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Treatment patterns after prior double exposure to Bruton tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL2i) in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

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Background: Targeted therapies, including BTKi and BCL2i, are commonly used for patients (pts) with CLL/SLL. However, pts needing subsequent lines of therapy (sLOT) after exposure to both BTKi and BCL2i (double-exposed) have limited treatment (tx) options and poor prognosis. This study aims to describe tx patterns among BTKi/BCL2i double-exposed pts with CLL/SLL.

Methods: This retrospective observational study used the Symphony Integrated Dataverse. Eligible pts had a diagnosis of CLL/SLL and prior exposure to both BTKi (zanubrutinib [Z], acalabrutinib [A], ibrutinib [I], or pirtobrutinib [P]) and BCL2i (venetoclax [V]). The index date was the end date of the qualifying regimen, either a BTKi-based regimen (ie, BTKi monotherapy or BTKi + BCL2i) or a BCL2i-based regimen (ie, BCL2i monotherapy or BCL2i + anti-CD20 antibody) that established exposure to both classes. The index period was from Jun 8, 2018 to Dec 31, 2025. Pts were required to have continuous enrollment for 12 months before index and 90 days after. Tx patterns post BTKi/BCL2i double exposure were summarized. Among pts who started a sLOT post double exposure, time to tx discontinuation (TTD) was estimated using the Kaplan-Meier method.

Results: A total of 4734 BTKi/BCL2i double-exposed pts were identified; most were male (63.7%), White (69.4%), and aged ≥65 years (76.2%), with a median age of 72

years and a median Charlson Comorbidity Index (CCI) of 2. Overall, 1112 (23.5%) had a BTKi-based regimen (eg, V-based regimen to BTKi in a different LOT or BTKi + V in the same LOT), and 3622 (76.5%) had a V-based regimen (BTKi to V in a different LOT) as a qualifying regimen for double-exposed status. Most pts had a qualifying regimen post second line (2L; 44.8%) and third line (3L; 35.7%).

Overall, 1527/4734 pts (32.3%) initiated a sLOT; 1222/3622 pts (33.7%) with a V-based qualifying regimen initiated a sLOT, and 305/1112 (27.4%) with a BTKi-based qualifying regimen initiated a sLOT. Demographics of the pts who initiated a sLOT (male [63.3%]; White [68%]; ≥65 years [75.6%]; median age, 72 years; median CCI, 2) were similar to those of the overall double-exposed pts. Among the pts with a sLOT, the qualifying regimen occurred post first line (1L) in 119 (7.8%), 2L in 648 (42.4%), 3L in 521 (34.1%), and fourth line or later (4L+) in 239 pts (15.7%).

Among the pts with a sLOT, 1285 (84.2%) received one sLOT, 202 (13.2%) two sLOTs, and 40 (2.6%) three or more sLOTs. The immediate sLOT included covalent (c) BTKi-based regimens (478 [31.3%]: 254 A-based, 65 I-based, and 159 Z-based), V-based (574 [37.6%]), P-based (290 [19.0%]), and other regimens (185 [12.1%]).

sLOT tx patterns differed by qualifying regimen. Among 305 pts with a BTKi-based qualifying regimen, 184 (60.3%) received V-based regimens as the immediate sLOT, 48 (15.7%) a cBTKi-based regimen (19 A-based, 11 I-based, and 18 Z-based regimens), and 34 (11.1%) P-based regimens. Among 1222 pts with a V-based qualifying regimen, the immediate sLOT was more evenly distributed: 430 (35.2%) received cBTKi-based (235 A-based, 54 I-based, and 141 Z-based), 388 (31.8%) V-based, and 256 (20.9%) P-based regimens.

From sLOT initiation, median (interquartile range [IQR]) follow-up was 17.4 (7.8-31.1) months. Overall median TTD was 14.6 (IQR, 6.9-28.2) months, which was longer among pts who started a sLOT in earlier lines: 23.0 (12.6-27.7) months for pts initiating 2L as the sLOT, 14.6 (7.4-28.6) months for 3L, 13.9 (5.8-30.0) months for 4L, and 10.8 (5.5-23.6) months for fifth line or later (5L+).

The estimated 360-day discontinuation rate for the sLOT was 42.2% (95% CI, 39.5-45.1) overall and was lower among pts who started a sLOT earlier: 21.9% (15.1-31.1)

for 2L, 41.7% (37.5-46.2) for 3L, 44.0% (39.3-49.0) for 4L, and 51.0% (43.9-58.5) for 5L+.

Conclusions: In this real-world study of BTKi/BCL2i double-exposed pts with CLL/SLL, about one-third initiated subsequent tx and a high percentage received a cBTKi- or BCL2i-based regimen again; the reliance of recycling pts with previously exposed drug classes highlights a severe lack of novel mechanisms of action. Immediate subsequent tx patterns differed by prior regimen. Despite subsequent therapy, tx durability was limited, with high 1-year discontinuation rates, particularly among pts treated in later lines. These findings highlight the persistent unmet need in the post-BTKi and post-BCL2i settings for the continued development of more effective and durable tx strategies.