Updated Safety and Efficacy of All-Oral Sonrotoclax + Zanubrutinib in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Including Patients With del(17p)/*TP53*

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Background: BCL2 + BTK inhibition is an effective 1L treatment (tx) strategy for CLL/SLL but undetectable minimal residual disease (uMRD) rates are suboptimal. Sonrotoclax (BGB-11417; sonro), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Zanubrutinib (zanu), a next-generation BTK inhibitor, has shown superior progression-free survival (PFS) with fewer cardiac adverse events vs ibrutinib in R/R CLL/SLL.

Aims: To report updated safety/efficacy for sonro + zanu (SZ) in patients (pts) with R/R CLL/SLL from BGB-11417-101 (NCT04277637), a phase 1/1b global study.

Methods: Pts with R/R CLL/SLL (≥1 prior tx; no progressive disease [PD] on prior BTK inhibitor) received zanu (320 mg QD or 160 mg BID) for 8-12 wk before sonro was added by ramp-up to target dose (40/80/160/320/640 mg QD). Tx continued until PD, unacceptable toxicity, or protocol-defined elective discontinuation after 96 wk. The primary endpoint was safety/tolerability. Secondary/exploratory endpoints included

overall response rate (ORR; partial response [PR] with lymphocytosis or better per iwCLL 2018) and peripheral blood (PB) uMRD4 by flow cytometry, respectively.

Results: As of 06Dec2025, 47 pts with R/R CLL/SLL were enrolled, including 22 to the sonro 320-mg cohort. Median age was 65 y (range, 36-76); 37% (16/43) had *TP53* mutation or del(17p) and 77% (34/44) had unmutated IGHV. Pts had a median of 1 prior tx (range, 1-3); median duration of last systemic tx was 5.0 mo (range, 0.1-86.6). Seven pts had a BTK inhibitor as a last prior tx. Overall, median study follow-up was 37.8 mo (range, 10.2-57.8). Of 47 pts, 16 (34%) remained on tx and 31 (66%) discontinued SZ, most due to protocol-defined elective discontinuation (51%); 3 pts (2%) discontinued due to PD.
TEAEs led to discontinuation of SZ in 4 pts (8%; arthralgia, myelodysplastic syndrome, meningococcal sepsis, and multiple myeloma) and zanu alone in 1 pt (2%; intracranial hemorrhage). Grade ≥3 TEAEs occurred in 72%, most commonly neutropenia (28%), hypertension (11%), and pneumonia (11%). Serious TEAEs occurred in 47%; pneumonia (11%), cellulitis (9%), and pyrexia (4%) were those seen in >1 pt. No TLS occurred, and no TEAEs led to death.

In 46 efficacy-evaluable pts, ORR was 98% and complete response (CR) rate was 54%. Median time to response was 2.6 mo (range, 1.5-24.6). Overall, 36-mo PFS rate was 95% (95% CI, 83%-99%). In 21 efficacy-evaluable pts in the sonro 320-mg cohort, ORR was 100% (52% CR) and median time to response was 2.5 mo (range, 1.6-6.9). Of 3 evaluable BTK inhibitor-pretreated pts, 3 achieved PR. For the sonro 320-mg cohort (median follow-up, 28.7 mo [range, 20.1-48.9]), the 24-month PFS rate was 94% (95% CI, 67%-99%). Only 1 PD was observed, in a pt with *TP53* mutation/del(17p)/mutated IGHV. In 24 pts who electively discontinued, median time off tx was 11.3 mo (range, 0.2-21.5).

In 21 MRD-evaluable pts in the sonro 320-mg cohort, the best PB uMRD4 rate was 86% (18/21). Median time from reaching sonro target dose to uMRD4 was 5.3 mo (range, 2.5-16.3). Best uMRD4 rates by wk 24, 48, and 96 were 52% (11/21), 81% (17/21) and 82% (14/17), respectively. No pt with uMRD4 reverted to MRD4+.

Summary/Conclusion: In pts with R/R CLL/SLL, sonro 320 mg + zanu was well tolerated, with low rates of tx discontinuation due to TEAEs, and continued to demonstrate substantial antitumor activity (ORR 100%; CR 52%; uMRD4 86%), including in BTK inhibitor-pretreated pts.