FIRST INTERIM ANALYSIS OF ALPINE STUDY: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VS IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL)

Author(s): Wojciech Jurczak[1], Barbara Eichhorst[2], Jennifer J. Brown[3], Nicole Lamanna[4], Susan O'Brien[5], Constantine S. Tam[6,7,8,9], Lugui Qiu[10], Maciej Kazmierczak[11], Keshu Zhou[12], Martin Šimkovič[13,14], Jiri Mayer[15], Amanda Gillespie-Twardy[16], Mazyar Shadman[17,18], Alessandra Ferrajoli[19], Peter S. Ganly[20,21], Robert Weinkove[22,23], Tommi Salmi[24], Kenneth Wu[24], William Novotny[24], Peter Hillmen[25]

Affiliations: [1]Maria Sklodowska-Curie National Institute of Oncology, Cracovie, Poland; [2]Department of Internal Medicine, Université de Cologne, Cologne, Germany; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [4]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA ; [5]Chao Family Comprehensive Cancer Center, University of California, Irvine, CA, USA; [6]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [7]University of Melbourne, Parkville, Victoria, Australia; [8]St Vincent's Hospital, Fitzroy, Victoria, Australia; [9]Royal Melbourne Hospital, Parkville, Victoria, Australia; [10]Chinese Academy of Medical Sciences, Peking Union Medical College, Tianjin, China; [11]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland; [12]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [13]4th Department of Internal Medicine - Hematology, University Hospital, Hradec Kralove, Czech Republic; [14]Faculty of Medicine, Charles University, Prague, Czech Republic; [15]Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital, Brno, Czech Republic; [16]Blue Ridge Cancer Care, Roanoke, VA, USA; [17]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [18]Department of Medicine, University of Washington, Seattle, WA, USA; [19]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [20]Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; [21]Department of Pathology and Biomedical Science, University of Otago, Christchurch, New Zealand; [22]Wellington Blood and Cancer Centre, Capital and Coast

District Health Board, Wellington, New Zealand; [23]Malaghan Institute of Medical Research, Wellington, New Zealand; [24]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [25]St James's University Hospital, Leeds, UK

ABSTRACT

CLL/SLL treatment has been transformed with Bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib. Zanubrutinib, a next-generation BTKi, was designed to maximize BTK occupancy and minimize toxicity. ALPINE (NCT03734016) is a global, randomized, phase 3 study of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL; presented here is a preplanned interim analysis conducted ~12 months after 415 patients enrolled between 5Nov2018–20Dec2019. Patients were randomized 1:1 to zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily) arms; stratification factors were age (<65 y vs ≥65 y), geographic region, refractory status, and del(17)p/*TP53* mutation. Primary endpoint was investigator-assessed overall response rate (ORR) per 2008 IWCLL guidelines or Lugano criteria; noninferiority of zanubrutinib-to-ibrutinib response ratio was evaluated at noninferiority margin of 0.8558. If noninferiority was demonstrated, superiority of zanubrutinib vs ibrutinib in ORR was tested. Baseline characteristics (zanubrutinib vs ibrutinib): age ≥65 y: 62.3% vs 61.5%; male sex: 68.6% vs 75%; >3 prior therapies: 7.2% vs 10.1%; del(17)p: 11.6% vs 12.5%; *TP53* mutation without del(17)p: 8.2% vs 5.8%. With median follow-up of 15 months, ORR was 78.3% vs 62.5% for zanubrutinib vs ibrutinib, respectively (2-sided *P*=0.0006, prespecified α=0.0099). ORR was higher for zanubrutinib in patients with del(11)q (83.6% vs 69.1%) and del(17)p (83.3% vs 53.8%); zanubrutinib had higher overall 12-months progression-free survival (PFS; 94.9% vs 84.0%) and overall survival (97.0% vs 92.7%). Significantly fewer patients had atrial fibrillation/flutter (AF) with zanubrutinib vs ibrutinib (2.5% vs 10.1%, 2-sided *P*=0.0014, prespecified α=0.0099). Zanubrutinib had lower rates of major bleeding (2.9% vs 3.9%), adverse events leading to discontinuation (7.8% vs 13.0%), and death (3.9% vs 5.8%). Zanubrutinib had higher neutropenia rate (28.4% vs 21.7%) while grade ≥3 infections (12.7% vs 17.9%) were lower. In summary, this interim analysis showed zanubrutinib had a superior ORR, improved PFS, and lower AF rate compared with ibrutinib.