***Title (Italian)*:** ZANUBRUTINIB (ZANU) VS BENDAMUSTINE + RITUXIMAB (BR) IN PAZIENTI (PTS) CON LEUCEMIA LINFATICA CRONICA/LINFOMA A PICCOLI LINFOCITI (LLC/LSL)NAIVE AL TRATTAMENTO: FOLLOW-UP ESTESO DELLO STUDIO SEQUOIA

***Title (English)*:** ZANUBRUTINIB (ZANU) VS BENDAMUSTINE + RITUXIMAB (BR) IN PATIENTS (PTS) WITH TREATMENT-NAIVE (TN) CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL): EXTENDED FOLLOW-UP OF THE SEQUOIA STUDY

Authors: T. Munir[1], M. Shadman[2], T. Robak[3], J.R. Brown[4], B.S. Kahl[5], P. Ghia[6], K. Giannopoulos[7,8], M. Šimkovič[9], A. Österborg[10], L. Laurenti[11], P. Walker[12], S. Opat[13], H. Ciepluch[14], R. Greil[15-17], M. Hanna[18], M. Tani[19], M. Trněný[20], D.M. Brander[21], I.W. Flinn[22], S. Grosicki[23], E. Verner[24,25], A. Tedeschi[26], S. De Guibert[27], G. Tumyan[28], K. Laribi[29], J.A. García[30], J.-Y. Li[31], T. Tian[32], V. Ramakrishnan[32], Y. Liu[32], A. Szeto[32] J. Paik[32], A. Cohen[32], C.S. Tam[33], W. Jurczak[34]

Affiliations: 1. Haematology, Haematological Malignancy Diagnostic Service (HMDS), St. James's Institute of Oncology; 2. Fred Hutchinson Cancer Research Center, University of Washington; 3. Medical University of Lodz; 4. Dana-Farber Cancer Institute; 5. Washington University School of Medicine; 6. Strategic Research Program on Chronic Lymphocytic Leukemia, Division of Experimental Oncology, IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele; 7. Experimental Hematooncology Department, Medical University of Lublin; 8. Hematology Department, St John's Cancer Centre; 9. 4th Department of Internal Medicine – Haematology, Faculty of Medicine in Hradec Králové, University Hospital and Charles University; 10. Department of Hematology, Karolinska University Hospital Solna; 11. Fondazione Policlinico Universitario A. Gemelli IRCCS; 12. Peninsula Health and Peninsula Private Hospital; 13. Monash Health and Clinical Haematology Unit, Monash University; 14. Department of Hematology, Copernicus Regional Oncology Centre; 15. Third Medical Department With Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University; 16. Salzburg Cancer Research Institute Center for Clinical Cancer and Immunology Trials; 17, Cancer Cluster Salzburg; 18. Department of Haematology, Waitemata District Health Board; 19. Hematology Unit, Santa Maria delle Croci Hospital; 20. First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital; 21. Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine; 22. Sarah Cannon Research Institute/Tennessee Oncology; 23. Department of Hematology and Cancer Prevention, School of Public Health, Silesian Medical University; 24. Concord Repatriation General Hospital; 25. University of Sydney; 26. Department of Hematology, Azienda Socio Sanitaria Territoriali Grande Ospedale Metropolitano Niguarda; 27. Hôpital de Pontchaillou; 28. Department of Chemotherapy of Hemoblastosis, Blokhin Russian Cancer Research Center; 29. Hematology Department, Centre Hospitalier du Mans; 30. Laboratorio de Citometría de Flujo, Servicio de Hematología y Hemoterapia, Hospital Universitario de Getafe; 31. Department of Hematology, Jiangsu Province Hospital; 32. BeiGene USA; 33. Alfred Health and Monash University; 34. Maria Skłodowska-Curie National Research Institute of Oncology

Cities: 1. Leeds (UK), 2. Seattle (USA), 3. Lodz (PL), 4. Boston (USA), 5. St Louis (USA), 6. Milan (IT), 7.8. Lublin (PL), 9. Hradec Králové (CZ), 10. Stockholm (SE), 11. Rome (IT), 12. Frankston (AU), 13. Clayton (AU), 14. Gdansk (PL), 15.16. Salzburg (AT), 17. Takapuna (NZ), 18. Ravenna (IT), 19. Prague (CZ), 20. Durham (USA), 21. Nashville (USA), 22. Katowice (PL), 23. Concord (AU), 24. Sydney (AU), 25. Milan (IT), 26. Rennes (FR), 27. Moscow (RU), 28. Le Mans (FR), 29. Madrid (ES), 30. Nanjing (CN), 31. San Mateo (USA), 32. Melbourne (AU), 33. Krakow (PL)

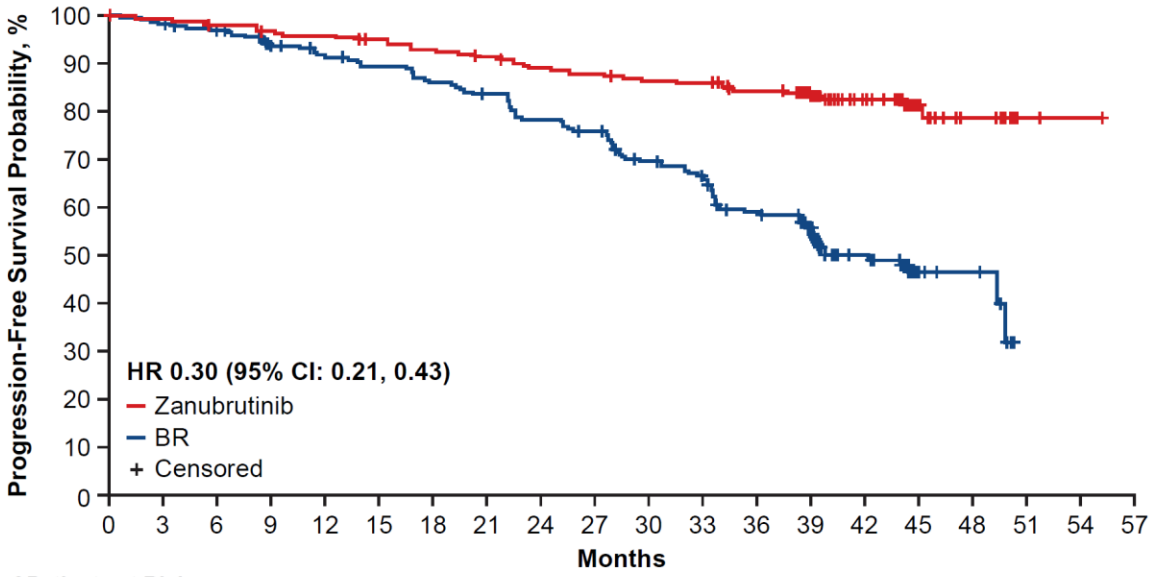
Background: Zanu is a next-generation BTKi designed to limit off-target binding and side effects. Results from SEQUOIA (NCT03336333) showed superior PFS with zanu vs BR in pts with TN CLL/SLL without (w/o) del(17p); pts with del(17p) treated with zanu in a separate cohort had similar outcomes. Here we report updated results from SEQUOIA (further 18 mo of follow-up).

Methods: Pts w/o del(17p) were randomized to receive zanu or BR. Pts with del(17p) received zanu monotherapy. PFS, OS, ORR, and safety were evaluated. AEs were recorded until progression or start of next-line therapy.

Results: As of 31 Oct 2022, 479 pts w/o del(17p) were randomized to receive zanu (n=241) or BR (n=238) (median follow-up, 43.7 mo; range, 0-60 mo). Median PFS was not reached with zanu and was 42.2 mo with BR (HR, 0.30; 95% CI, 0.21-0.43) (**Figure**); 42-mo PFS was 82.4% with zanu. PFS was improved with zanu vs BR in pts with mutated *IGHV* (HR, 0.35; 95% CI, 0.19-0.64) and was sustained in pts with unmutated *IGHV* (HR, 0.23; 95% CI, 0.14-0.37). CR/CRi rates in pts w/o del(17p) were 17.4% with zanu and 21.8% with BR. Median OS was not reached in either arm (zanu vs BR: HR, 0.87; 95% CI, 0.50-1.48); OS at 42 mo was 89.4% with zanu and 88.3% with BR. In 110 pts with del(17p) (zanu monotherapy), median follow-up was 47.9 mo; 42-mo PFS and OS rates were 79.4% and 89.5%, respectively, and the CR/CRi rate was 14.5%. Treatment (tx) continued in 74.7% of pts w/o del(17p) and 70.3% with del(17p). The most common causes of tx discontinuation were AEs and progressive disease in those w/o (14.9% and 5.8%, respectively) and with del(17p) (13.5% each). Any-grade AEs of interest (AEI) included atrial fibrillation/flutter (zanu, BR: 5.0%, 2.6%), hypertension (17.5%, 13.7%), bleeding (48.8%, 12.3%), infection (72.9%, 62.6%), anemia (7.1%, 20.7%), thrombocytopenia (6.3%, 18.1%), and neutropenia (16.7%, 56.8%); grade ≥3 AEI included bleeding (5.8%, 1.8%), infection (23.8%, 22.0%), anemia (0.4%, 2.2%), thrombocytopenia (2.1%, 7.9%), and neutropenia (12.5%, 51.1%).

Conclusions: Extended follow-up in SEQUOIA showed that efficacy and safety of zanu were maintained in pts w/o del(17p). Longer follow-up showed benefit in pts with mutated *IGHV*, and pts with del(17p) continue to show PFS benefit consistent with that in the randomized cohort. Atrial fibrillation rates remain low with no new safety signals. Zanu remains well tolerated with low rates of tx discontinuation and is a valuable frontline option for CLL/SLL.

Figure: Progression-Free Survival by Investigator Assessment



No. of Patients at Risk																			
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0
BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0		

.