Improved efficacy and safety of zanubrutinib versus ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL) in China: A subgroup of ALPINE

Authors: Lugui Qiu,[1] Keshu Zhou,[2] Tingyu Wang,[3] Ling Pan,[4] Wei Xu,[5] Jie Jin,[6] Wei Zhang,[7] Yu Hu,[8] Jianda Hu,[9] Ru Feng,[10] Ping Li,[11] Zhuogang Liu,[12] Peng Liu,[13] Hongmei Jing,[14] Sujun Gao,[15] Huilai Zhang,[16] Kang Yu,[17] Zhao Wang,[18] Xiongpeng Zhu,[19] Zimin Sun,[20] Fei Li,[21] Dongmei Yan,[22] Jianyu Weng,[23] Lina Fu,[24] Tommi Salmi,[25] Kenneth Wu,[26] Liping Wang,[24] and Jennifer R. Brown[27]

Affiliations: [1]National Clinical Research Center for Blood Diseases and State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Experimental Hematology, Tianjin, China; [2]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Hematology, Zhengzhou, China; [3]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and Tianjin Institutes of Health Science, Tianjin, China; [4]West China Hospital, Sichuan University, Hematology, Sichuan, China; [5]Jiangsu Province Hospital, Hematology, Zhejiang, China; [6]The First Hospital of Zhejiang Province, Hematology, Zhejiang, China; [7]Peking Union Medical College Hospital, Hematology, Beijing, China; [8]Union Hospital of Tongji Medical College, Hematology, Wuhan, China; [9]Fujian Medical University Union Hospital, Hematology, Fuzhou, China; [10]Nanfang Hospital of Southern Medical University, Hematology, Guangzhou, China; [11]Tongji Hospital of Tongji University, Hematology, Wuhan, China; [12]Shengjing Hospital of China Medical University, Hematology, Shenyang, China; [13]Zhongshan Hospital of Fudan University, Hematology, Shanghai, China; [14]Peking University Third Hospital, Hematology, Beijing, China; [15]The First Hospital of Jilin University, Hematology, Oncology, Changchun, China; [16]Tianjin Medical University Cancer Institute & Hospital, Hematology, Oncology, Tianjin, China; [17]The First Affiliated Hospital of Wenzhou Medical University, Hematology, Zhejiang, China; [18]Beijing Friendship Hospital, Hematology, Beijing, China; [19]Quanzhou First Hospital of Fujian Province, Hematology, Quanzhou, China; [20]Anhui Provincial Hospital, Hematology, Hefei, China; [21]The First Affiliated Hospital of Nanchang University, Hematology, Nanchang, China; [22]The Affiliated Hospital of Xuzhou Medical University, Hematology, Jiangsu, China; [23]Guangdong Provincial People's Hospital, Hematology, Guangzhou, China; [24]BeiGene (Shanghai) Co., Ltd, Shanghai China; [25]Beigene International, GmbH, Basel, Switzerland; [26]BeiGene USA, Inc., San Mateo, CA, USA; and [27]Dana-Farber Cancer Institute, Boston, MA, USA

Introduction: Zanubrutinib is an irreversible, potent, next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target inhibition. In a randomized phase 3 study (ALPINE; NCT03734016), zanubrutinib was compared head to head with ibrutinib as a treatment for R/R CLL (including small lymphocytic lymphoma [SLL]). In the predefined progression-free survival (PFS) final analysis, zanubrutinib demonstrated superior efficacy and a favorable safety profile vs ibrutinib (Brown et al. *NEJM* 2022). Data from the prespecified subgroup in pts from China are reported here.

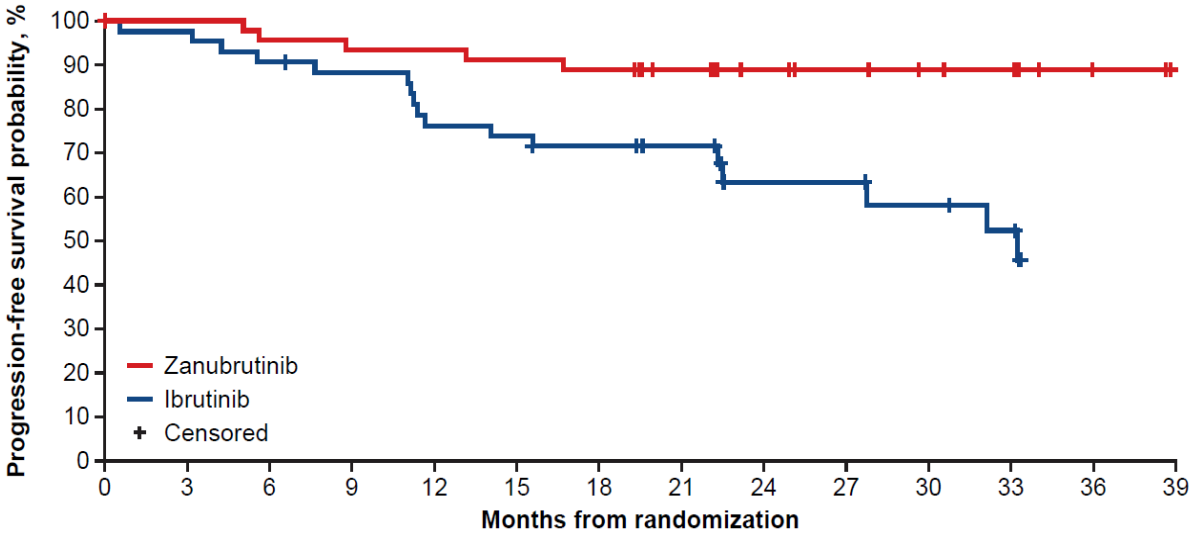
Methods: Patients (pts) with R/R CLL/SLL who had received ≥1 prior line of therapy and had measurable disease by imaging were randomized (1:1) to receive zanubrutinib 160 mg twice

daily or ibrutinib 420 mg once daily, until disease progression or unacceptable toxicity. Randomization included stratification by geographical region (**China vs non-China**). Data from the subgroup in pts from China were descriptively analyzed.

Results: A total of 90 pts in China with R/R CLL/SLL (zanubrutinib, n=47; ibrutinib, n=43) were enrolled. Disease characteristics and baseline demographics were balanced between zanubrutinib and ibrutinib (aged ≥65 y [40% vs 37%]; unmutated IGHV [59.6% vs 62.8%]; del17p/*TP53* mutated [34.0% vs 32.6%]) with a median age of 60 and 61 y, respectively. Median number of prior therapies was 1. At a median follow-up of 25.3 mo, PFS by independent review committee (IRC) was improved with zanubrutinib vs ibrutinib (hazard ratio [HR]: 0.24; 95% CI 0.09-0.64; nominal 2-sided *P* = 0.002) with 18-mo landmark PFS rates of 88.9% vs 71.6% for zanubrutinib and ibrutinib, respectively (**Figure**). Additionally, zanubrutinib was more favorable in high-risk del17p/*TP53* mutation (18-mo landmark 80.0% vs 64.3%; HR: 0.51; 95% CI 0.12-2.13). ORR also favored zanubrutinib over ibrutinib (87.2% vs 76.7%; 95% CI 0.93-1.38) by IRC. The treatment discontinuation rate was lower with zanubrutinib (14.9%) vs ibrutinib (41.9%) with most due to progressive disease (6.4% vs 20.9%) and adverse events (AEs; 6.4% vs 14.0%). Rates of grade ≥3 AEs (64.4% vs 72.1%) and serious AEs (35.6% vs 51.2%) were lower with zanubrutinib vs ibrutinib. With zanubrutinib, 4 deaths (8.5%) were reported compared to 8 deaths (18.6%) with ibrutinib (HR: 0.45; 95% CI 0.14-1.50).

Conclusions: Zanubrutinib showed improved PFS over ibrutinib in the ALPINE study in pts from China, including high-risk pts, consistent with that of the global population. A favorable safety profile was also observed in pts from China with zanubrutinib compared with ibrutinib, with lower rates of treatment discontinuations and serious AEs in patients with R/R CLL/SLL.

Figure. Kaplan-Meier Plot of PFS by IRC for the Subgroup in pts from China



No. of patients at risk														
Zanubrutinib	47	45	43	42	42	41	40	32	21	19	17	16	3	0
Ibrutinib	43	42	39	37	32	31	29	25	13	13	11	9	0	