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Title: Qualitative assessment of physician-documented drivers for switching cBTK inhibitors in CLL/SLL in real-world practice

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Introduction: Covalent Bruton tyrosine kinase inhibitors (cBTKis) have improved outcomes for patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but long-term treatment may be limited by off-target toxicities, prompting some pts to switch therapies. Prospective studies have evaluated zanubrutinib (zanu) after intolerance to acalabrutinib (acala) or ibrutinib (ibru), but real-world drivers of cBTKi switching remain uncharacterized. Evaluating clinical notes may provide context into physician-patient decision-making.

Methods: This qualitative evaluation of the free-text rationales documented by physicians used the US Flatiron Health electronic health record-derived de-identified database. Adults with CLL/SLL who initiated 1L cBTKi monotherapy or combination with anti-CD20 therapy from 01/01/2020-11/30/2025 and switched to another cBTKi in second line (2L) were included (data cut-off: 02/28/2026). Switching rationales were identified from unstructured clinical documents using a large language model and grouped into themes informed by literature and clinical expertise. Multiple rationale categories could be assigned per patient. Switching rationales were assessed overall and by regimen.

Results: A total of 4370 pts initiated 1L cBTKi therapy, including 1696 (38.8%) receiving ibru, 2000 (45.8%) acala, and 674 (15.4%) zanu. Overall, 396 (9.1%) pts switched to another cBTKi at 2L. Compared with overall 1L cohort, pts who switched were slightly younger (median age at 1L, 72 years [IQR: 63-79] vs 73 years [IQR: 65, 79]) and more likely to be female (45.7% vs 40.2%), non-Hispanic White (64.4% vs 61%), and treated in community practice (83.3% vs 79.4%). Pts who switched were also more likely to have del17p (9.8% vs 6.6% in overall 1L).

Among the 396 pts who switched cBTKis, 280 (70.1%) received ibru, 94 (23.7%) acala, and 22 (5.6%) zanu at 1L. Following the switch, 212 (53.5%) received acala, 166 (41.9%) zanu, and 18 (4.5%) ibru at 2L. Pts who switched to zanu were older (74 years) and more likely to be female (50.6%) and have del17p (9.0%) than those who switched to acala (73 years; 40.6% female; 4.7% del17p).

Among 166 pts who switched to zanu, 88 (53%) switched from ibru and 78 (47%) from acala; 90.4% pts switched in 2023 or later. Among 212 pts who switched to acala, 192 (90.6%) pts switched from ibru and 20 (9.4%) from zanu; 51.9% switched before 2023. Median time from 1L initiation to switch was 13.6 months (mo) overall and was shortest among pts who switched to ibru (3.1 mo) followed by acala (11.3 mo) and zanu (18.0 mo). Median follow-up after switching was 19.6, 29.8, and 34.0 mo for zanu, acala, and ibru, respectively.

Among all pts who switched cBTKis, 344 (86.9%) had at least one documented rationale. Tolerability was the most common reason (87.8%), including adverse events (AEs; 81.7%); cardiac comorbidities and bleeding were the most frequently documented AEs. Pt preference (19.2%) was the second most common rationale overall and across groups (switch to zanu: 21.2%; switch to acala: 16.3%). Other rationales included health status (eg, comorbidities; 7.8%), efficacy (7.8%), labs (6.7%), and quality of life (5.8%). Top rationales were consistent across cBTKis. Among pts who switched to zanu, efficacy (10.2%), labs (9.5%), and progression (6.6%) were more frequent. Pts switching to acala more often mentioned health status (8.9%). Age, travel, disease burden, guidelines, route, staging, biomarkers, or clinical trial were infrequent rationales.

Health status was a common reason for pts switching from 1L ibru (9.5% vs 4.9% for acala and 0% for zanu). Pts switching from 1L acala more frequently had efficacy (9.9%), quality of life (8.6%), and labs (7.4%) as rationale. Tolerability was documented less often among pts who switched before 2023 (93.4% vs 84.7%), whereas pt preference was more frequently documented among pts who switched in 2023 or after (17.2% vs 20.3%).

Conclusions: This qualitative assessment shows that reasons for cBTKi switching in CLL/SLL are well documented in academic and community practice. 1L cBTKis were well tolerated, with <10% pts switching therapy, mostly to acala or zanu. Tolerability and AEs were the most frequent rationales, while pt preference was consistently documented, suggesting shared decision-making. Patient specific clinical characteristics, efficacy, labs, and quality of life also underscore that cBTKi selection is individualized and multifactorial.