

SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB (BR) IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL)

Authors: Tadeusz Robak, MD, PhD¹; Krzysztof Giannopoulos, MD, PhD^{2,3}; Wojciech Jurczak, MD, PhD⁴; Martin Šimkovič, MD, PhD^{5,6}; Mazyar Shadman, MD, MPH^{7,8}; Anders Österborg, MD, PhD^{9,10}; Luca Laurenti, MD¹¹; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA¹²; Stephen Opat, MBBS (Hons), FRACP, FRCPA^{13,14}; Henry Chan, MBChB, FRACP, FRCPA¹⁵; Hanna Ciepluch, MD, PhD¹⁶; Richard Greil, MD^{17,18,19}; Monica Tani, MD²⁰; Marek Trněný, MD²¹; Danielle M. Brander, MD²²; Ian W. Flinn, MD, PhD²³; Sebastian Grosicki, MD, PhD²⁴; Emma Verner, MBBS, BMedSci, FRCPA, FRACP^{25,26}; Brad S. Kahl, MD²⁷; Paolo Ghia, MD, PhD²⁸; Jianyong Li, MD, PhD²⁹; Tian Tian, PhD³⁰; Lei Zhou, MD³⁰; Carol Marimpietri³⁰; Jason C. Paik, MD, PhD³⁰; Aileen Cohen, MD, PhD³⁰; Jennifer R. Brown MD, PhD³¹; Peter Hillmen, MBChB, PhD³²; Constantine S. Tam, MBBS, MD^{33,34,35,36}

Affiliations: ¹Medical University of Lodz, Lodz, Poland; ²Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; ³Hematology Department, St. John's Cancer Centre, Lublin, Poland; ⁴Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; ⁵Fourth Department of Internal Medicine - Haematology, University Hospital, Hradec Kralove, Czech Republic; ⁶Faculty of Medicine, Charles University, Prague, Czech Republic; ⁷Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ⁸Department of Medicine, University of Washington, Seattle, WA, USA; ⁹Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; ¹⁰Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; ¹¹Fondazione Policlinico Universitario A Gemelli UCSC, Rome, Italy; ¹²Peninsula Private Hospital, Frankston, Victoria, Australia; ¹³Monash Health, Clayton, Victoria, Australia; ¹⁴Monash University, Clayton, Victoria, Australia; ¹⁵North Shore Hospital, Auckland, New Zealand; ¹⁶Copernicus Regional Oncology Center, Gdansk, Poland; ¹⁷Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; ¹⁸Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria; ¹⁹Cancer Cluster Salzburg (CCS), Salzburg, Austria; ²⁰Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; ²¹First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; ²²Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; ²³Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; ²⁴Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; ²⁵Concord Repatriation General Hospital, Concord, New South Wales, Australia; ²⁶University of Sydney, Sydney, New South Wales, Australia; ²⁷Washington University School of Medicine, St Louis, MO, USA; ²⁸Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; ²⁹Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiansu Province Hospital, Nanjing, China; ³⁰BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; ³¹Dana-Farber Cancer Institute, Boston, MA, USA; ³²St James's University Hospital, Leeds, United Kingdom; ³³Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; ³⁴University of Melbourne, Parkville, Victoria, Australia; ³⁵St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; ³⁶Royal Melbourne Hospital, Parkville, Victoria, Australia

ABSTRACT

The Bruton tyrosine kinase (BTK) inhibitor, zanubrutinib, was designed for high BTK specificity and minimal toxicity. SEQUOIA (NCT03336333) is a global, open-label, randomized phase 3 study in treatment-naive patients with CLL/SLL without del(17p) who were unsuitable for fludarabine/cyclophosphamide/rituximab. Patients were randomized to receive zanubrutinib (160 mg twice daily) or bendamustine (day 1-2: 90 mg/m²) and rituximab (cycle 1: 375 mg/m²; cycles 2-6: 500 mg/m²); stratification factors were age (<65 y vs ≥65 y), Binet Stage, *IGHV* mutation, and geographic region. Primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS). Secondary endpoints included investigator-assessed (INV) PFS, overall response rate (ORR), overall survival (OS), and safety. From 31Oct2017–22Jul2019, 479 patients were enrolled (zanubrutinib=241; BR=238). Baseline characteristics (zanubrutinib vs BR): median age, 70.0 y vs 70.0 y; unmutated *IGHV*, 53.4% vs 52.4%; del(11q), 17.8% vs 19.3%. With median follow-up of 26.2 mo, PFS was significantly prolonged with zanubrutinib by IRC (HR 0.42; 2-sided $P<.0001$), and INV (HR 0.42; 2-sided $P=.0001$). Zanubrutinib treatment benefit occurred across age, Binet stage, bulky disease, del(11q) status and unmutated *IGHV* (HR 0.24; 2-sided $P<.0001$), but not mutated *IGHV* (HR 0.67; 2-sided $P=.1858$). For zanubrutinib vs BR, 24-mo PFS-IRC=85.5% vs 69.5%; ORR-IRC=94.6% vs 85.3%; complete response rate= 6.6% vs 15.1%; ORR-INV=97.5% vs 88.7%; and 24-mo OS=94.3% vs 94.6%. Select adverse event (AE) rates (zanubrutinib vs BR): atrial fibrillation (3.3% vs 2.6%), bleeding (45.0% vs 11.0%), hypertension (14.2% vs 10.6%), infection (62.1% vs 55.9%), and neutropenia (15.8% vs 56.8%). Treatment discontinuation due to AEs (zanubrutinib vs BR)=20 patients (8.3%) vs 31 patients (13.7%); AEs leading to death=11 patients (4.6%) vs 11 patients (4.8%). No sudden deaths occurred. In summary, zanubrutinib significantly improved PFS-IRC vs BR and was well tolerated, supporting the potential utility of frontline zanubrutinib in treatment-naive CLL/SLL.