Results from a Phase 1 Dose Escalation Study of HMPL-689, a Selective Oral Phosphoinositide 3-Kinase-Delta Inhibitor, in Chinese Patients with relapsed/refractory (R/R) Lymphoma

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Abstract

Introduction

HMPL-689 is a potent and highly selective small molecule inhibitor of phosphoinositide 3-kinase-delta (PI3Kδ). Despite available agents targeting the B-cell receptor (BCR) pathway, there remains a need for alternative therapies in the relapsed/refractory (R/R) setting due to agent-specific toxicities and suboptimal efficacy among lymphoma subtypes. This study (NCT03128164) is a phase 1, open-label, dose escalation and expansion study in China to assess the safety, pharmacokinetics (PK), and preliminary efficacy of HMPL-689 as a monotherapy in patients with R/R lymphomas. Here we present the preliminary results of the dose-escalation phase of the study.

Methods

In this dose escalation phase, patients with R/R lymphoma failed of standard therapy, at least 1 prior therapy, were eligible. The dose-escalation study consisted of cohort A (BID) and cohort B (QD), in which HMPL-689 was orally administered continuously on a 28-day cycle. The modified toxicity probability interval scheme-2 (mTPI-2) design was applied for the dose escalation and maximum tolerated dose (MTD) determination. Blood samples for PK and pharmacodynamics (PD) analyses were collected during Cycle 1 and Day 1 of each subsequent cycle.

Results

A total of 56 patients were enrolled, with 5 chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 23 follicular lymphoma (FL), 7 marginal zone lymphoma (MZL), 9 mantle cell lymphoma (MCL), 9 diffuse large B cell lymphoma (DLBCL), and 3 Hodgkin's lymphoma (HL) patients (Table 1). The median age was 56 years (range 26-73). The median number of prior therapies was 3 (range 1-8), of which 39 patients had prior exposure to rituximab. 29 patients received HMPL-689 in cohort A (BID): 2.5 mg (n=3), 5 mg (n=9), 7.5 mg (n=8), and 10 mg (n=9), while 27 patients were in cohort B (QD): 5 mg (n=3), 10 mg (n=3), 20 mg (n=9), 30 mg (n=9), and 40 mg (n=3). Median duration of HMPL-689 therapy was 7.6 months (range 0.4 –Not reached [NR]).

The most common Grade ≥3 non-hematologic treatment emergent adverse events (TEAEs) were pneumonia and hypertension. Grade ≥3 hematologic TEAEs were neutropenia (Table 2). No Grade 5 TEAE was reported. In cohort A, 4 dose limited toxicities (DLTs) were

observed, including Grade 3 asymptomatic amylase (2 pts, 5 mg), Grade 4 hypercalcemia (1 pt, 10 mg), Grade 3 lipase increased (1 pt, 10 mg). In cohort B, 5 DLTs including Grade 3 skin maculopapular (1 pt, 20 mg), hypertriglyceridemia (1 pt, 30 mg), QT interval prolongation (1 pt, 30 mg) and rash (2 pts, 40 mg) were reported.

Plasma PK data for the 5-30 mg QD and 2.5-10 mg BID multiple–dose regimens were determined. HMPL-689 drug exposures increased in a dose proportional fashion up to 30mg QD, as reflected in AUC and C_{max}. The geometric mean AUC_{tau} and C_{max} at 30 mg QD in patients were approximately 2150 h•ng/mL and 260 ng/mL, respectively at steady state. The median T_{max} was around 2 h and the arithmetic mean $t_{1/2}$ was within the range of 5-10 hours, consistent across all dose levels.

51 out of the 56 patients had post-baseline tumor assessment, with 6 complete response (CR) (2 CLL/SLL, 4 FL), 21 partial responses (PR) (2 CLL/SLL, 5 MZL, 7 FL, 4 MCL, 3 DLBCL) and 18 stable disease (SD) (2 MZL, 9 FL, 4 MCL, 1 DLBCL, 2 HL). This resulted in 52.9% (27/51) objective response rate (ORR) in efficacy evaluable patients. The median time to response (TTR) and duration of response (DOR) were 3.5 months (1.8-8.4) and 6.4 months (0.7-NR), respectively (Table 3). One patient with FL who achieved CR (per post hoc independent radiologic review) was on treatment > 586 days. Final data quality control/verification is ongoing.

As a result, 30 mg QD of HMPL-689 has been selected as recommended phase 2 dose (RP2D) based on overall safety and tolerability, PK/PD and preliminary efficacy data.

Conclusions:

HMPL-689 was well tolerated and the RP2D was determined to be 30 mg QD orally. It exhibited dose-proportional pharmacokinetics, a manageable toxicity profile, and promising single-agent clinical activity in R/R B-cell lymphoma patients. The dose expansion study is ongoing, evaluating the safety and efficacy of HMPL-689 in patients with R/R B-cell lymphoma.

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Authorship

Contribution: Junning Cao, Zhiming Li, Jianfeng Zhou conceived the project and designed the study; Dongmei Ji, Weina Shen, Peng Sun, Yu Wang, Dengju Li, Zhenya Hong, Gaoxiang Wang, Yun Zhu, Yiting Mo, Haitao Ruan were responsible for patient care; Jian Wang contributed to PK data analysis; Xiaoyun Jia, Linfang Wang, Yongxin Ren contributed to pharmacodynamic analysis data; Liu Yang and Linda Luo analyzed the data; Xianlin Duan wrote the first version of the abstract; and all authors reviewed the data and contributed to revisions of the abstract.

Table 1 Baseline characteristics of all patients with HMPL-689

Demographic	HMPL-689 (N=56)
Median Age, years(range)	56 (26-73)
Gender, n (%)	
Male	33 (58.9)
Female	23 (41.1)
ECOG score, n (%)	
0	11 (19.6)
1	45 (80.4)
Lymphoma subtype, n (%)	
CLL/SLL	5 (8.9)
FL	23 (41.1)
MZL	7 (12.5)
MCL	9 (16.1)
DLBCL	9 (16.1)
HL	3 (5.4)
Disease stage III-IV, n (%)	49 (87.5)
IPI score, intermediate to high risk, n (%)	34 (60.7)
Prior Systemic therapies, median (range)	3 (1-8)
≥ 3 prior systemic therapy, n (%)	24 (42.9)
prior rituximab treatment, n (%)	39 (69.7)
Month from last therapy to first dose	
<6 m, n (%)	23 (41.1)
≥6 m, n (%)	33 (58.9)

Table 2 Most Common Treatment-emergent Adverse Events (Occurred in ≥5% of patients)

Preferred Term	HMPL-689 (N=56)	
	All grade	Grade ≥3
Neutropenia	24 (42.9)	6 (10.7)
Leukopenia	15 (26.8)	2 (3.6)
Upper respiratory tract infection	12 (21.4)	0
Pneumonia	11 (19.6)	7 (12.5)
Cough	11 (19.6)	0
Alanine aminotransferase increased	11 (19.6)	1 (1.8)
Lipase increased	10 (17.9)	3 (5.4)
Reticulocyte percentage increased	9 (16.1)	0
Aspartate aminotransferase increased	8 (14.3)	1 (1.8)
Pyrexia	8 (14.3)	0
Blood bilirubin increased	7 (12.5)	1 (1.8)
Anaemia	7 (12.5)	0
Mouth ulceration	7 (12.5)	0
Blood creatinine increased	5 (8.9)	0
Thrombopenia	4 (7.1)	1 (1.8)
Hypertension	4 (7.1)	4 (7.1)
Hyperglycaemia	4 (7.1)	1 (1.8)

Table 3 The preliminary efficacy of HMPL-689 in R/R lymphoma (Data cut-off by 30 June 2020)

	Total (Evaluable*, N=51)	CLL/SLL N=5	MZL N=7	FL* N=21	MCL* N=8	DLBCL* N=7	HL N=3
Best response							
CBR, n (%)	45 (88.2)	4 (80.0)	7 (100)	20 (95.2)	8 (100)	4 (57.1)	-
ORR, n (%)	27 (52.9)	4 (80.0)	5 (71.4)	11 (52.4)	4 (50.0)	3 (42.8)	0
CR, n (%)	6 (11.7)	2 (40.0)	0	4 (19.1)	0	0	0
PR, n (%)	21 (41.2)	2 (40.0)	5 (71.4)	7 (33.3)	4 (50.0)	3 (42.8)	0
SD, n (%)	18 (35.3)	0	2 (28.6)	9 (42.9)	4 (50.0)	1 (14.3)	2 (66.7)
PD, n (%)	6 (11.8)	1 (20.0)	0	1 (4.8)	0	3 (42.8)	1 (33.3)
DoR, months (range)	6.4 (0.7-NR)	4.2 (2.1-NR)	6.5 (3.7-NR)	6.9 (1.1-NR)	9.1 (1.9-NR)	3.1 (0.7-NR)	-
TTR, months (range)	3.5 (1.8-8.4)	3.7 (1.9-6.6)	2.6 (1.8-3.7)	4.1 (1.8-8.4)	4.2 (1.9-5.6)	2.0 (1.9-2.1)	-

* Five patients (2 FL, 1 MCL and 2 DLBCL) were efficacy not evaluable (NE).

Abbreviations: CBR=Clinical benefit rate (CR+PR+SD); CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma; CR=complete response; DLBCL=diffuse large B cell lymphoma; DoR=Duration of response; FL=follicular lymphoma; HL=Hodgkin' lymphoma; IPI= Diffuse Lymphoma International Prognostic Index; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; NR=not reached; ORR=overall response (CR+PR); PD=progressive disease; PR= partial response; SD=stable disease; TTR=Time to response.