REAL-WORLD OUTCOMES AMONG MEDICARE BENEFICIARIES TREATED WITH FIRST-LINE (1L) BRUTON TYROSINE KINASE INHIBITORS (BTKIS) FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Background: Covalent BTKi monotherapies are standard of care for 1L CLL in the US. However, there is a lack of head-to-head BTKi trials in the 1L setting, and previous real-world studies had limited sample size and follow-up time. We used a large US database to evaluate clinical outcomes among patients treated with BTKis for 1L CLL.

Methods: This retrospective cohort study utilized the de-identified Medicare Fee-For-Services database. Eligible patients included those with a CLL/SLL diagnosis at age ≥65 years who started 1L BTKi monotherapy between 01/01/2020 and 06/30/2025 and had ≥12 months enrollment pre-1L. Outcomes included real-world overall survival (OS), time to next treatment or death (TTNT-D), and time to treatment discontinuation or death (TTD-D) from 1L start. Landmark treatment and survival probabilities at 12 and 24 months were estimated using Kaplan–Meier methods. Adjusted hazard ratios (aHRs) and 95% CIs were estimated using Cox proportional hazard models, adjusting for age, sex, race/ethnicity, Charlson Comorbidity Index (CCI) and year of 1L start. Subgroup analysis was performed by age groups (65-74, 75-84, ≥85 years).

Results: A total of 10,523 patients were included (zanubrutinib: 3006; acalabrutinib: 4309; ibrutinib: 3208). Median age at 1L was 77 years for zanubrutinib and acalabrutinib, and 76 years for ibrutinib. Most patients were male (58%), non-Hispanic White (91%), and resided in urban areas (78%). Median CCI score was 4 for zanubrutinib and acalabrutinib, and 3 for ibrutinib. Overall, 65% of patients had hypertension at baseline. Baseline atrial fibrillation was 17% for zanubrutinib and acalabrutinib, and 12% for ibrutinib.
Median follow-up was 16 months (range, 0-61) for zanubrutinib, 21 months (0-69) for acalabrutinib and 35 months (0-69) for ibrutinib. Median OS was not reached (NR) for all groups. Median TTNT-D was NR for zanubrutinib (95% CI, 45-NR), 40 months (38-42) for acalabrutinib, and 30 months (29-32) for ibrutinib. Median TTD-D was NR (NR-NR) for zanubrutinib, 24 months (22-25) for acalabrutinib, and 14 months (13-15) for ibrutinib. Patients on zanubrutinib had higher probability of survival, not advancing to next line of therapy and not discontinuing treatment at 12 and 24 months, than those receiving acalabrutinib and ibrutinib (**Table**; with 95% CIs). After adjusting for baseline

factors and year of 1L, patients on zanubrutinib had a statistically significantly lower risk of death, advancing to next line, or discontinuing treatment, than those on ibrutinib or acalabrutinib. Similar results were observed across age subgroups.

Summary/Conclusion: In this large cohort of patients aged ≥65 years with longest follow up to date, zanubrutinib monotherapy was associated with better survival and treatment outcomes, compared to ibrutinib and acalabrutinib.

Treatment	OS			TTNT-D			TTD-D		
	12 months %	24 months %	aHR	12 months %	24 months %	aHR	12 months %	24 months %	aHR
Zanubrutinib	91 (90-92)	86 (84-87)		82 (81-94)	71 (69-74)		72 (71-74)	63 (61-65)	
Ibrutinib (reference)	85 (84-86)	75 (74-77)	0.64 (0.54-0.77)	74 (72-75)	56 (55-58)	0.63 (0.55-0.71)	53 (51-55)	35 (33-37)	0.57 (0.51-0.64)
Acalabrutinib (reference)	87 (86-88)	80 (78-81)	0.77 (0.66-0.88)	78 (77-80)	67 (65-68)	0.87 (0.78-0.96)	63 (61-64)	49 (47-51)	0.86 (0.78-0.94)

aHR, adjusted hazard ratio; OS, overall survival; TTD-D, time to treatment discontinuation or death; TTNT-D, time to next treatment or death.