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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

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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 6 th 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 ≥20% subjects included neutropenia, platelet count decreased and anemia, most of which were Grade 1 or 2 (as detailed in Table 1). ≥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≥10%)

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

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

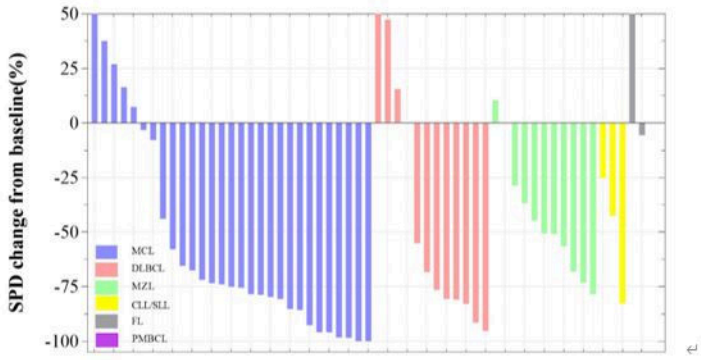

Figure 1

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