

Title: ZANUBRUTINIB MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA: 34-MONTH FOLLOW-UP RESULTS

Authors: Wei Xu, MD, PhD¹; Shenmiao Yang, MD, PhD²; Keshu Zhou, MD, PhD³; Ling Pan, MD, PhD⁴; Zengjun Li, MD, PhD⁵; Jianfeng Zhou, MD, PhD⁶; Sujun Gao, MD, PhD⁷; Daobin Zhou, MD, PhD⁸; Jianda Hu, MD, PhD⁹; Ru Feng, MD¹⁰; Haiwen Huang, MD, PhD¹¹; Tingyu Wang, MD, PhD⁵; Meng Ji, MD¹²; Haiyi Guo, MD¹²; Jane Huang, MD¹²; William Novotny, MD¹²; Shibao Feng, PhD¹²; and Jianyong Li, MD, PhD¹

Affiliations: ¹The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China; ²Peking University Peoples Hospital, Peking University Institute of Hematology, Beijing, China; ³Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; ⁴West China Hospital of Sichuan University, Chengdu, China; ⁵Blood Disease Hospital, Chinese Academy of Medical Science, Tianjin, China; ⁶Tongji Hospital, Tongji Medical College, Wuhan, China; ⁷The First Hospital of Jilin University, Changchun, China; ⁸Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; ⁹Fujian Institute of Hematology, Fujian Provincial Key Laboratory on Hematology, Fujian Medical University Union Hospital, Fuzhou, China; ¹⁰Nanfang Hospital of Southern Medical University, Guangzhou, China; ¹¹The 1st Hospital of Soochow University, Suzhou, China; ¹²BeiGene (Beijing) Co., Ltd., Beijing, China, BeiGene (Shanghai) Co., Ltd., Shanghai, China, and BeiGene USA, Inc., San Mateo, CA, USA

Background: Zanubrutinib is a highly selective, potent, and irreversible Bruton's tyrosine kinase (BTK) inhibitor approved in China for the treatment of adult patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The previous publication of this study reported that zanubrutinib is highly active in R/R CLL/SLL, with a well-tolerated safety profile (*J Hematol Oncol.* 2020;13:48). We present here the long-term results of this study.

Aims: To evaluate the efficacy, safety, and tolerability of zanubrutinib in patients with R/R CLL/SLL.

Methods: In this single-arm, multicenter, phase 2 study (NCT03206918), patients with R/R CLL/SLL received oral zanubrutinib (160 mg twice a day) continuously until progressive disease (PD) or unacceptable toxicity. Efficacy endpoints including overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS) were assessed by an independent review committee (IRC) per International Workshop on CLL guidelines (*Blood.* 2008;111:5446) or the Lugano Classification (*J Clin Oncol.* 2014;32:3059) for CLL and SLL, respectively.

Results: Ninety-one patients (82 with CLL; 9 with SLL) were enrolled from 11 sites in China. Median age was 61 years (range, 35-87). Most patients had ≥ 1 poor prognostic variable, including unmutated immunoglobulin heavy chain variable region gene (*IGHV*; 56.0%), del(17p) or TP53 mutation (24.2%), and del(11q) (22%).

With a median 33.9-mo follow-up period (range, 0.8-41.4), 31 patients (34.1%) discontinued treatment primarily due to progressive disease (PD) in 15 patients and adverse events (AEs), regardless of relation to study drug, in 14 patients. Most patients (66%) were still on zanubrutinib treatment. The efficacy data are presented in the **Table**. The overall response rate was generally consistent across all subgroups analyzed, including those with unfavorable prognostic factors. Patients with del(17p) and/or TP53 mutation and del(11q) achieved high response rates of 91% (95% CI, 70.8%-98.9%) and 100% (95% CI, 83.2%-100%), respectively.

The most commonly reported treatment-emergent adverse events (TEAEs) are listed in the **Table**. Most AEs regarding to lab abnormalities were with low CTCAE severity (grade 1-2) and without clinical consequences. Second primary malignancies were reported in 5 patients (2 gastric adenocarcinoma; 1 each of colon cancer, breast cancer, and rectal cancer). Only 1 patient reported atrial fibrillation (grade 2). TEAEs leading to death were reported in 6 patients (2 pneumonia; 1 each for cardiopulmonary failure, brain herniation, and multiple organ dysfunction syndrome; 1 with cardiac failure, pneumonia, and respiratory failure). TEAEs leading to dose modification were reported in 42 (46.2%) patients. Commonly reported TEAEs leading to treatment discontinuation included pneumonia (n=4) and hepatitis B (n=2).

Conclusion/summary: Results with longer follow-up continue to show a high response rate. Deep and durable responses were achieved in all patient subgroups including patients with high-risk cytogenetics. Data support the tolerability of long-term zanubrutinib treatment in R/R CLL/SLL, with no new safety signals identified.

Table.

Efficacy, n (%)	N=91
CR	6 (6.6)
PR	63 (69.2)
PR-L	11 (12.1)
SD	3 (3.3)
PD	3 (3.3)
Not evaluable ^a	2 (2.2)
Discontinued before first assessment, n (%)	3 (3.3)
Overall response rate (95% CI) (%)	87.9 (79.4, 93.8)
Estimated progression/death event free rate at	
24 months (95% CI) (%)	80.5 (70.5, 87.4)
36 months (95% CI) (%)	68.1 (56.6, 77.4)
DOR event free rate at	
24 months (95% CI) (%)	83.4 (73.2, 90.0)

36 months (95% CI) (%)	69.9 (57.0, 79.6)	
Common nonhematologic AEs (>30% any grade), n (%)	Any Grade	Grade ≥3
Upper respiratory tract infection	51 (56.0)	11 (12.1)
Hematuria	39 (42.9)	0
Pneumonia	34 (37.4)	22 (24.2)
Purpura	31 (34.1)	0
Hypokalemia	28 (30.8)	7 (7.7)
Common hematologic AEs,^b n (%)		
Neutropenia	71 (78.0)	46(50.5)
Thrombocytopenia	48 (52.7)	15 (16.5)
Anemia	36 (39.6)	10 (11.0)

AE, adverse event; CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

^a 'Not evaluable' were due to missing anatomy imaging of 2 patients.

^b Incidence of neutropenia, thrombocytopenia, and anemia were summarized based on group term.