



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

A Novel Dual Covalent and Non-Covalent Next Generation Inhibitor of Bruton's Tyrosine Kinase LP-168 in Patients with Relapsed/Refractory B Cell Non-Hodgkin Lymphoma: Safety and Efficacy Results from a Phase 1 Study

Yuqin Song, MD¹, Qingqing Cai, PhD², Ming Jiang³, Keshu Zhou, MD⁴, Lei Zhang, MD⁵, Xiuhua Sun⁶, Zhengming Jin, B.S.⁷, Lanfang Li⁸, Hongmei Jing⁹, Zhigang Peng, MD¹⁰, Haiyan Yang¹¹, Junyuan Qi, MD¹², Hui Zhou¹³, Wei Yang, MD¹⁴, Min Zhou¹⁵, Chunyan Ji, MD PhD¹⁶, Wei Xu¹⁷, Kaiyang Ding¹⁸, Li Yu¹⁹, Zheng Wang²⁰, Nawei Liu²⁰, Yejiang Lou²⁰, Yue Shen, PhD²⁰, Yi Chen, PhD²¹, Fenlai Tan²⁰, Jun Zhu²²

¹ Department of Lymphoma, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, BEIJING, China

² Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University Cancer Center, Guangzhou, China

³ The State Key Laboratory of Pathogenesis and Prevention of Central Asian High Incidence Diseases, Urumqi, China

⁴ Department of Hematology, Cancer Hospital Affiliated to Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China

⁵ Department of Oncology, The First Affiliated Hospital of Zhengzhou University & Lymphoma Diagnosis and Treatment Center of Henan Province, Zhengzhou, China

⁶ The Second Hospital of Dalian Medical University, Dalian, China

⁷ Department of Hematology, Collaborative Innovation Center of Hematology, Institute of Blood and Marrow Transplantation, the First Affiliated Hospital of Soochow University, Suzhou, China

⁸ Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

⁹ Peking University Third Hospital, Beijing, China

¹⁰ Department of Medical Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

¹¹ Zhejiang Cancer Hospital, Hangzhou, China

¹² Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences, Tianjin, China

¹³ Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

¹⁴ Shengjing Hospital of China Medical University, Shenyang, China

¹⁵ Department of Medical Oncology, Affiliated Cancer Hospital and Institute of Guangzhou Medical University, Guangzhou, China

¹⁶ Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

¹⁷ Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China

¹⁸ Department of Hematology, The First Affiliated Hospital of University of Science and Technology of China, Anhui, China

¹⁹ The Second Affiliated Hospital of Nanchang University, Nanchang, China

²⁰ Guangzhou Lupeng Pharmaceutical Co., Ltd., Guangzhou, China

²¹ Newave Pharmaceutical Inc., Pleasanton, CA

²² Department of Lymphoma, Peking University Cancer Hospital and Institute, BEIJING, China

Background: Covalent (c) Bruton tyrosine kinase inhibitors (BTKis) have improved clinical outcomes and revolutionized the treatment landscape of several B cell Non-Hodgkin Lymphoma (B-NHL), including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL). However, cBTKi intolerance and resistance remain the main causes of treatment failure. LP-168 is a highly selective, next-generation BTKi with high bioavailability and potency. It can act as a cBTKi which irreversibly inhibits wildtype BTK while can overcome the resistance of cBTKi by non-covalent binding and reversible inhibition of C481 mutated BTK. In this abstract are the results from a Phase 1 trial (NCT04993690) that evaluates the safety and efficacy of LP-168 monotherapy in Chinese patients with relapsed/refractory (R/R) B-NHL.

Methods: This multicenter Phase 1 study contains a "3+3" dose escalation part (Phase 1a) followed by a dose expansion part (Phase 1b). Subjects with R/R B-NHL are eligible to receive LP-168 once daily treatment until disease progression or unacceptable toxicity. This study was designed to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of LP-168. The efficacy assessment was based on Lugano 2014, 2018 International Workshop on CLL (iwCLL) and the 6th International Workshop for WM response criteria.

Results: Between 10 August 2021 and 31 May 2023, 68 subjects (33 MCL, 14 diffuse large B cell lymphoma [DLBCL], 15 marginal zone lymphoma [MZL], 3 CLL/SLL, 2 follicular lymphoma [FL] and 1 primary mediastinal large B cell lymphoma [PMBCL]) were enrolled. Cohorts of 100 mg (N=13) 150 mg (N=40) and 200 mg (N=15) taken QD were treated respectively. The median age was 59.2 (range, 32-79) years old; 22 (64.7%) were male. The median number of prior therapies was 2 (range, 1-10) and 25 (36.8%) subjects had received at least a cBTKi-containing regimen. The median follow-up was 4.5 (0.3-21.3) months with 46 subjects remaining on treatment.

No dose-limiting toxicities (DLTs) were observed during dose escalation from 100mg QD, 150mg QD to 200mg QD, and the maximum tolerated dose (MTD) was not reached. The most common treatment-emergent adverse events (TEAEs) occurring in $\geq 20\%$ subjects included neutropenia, platelet count decreased and anemia, most of which were Grade 1 or 2 (as detailed in Table 1). \geq Grade 3 treatment related adverse events (TRAEs, including possibly related, probably related and definitely related) included neutropenia (7.4%), lung infection (2.9%), lymphopenia, leukocytosis, lymphocytosis and oral cavity infection (1.5% each). 9 (13.2%) subjects experienced Serious Adverse Event (SAE). Serious adverse reactions included lung infection, oral cavity infection and lymphocytosis. No major bleeding, hypertension, or atrial fibrillation was observed in this study. Dose reduction occurred in only 1 subject due to AE (immune-mediated pancreatitis, unlikely related). No TEAE led to drug discontinuation. 1 subject experienced Grade 5 lung infection (not related to LP-168). Of 60 efficacy-evaluable subjects, overall response rate (ORR) was 65.0%. In particular, ORR in R/R MCL (N=31) was 77.4% with a CR of 38.7%, non-GCB DLBCL (N=10) had an ORR of 70.0% with a CR of 40.0% and MZL (N=11) had an ORR of 72.7% with a CR of 9.1% (Figure 1). LP-168 steady state plasma exposure increases dose-dependently with limited accumulation at 100 to 200 mg. Plasma concentration peaks at approximately 2 to 3 hours at fasted state, the average terminal half-life was 15.1 hours, supporting once daily dosing.

Conclusion: The current results of the Phase 1 study showed that LP-168 was well tolerated at 100-200 mg QD with favorable PK profile and has demonstrated encouraging efficacy in multiple B-cell malignancies, including those who had progressed on prior cBTKi.

Disclosures Shen: *Guangzhou Lupeng Pharmaceutical Co:* Current Employment. **Chen:** *Newave Pharmaceutical Inc:* Current Employment, Current holder of *stock options* in a privately-held company, Honoraria, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: Newave Pharmaceutical Inc.

Table 1. Common TEAEs (incidence $\geq 10\%$)^a

TEAE (N=68) ^a	All Grade ^a	Grade 3 ^a	Grade 4 ^a
Neutropenia ^a	20 (29.4%) ^a	3 (4.4%) ^a	2 (2.9%) ^a
Platelet count decreased ^a	18 (26.5%) ^a	0 ^a	0 ^a
Anemia ^a	16 (23.5%) ^a	1 (1.5%) ^a	0 ^a
COVID-19 ^a	13 (19.1%) ^a	0 ^a	0 ^a
White blood cell count decreased ^a	12 (17.6%) ^a	1 (1.5%) ^a	0 ^a
Hyperuricemia ^a	11 (16.2%) ^a	0 ^a	0 ^a
Petechiae ^a	10 (14.7%) ^a	0 ^a	0 ^a
Lymphocyte count decreased ^a	9 (13.2%) ^a	2 (2.9%) ^a	0 ^a
Blood creatinine increased ^a	9 (13.2%) ^a	0 ^a	0 ^a
Rash ^a	8 (11.8%) ^a	0 ^a	0 ^a
Hyperlipidemia ^a	7 (10.3%) ^a	1 (1.5%) ^a	0 ^a
upper respiratory tract infection ^a	7 (10.3%) ^a	0 ^a	0 ^a

^a

Figure 1. Waterfall plot of maximum change in target lesion SPD from baseline^a

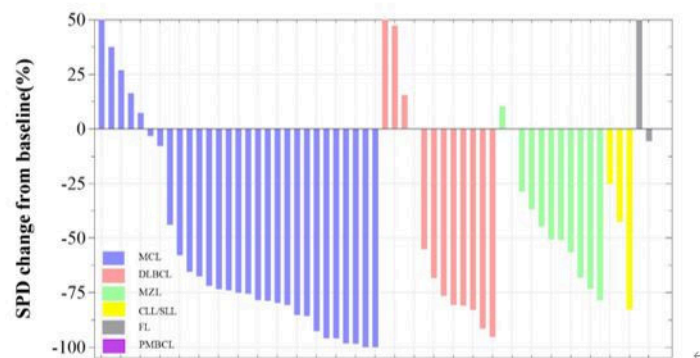


Figure 1

<https://doi.org/10.1182/blood-2023-180485>