Real-World Comparative Effectiveness of First-Line Bruton Tyrosine Kinase Inhibitors in Patients With Chronic Lymphocytic Leukemia

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Background
Next-generation Bruton tyrosine kinase (BTK) inhibitor monotherapy is a preferred first-line (1L) treatment option, as categorized by the National Comprehensive Cancer Network (NCCN) guidelines, for patients with chronic lymphocytic leukemia (CLL). In phase 3 randomized trials among patients with relapsed or refractory CLL, zanubrutinib demonstrated superior efficacy versus ibrutinib, while acalabrutinib only showed noninferiority to ibrutinib.

Aims
In the absence of head-to-head trial comparison, we evaluated real-world (rw) clinical outcomes in 1L BTK inhibitor monotherapy in patients with CLL in a large US population.

Methods
This is a retrospective observational study utilizing the US nationwide Flatiron Health electronic health record–derived de-identified database. Eligible patients included those with a CLL diagnosis who started 1L BTK inhibitor monotherapy between January 1, 2020, and August 31, 2024. Outcomes included rw time to next treatment or death (rwTTNT), time to treatment discontinuation or death (rwTTD), and overall survival (rwOS). Landmark treatment and survival probabilities were estimated using Kaplan–Meier methods. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models, adjusting for age, sex, race/ethnicity, practice type, Eastern Cooperative Oncology Group (ECOG) performance status, immunoglobulin heavy chain variable region (IGHV), and del17p/*TP53* mutation status.

Results
A total of 2515 patients with CLL were included (zanubrutinib n=310, acalabrutinib n=1111, ibrutinib n=1094). 1L use of ibrutinib decreased over time, with zanubrutinib being most common in 2024 (49% vs 44% acalabrutinib, 7% ibrutinib). Median age was 73, 74, and 72 years for zanubrutinib, acalabrutinib, and ibrutinib, respectively. More patients with zanubrutinib had del17p/*TP53* mutation (16% vs 12% acalabrutinib, 11% ibrutinib). Median follow-up was 12 months for zanubrutinib, 23 for acalabrutinib and 33 for ibrutinib. Landmark treatment probabilities and 95% CI are provided in the Table. Median rwTTNT was not reached (NR; 95% CI: NR, NR) for zanubrutinib and acalabrutinib, and was 38.2 months (95% CI: 33.2, 42.3) for ibrutinib. Median rwTTD was NR (95% CI: NR, NR) for zanubrutinib, 43.7 months (95% CI: 34.4, NR) for acalabrutinib, and 21.9 months (95% CI: 18.3, 25.7) for ibrutinib. Patients on zanubrutinib had numerically higher probability of not advancing to next line of therapy and not discontinuing treatment at 6, 12, and 18 months than those on acalabrutinib and ibrutinib (Table). Median rwOS was NR for all groups. Compared with patients on ibrutinib, patients on zanubrutinib had statistically significant lower risks of rwTTNT (HR: 0.59; 95% CI: 0.44, 0.79), rwTTD (0.56; 0.44, 0.72), and rwOS (0.46; 0.28, 0.76). Compared with patients on acalabrutinib, patients on zanubrutinib had numerically lower risks of rwTTNT, rwTTD, and rwOS.

Conclusions

Patients on zanubrutinib had significantly longer rwTTNT, rwTTD, and rwOS compared to those on ibrutinib, and had longer trends compared with those on acalabrutinib. Limitations include limited follow-up time for zanubrutinib versus ibrutinib and acalabrutinib.

Landmark probabilities of not advancing to next treatment or not discontinuing treatment for patients on Bruton tyrosine kinase inhibitors

	Zanubrutinib n=310	Acalabrutinib n=1111	Ibrutinib n=1094
rwTTNT, % (95% CI)			
6 months	91 (87, 94)	88 (86, 90)	85 (83, 87)
12 months	83 (77, 87)	81 (78, 83)	75 (72, 78)
18 months	78 (72, 84)	74 (71, 77)	67 (64, 69)
rwTTD, % (95% CI)			
6 months	85 (80, 88)	81 (78, 83)	75 (72, 77)
12 months	76 (70, 81)	72 (69, 75)	62 (59, 65)
18 months	70 (63, 76)	66 (63, 69)	53 (50, 56)

CI, confidence interval; rwTTNT, real-world time to next treatment or death; rwTTD, real-world time to treatment discontinuation or death