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Subsequent therapies and time to second progression-free survival events (PFS2) in treatment naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL) previously treated with zanubrutinib (zanu) or bendamustine-rituximab (BR) in SEQUOIA

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Background: Cohort 1 of the phase 3 SEQUOIA trial assessed zanu, a next-generation BTKi, compared to BR in TN CLL/SLL without del(17p). Zanu previously demonstrated sustained superiority in progression free survival (PFS) and time to next treatment (TTNT) vs BR. However, evidence regarding outcomes on subsequent therapies (tx) after progressive disease (PD) on zanu remain limited. Here, we present results on follow-up (FU) tx after zanu, including PFS2.

Methods: Pts without del(17p) were randomized to receive continuous zanu or six cycles of BR. Pts who received BR could crossover to receive zanu after PD. All pts were followed post-PD for details on any subsequent anti-CLL treatments. This analysis evaluated PFS, TTNT, TTNT or death (TTNT-D) and PFS2. *P*-values are descriptive.

Results: In total 479 pts were randomized; 241 to zanu and 238 to BR. Baseline demographics and disease characteristics were well balanced between the arms. As of 31 October 2025, median FU was 78.7mo (range, 0.0-96.0). Sustained PFS superiority with zanu vs BR was observed (HR, 0.28; 95% CI, 0.21-0.38; *P*<.0001) with 78mo PFS estimates of 70.9% (95% CI, 64.2-76.6) for zanu and 28.6% (21.7-35.8) for BR. Overall, 211/241 (87.6%) of pts treated with zanu had not received subsequent tx and 34 pts had died without subsequent tx. TTNT and TTNT-D favored zanu over BR (HR, 0.23 [95% CI, 0.15- 0.35; *P*<.0001] and 0.37 [0.27-0.50; *P*<.0001], respectively). Overall, 24/241 (10.0%) zanu pts and 82/238 (34.0%) BR pts had PD after study treatment and received subsequent tx. Of the 24 zanu pts receiving subsequent tx after PD, 13 (54.2%) received BCL2i-based regimens, 8 (33.3%) received chemoimmunotherapy (CIT) (incl. anti-CD20 antibody monotherapy), and 3 (12.5%) received BTKi. Of the 82 BR pts receiving subsequent tx after PD, 77 (93.9%) received BTKi (incl. 71 crossover pts), 3 (3.7%) received BCL2i-based regimens and 2 (2.4%) received CIT. Median time from PD following first tx to initiation of next tx was 2.1mo for zanu (range 0-25.7) and 7.4mo (0.3-48.0) for BR. Zanu pts who had PD and received subsequent BCL2i-based tx had a median FU of 33.5mo from initiation of next-line tx. Among these pts, 10 remain alive and without PD, two had died, and one had PD. Overall, PFS2 significantly favored zanu over BR (HR, 0.66; 95% CI, 0.45-0.98; *P*<.05) with 78mo PFS2 estimates of 81.3% (95% CI, 75.6-85.8) vs 73.8% (67.2-79.3), respectively.

Conclusions: PFS2 remained superior with zanu despite broad use of novel subsequent tx (including crossover) in BR pts. Importantly, BCL2i-based salvage after initial zanu achieved high PFS rates at almost 3

years of FU. Together, these findings support that initial zanu provides durable benefit while preserving sensitivity to effective subsequent tx.