Title: Zanubrutinib Monotherapy in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia: 34-month Follow-up Results

Authors: Wei Xu, MD, PhD[1]; Shenmiao Yang, MD, PhD[2]; Keshu Zhou, MD, PhD[3]; Ling Pan, MD, PhD[4]; Zengjun Li, MD, PhD[5]; Jianfeng Zhou, MD, PhD[6]; Sujun Gao, MD, PhD[7]; Daobin Zhou, MD, PhD[8]; Jianda Hu, MD, PhD[9]; Ru Feng, MD[10]; Haiwen Huang, MD, PhD[11]; Tingyu Wang, MD, PhD[5]; Meng Ji, MD[12]; Haiyi Guo, MD[12]; Jane Huang, MD[12]; William Novotny, MD[12]; Shibao Feng, PhD[12]; and Jianyong Li, MD, PhD[1]
Affiliations: *[1]l, Nanjing, China; [2]Peking University Peoples Hospital, Peking University Institute of Hematology, Beijing, China; [3]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [4]West China Hospital of Sichuan University, Chengdu, China; [5]Blood Disease Hospital, Chinese Academy of Medical Science, Tianjin, China; [6]Tongji Hospital, Tongji Medical College, Wuhan, China; [7]The First Hospital of Jilin University, Changchun, China; [8]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [9]Fujian Institute of Hematology, Fujian Provincial Key Laboratory on Hematology, Fujian Medical University Union Hospital, Fuzhou, China; [10]Nanfang Hospital of Southern Medical University, Guangzhou, China; [11]The 1st Hospital of Soochow University, Suzhou, China; [12]BeiGene (Beijing) Co., Ltd., Beijing, China, BeiGene (Shanghai) Co., Ltd., Shanghai, China, and BeiGene USA, Inc., San Mateo, CA, USA*

Introduction: Zanubrutinib is a highly selective, potent, and irreversible Bruton 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. The aim of the BGB-3111-205 study is 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 or unacceptable toxicity. Efficacy endpoints, including overall response rate, duration of response (DOR), and progression-free survival (PFS), were assessed by an independent review committee 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 at 11 sites in China. The median age was 61 years (range, 35-87). Most patients had at least 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 follow-up period of 33.9 months (range, 0.8-41.4 months), 31 patients (34.1%) discontinued treatment primarily due to progressive disease in 15 patients, and adverse events, regardless of relation to study drug, in 14 patients. Most patients (66%) were still on zanubrutinib treatment at the time of data cutoff. 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 adverse events in regard to lab abnormalities were low CTCAE severity (grade 1-2) 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).

Conclusions: Results with longer follow-up continue to show a high response rate. Deep and durable responses were achieved in all patient subgroups, including in 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/Figure (if applicable)**:**

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' was due to missing anatomy imaging of 2 patients.

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