SUBSEQUENT THERAPIES AND TIME TO SECOND PROGRESSION-FREE SURVIVAL EVENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA PREVIOUSLY TREATED WITH ZANUBRUTINIB OR BENDAMUSTINE-RITUXIMAB

Authors: Constantine S. Tam[1], Brad S. Kahl[2], Talha Munir[3], Tadeusz Robak[4], Jennifer R. Brown[5], Paolo Ghia[6], Stephen S. Opat[7], Patricia A. Walker[8], Masa Lasica[9], Ian W. Flinn[10], Wojciech Jurczak[11], Jiayi Shen[12], Marcus Lefebure[13], Jamie Hirata[12], Mazyar Shadman[14,15]

Affiliations: [1]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [2]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [3]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [4]Copernicus Memorial Hospital, Medical University of Lodz, Lodz, Poland; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Università Vita-Salute San Raffaele, Milano, Italy and Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; [7]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [8]Peninsula Health and Peninsula Private Hospital, Melbourne, VIC, Australia; [9]St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [10]Tennessee Oncology/OneOncology, Nashville, TN, USA; [11]Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland; [12]BeOne Medicines, Ltd, San Carlos, CA, USA; [13]BeOne Medicines, Ltd, London, UK; [14]Fred Hutchinson Cancer Center, Seattle, WA, USA: [15]University of Washington, Seattle, WA, USA

Background: Cohort 1 of the phase 3 SEQUOIA trial assessed zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor (BTKi), compared with bendamustine-rituximab (BR) in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL) without del(17p). Zanubrutinib previously demonstrated sustained superiority in progression-free survival (PFS) and time to next treatment (TTNT) vs BR. However, evidence regarding outcomes on subsequent therapies after progressive disease (PD) on zanubrutinib remains limited. Here, we present results on follow-up therapies after zanubrutinib, including second progression-free survival events (PFS2)**.**

Methods: Patients without del(17p) were randomized to receive continuous zanubrutinib or six cycles of BR. Patients who received BR could crossover to receive zanubrutinib after PD. All patients 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 patients were randomized; 241 to zanubrutinib and 238 to BR. Baseline demographics and disease characteristics were well balanced between the arms. As of 31 October 2025, median follow-up was 78.7 months (range, 0.0-96.0). Sustained PFS superiority with zanubrutinib vs BR was observed (HR, 0.28; 95% CI, 0.21-0.38; *P*<.0001) with 78-month PFS estimates of 70.9% (95% CI, 64.2-76.6) for zanubrutinib and 28.6% (21.7-35.8) for BR. After adjustment for COVID, PFS estimates were 73.7% (67.0, 79.3) for zanubrutinib and 29.0% (22.1, 36.3) for BR. Overall, 211/241 (87.6%) of patients treated with zanubrutinib had not received subsequent therapy and 34 patients had died without subsequent therapy. TTNT and TTNT-D

favored zanubrutinib 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%) zanubrutinib patients and 82/238 (34.0%) BR patients had PD after study treatment and received subsequent therapy. Of the 24 zanubrutinib patients receiving subsequent therapy after PD, 13 (54.2%) received B-cell lymphoma 2 inhibitor (BCL2i)-based regimens, 8 (33.3%) received chemoimmunotherapy (CIT) (including anti-CD20 antibody monotherapy), and 3 (12.5%) received BTKi. Of the 82 BR patients receiving subsequent therapy after PD, 77 (93.9%) received BTKi (including 71 crossover patients), 3 (3.7%) received BCL2i-based regimens and 2 (2.4%) received CIT. Median time from PD following first therapy to initiation of next therapy was 2.1 months for zanubrutinib (range 0-25.7) and 7.4 months (0.3-48.0) for BR. Zanubrutinib patients who had PD and received subsequent BCL2i-based therapy had a median follow-up of 33.5 months from initiation of nextline therapy. Among these patients, 10 remain alive and without PD, two had died, and one had PD. Overall, PFS2 significantly favored zanubrutinib over BR (HR, 0.66; 95% CI, 0.45-0.98; *P*<.05) with 78-month PFS2 estimates of 81.3% (95% CI, 75.6-85.8) vs 73.8% (67.2-79.3), respectively (**Figure**).

Summary/Conclusion: PFS2 remained superior with zanubrutinib despite broad use of novel subsequent therapy (including crossover) in BR patients. Importantly, BCL2i-based salvage after initial zanubrutinib achieved high PFS rates at almost 3 years of follow-up. Together, these findings support that initial zanubrutinib provides durable benefit while preserving sensitivity to effective subsequent therapy.

Figure. Time to Second PFS Event