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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 (pts) treated with BTKis for 1L CLL.

Methods: This retrospective cohort study utilized the de-identified Medicare Fee-For-Services database. Eligible pts included those with a CLL/SLL diagnosis at age ≥65 y who started 1L BTKi monotherapy between 01/01/2020 and 06/30/2025 and ≥12 months (mos) enrollment pre-1L. Outcomes included real-world overall survival (OS), time to next treatment (tx) or death (TTNT), and time to tx discontinuation or death (TTD) from 1L start. Landmark tx and survival probabilities at 12 and 24 mos 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 y).

Results: A total of 10,523 pts were included (zanubrutinib [zanu]:3006; acalabrutinib [acala]:4309; ibrutinib [ibr]:3208). Median age at 1L was 77 y for zanu and acala, and 76 y for ibr. Most pts were male (58%), non-Hispanic White (91%), and resided in urban areas (78%). Median CCI score was 4 for zanu and acala, and 3 for ibr. At baseline, hypertension was 65% overall, and atrial fibrillation was 17% for zanu and acala, and 12% for ibru.

Median follow-up was 16 mos (range: 0-61) for zanu, 21 mos (0-69) for acala and 35 mos (0-69) for ibr. Median OS was not reached (NR) for all groups. Median TTNT was NR for zanu (95% CI, 45-NR), 40 mos (38-42) for acala, and 30 mos (29-32) for ibr. Median TTD was NR (NR-NR) for zanu, 24 mos (22-25) for acala, and 14 mos (13-15) for ibr. Pts on zanu had higher probability of survival, not advancing to next line of therapy and not discontinuing tx at 12 and 24 mos, than those receiving acala and ibr (Table; with 95% CIs). After adjusting for baseline factors and year of 1L, pts on zanu had a statistically significantly lower risk of death, advancing to next line, or discontinuing tx, than those on ibr or acala. Similar results were observed across age subgroups.

Conclusions: In this large cohort of pts aged ≥65 yrs with longest follow up to date, zanu monotherapy was associated with better survival and tx outcomes, compared to ibr and acala.

Tx	OS	OS	OS	TTNT	TTNT	TTNT	TTD	TTD	TTD
	12 mos %	24 mos %	aHR	12 mos %	24 mos %	aHR	12 mos %	24 mos %	aHR
Zanu	91 (90-92)	86 (84-87)		82 (81-94)	71 (69-74)		72 (71-74)	63 (61-65)	
Ibr (ref)	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)
Acala (ref)	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)