveness, safety, and healthcare resource utilization (HCRU) associated with cBTKis in CLL/SLL.

Methods: Using a two-step process, an AI-assisted systematic literature review (SLR) was conducted to identify comparative observational studies of adults with CLL/SLL treated with cBTKis in any line setting. Searches were performed in PubMed, Embase, and major oncology and hematology conferences. Outcomes included overall survival (OS), time to next treatment (TTNT), time to treatment discontinuation (TTD), safety, and HCRU. AI-assisted search strategy development, study screening, and data extraction were conducted with human oversight. Next, pairwise meta-analyses were performed for outcomes reported by ≥3 studies with adjusted hazard ratios (HRs). Pooled treatment effects were estimated using a random-effects model. I^2 measured between-study heterogeneity, with lower values indicating less heterogeneity.

Results: Of 1713 records screened, 43 comparative real-world studies met the eligibility criteria. Data sources included electronic health records (44.2%), administrative claims databases (18.6%), institutional cohorts (11.6%), clinical registries (11.6%), government healthcare databases (11.6%), and other sources (2.3%). Overall, 21 studies (48.8%) evaluated treatment-naive pts, 3 (7.0%) evaluated R/R pts, and 19 (44.2%) evaluated mixed populations. Twenty-five studies reported effectiveness outcomes, 30 reported safety, and 6 reported HCRU. Among effectiveness studies, 11 evaluated OS, 13 evaluated TTNT, and 12 evaluated TTD; 10 studies reporting HRs were included in the meta-analysis.

Ages ranged from 72-77 years at treatment initiations. Across the 9 studies reporting baseline comorbidity burden, the median Charlson Comorbidity Index (CCI) ranged from 2-4; approximately 39% of Medicare pts had severe comorbidity (CCI ≥ 5), and more than half of pts in one registry had a Cumulative Illness Rating Scale > 6.

For efficacy, zanu was consistently associated with longer TTNT, TTD, and favorable OS vs ibru and acala. In meta-analyses, zanu was associated with a 36% lower risk of discontinuation vs acala (pooled HR=0.64; 95% CI: 0.43-0.94; k [number of studies]=4; P =0.024; I^2=93%), 13% lower risk of initiating subsequent treatment (pooled HR=0.87, 95% CI: 0.82-0.93; k=5; P<0.001; I^2=0%) and a 22% lower risk of death (pooled HR=0.78, 95% CI 0.71–0.86; k=4; P<.0001; I^2=0%). Zanu was associated with improved TTD (pooled HR 0.57, 95% CI 0.52–0.63; k=4; P<0.001; I^2=0%), TTNT (pooled HR 0.54, 95% CI 0.40–0.73; k=3; P <0.001; I^2=71%) vs ibru. Only 2 studies reported OS HRs, but both significantly favored zanu vs ibru (HR=0.46, 0.64). Compared with ibru, acala was associated with improved TTD (pooled HR 0.55, 95% CI 0.45–0.67; k=3; P<0.001; I^2=20%). Acala-vs-ibru comparisons for TTNT and OS were limited by the small number of studies, and available TTNT evidence seems to favor acala vs ibru (HR<1) while OS evidence favors ibru (HR>1).

Compared with ibru, zanu was associated with lower rates of cardiotoxicity (2.1% vs 9.5%), atrial fibrillation (5–8% vs 10–16%), hypertension (4–14% vs 9–18%), and fewer toxicity-related discontinuations (7.8-12.6% vs 11.1-21.4%). Compared with acala, zanu had similar or lower rates of atrial fibrillation/flutter (4.8–8.0% vs 8.0–8.1%), and serious infections (9-12% vs 13-20%), with several studies reporting fewer bleeding events, cytopenias, and toxicity-related discontinuations. HCRU studies also suggested that zanu had lower inpatient utilization (46.4% vs 60.4% for acala, 51.5% for ibru) and fewer outpatient visits per patient-year (9.7 vs 10.9 for acala and 11.5 for ibru).

Conclusions: Comparative real-world evidence indicates that zanu has the most consistent and favorable effectiveness profile among cBTKis for CLL/SLL, with prolonged TTD, TTNT, and OS vs acala and ibru. Zanu had more favorable toxicity than ibru and fewer bleeding events, cytopenia, discontinuations, and inpatient use than acala, highlighting differences among second-generation cBTKis.