2020 ASH Abstract: Poster Presentation (Abstract #1135)

Results from a Phase 1 Dose Escalation Study of HMPL-689, a Selective Oral PI3Kδ Inhibitor, in Chinese Patients with Relapsed/Refractory Lymphomas

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Conflict of Interest Disclosure

- There are no relationships to disclose.

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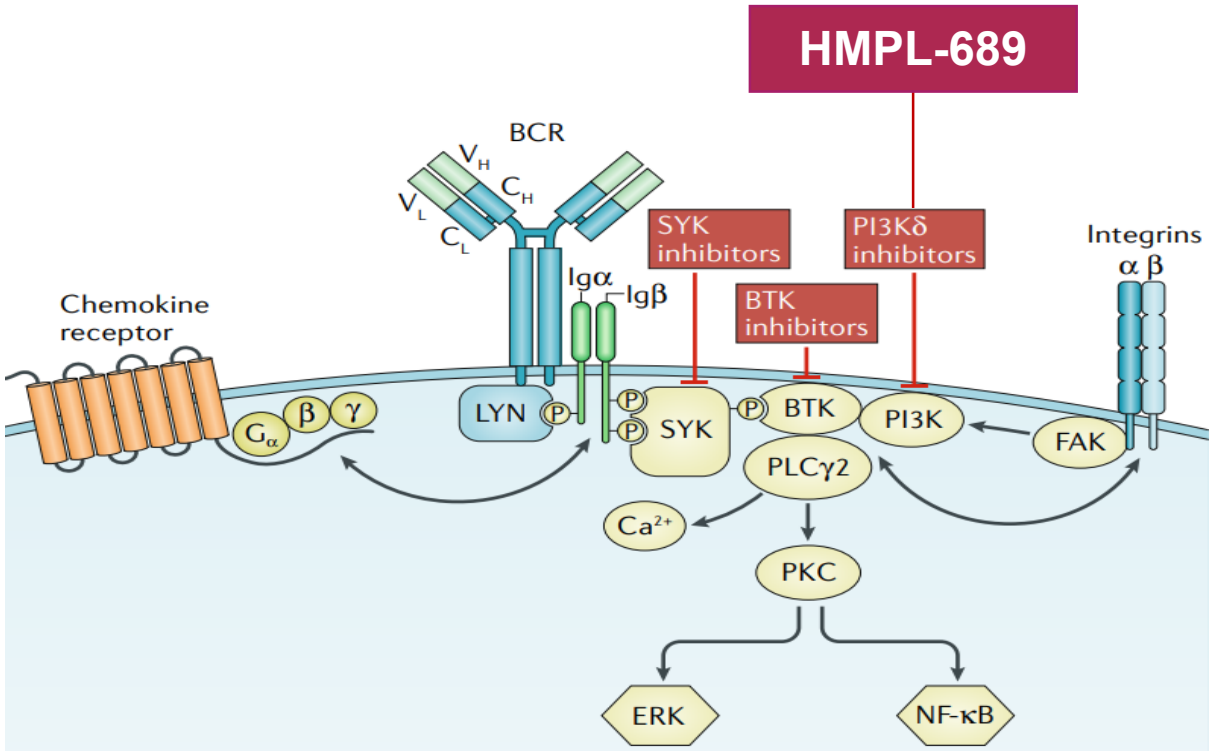
Introduction

- The approval of a range of new targeted therapies within the past 5 years has revolutionized B cell lymphoma treatment. Targeting the BCR-related Kinase inhibitors (BTK, PI3Kδ, and SYK) can greatly improve the outcomes of patients with various B cell malignancies[1,2]

- 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 across different lymphoma subtypes.
- HMPL-689 is a potent and highly selective small molecule inhibitor of phosphoinositide 3-kinase-delta (PI3Kδ).



1. Byrd JC, et al. N Engl J Med. Jul 2014;371(3):213-223.
2. Brown JR, et al. Blood. May 2014;123(22):3390-3397.

Study design

Key Inclusion Criteria:

- Signed Informed Consent Form (ICF)
- Age≥18 yrs
- PS: 0-1
- Relapsed/refractory B-cell Lymphoma
- With measurable disease

Dose-escalation

Cohort A – HMPL-689 BID
Oral twice daily 28-day cycles starting from 2.5 mg

Cohort B – HMPL-689 QD
Oral once daily 28-day cycles starting from 5 mg

mTPI-2: modified toxicity probability interval scheme-2

Primary endpoint:

- DLT, MTD, RP2D

Secondary endpoint:

- PK
- safety and tolerability

Patients will receive single agent HMPL-689 continuously in sequential 28-day treatment cycles until disease progression, death, intolerable toxicity, at investigator's discretion that the patient can no longer benefit from the study treatment, withdrawal from study treatment or withdrawal of consent, lost to follow up or the end of study, whichever comes first.

Baseline characteristics

Demographic	Dose-escalation stage N=56
Median Age, years(range)	57 (26-73)
Gender, n(%)	
Male	32 (57.1)
Female	24 (42.9)
ECOG score, n(%)	
0	11 (19.6)
1	45 (80.4)
Disease type, n(%)	
CLL/SLL	5 (8.9)
FL	23 (41.1)
MZL	7 (12.5)
DLBCL	9 (16.1)
MCL	9 (16.1)
HL	3 (5.4)
Prior Systemic therapies, median (range)	2 (1-8)
≥ 3 prior systemic therapy, n(%)	26 (46.4)
prior rituximab treatment, n(%)	39 (69.7)

CLL/SLL = chronic lymphocytic leukemia / small lymphocytic lymphoma; **FL** = follicular lymphoma; **MZL** = marginal zone lymphoma; **DLBCL** = diffuse large B cell lymphoma; **MCL** = mantle cell lymphoma; **HL** = Hodgkin's lymphoma.

Data cut-off date: September 15, 2020

Dose escalation and RP2D selection

	Dose-escalation	DLT evaluable pts	Dose limited toxicity (DLT)
Cohort A (BID)	2.5mg BID	3	0
	5mg BID	9	2 (G3 amylase increased)
	7.5mg BID	7	0
	10mg BID	9	2 (G4 hypercalcemia and G3 lipase increased)
Cohort B (QD)	5mg QD	3	0
	10mg QD	3	0
	20mg QD	9	1 (G3 maculopapule)
	30mg QD	9	2 (G3 hypertriglyceridemia and G3 QTc interval prolongation)
	40mg QD	3	2 (G3 Rash)

Based on safety, preliminary efficacy and drug exposures, 30mg QD was selected as RP2D

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All grade TEAEs (≥10%) and grade ≥3 TEAEs

Preferred Term	All grade TEAEs (≥10%), n(%)
Neutropenia	24 (42.9)
Leukopenia	16 (28.6)
ALT increased	15 (26.8)
Pneumonia	14 (25.0)
AST increased	12 (21.4)
Lipase increased	11 (19.6)
Cough	10 (17.9)
Anaemia	9 (16.1)
Blood bilirubin increased	9 (16.1)
Mouth ulceration	8 (14.3)
Pyrexia	8 (14.3)
Upper respiratory tract infection	8 (14.3)
Bilirubin unconjugated increased	7 (12.5)
Asthenia	6 (10.7)
Blood creatinine increased	6 (10.7)
Constipation	6 (10.7)
Hyperglycaemia	6 (10.7)
Hypertriglyceridaemia	6 (10.7)
Rash	6 (10.7)
Thrombocytopenia	6 (10.7)

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase.

Preferred Term	Grade ≥3 TEAEs (≥ 5%), n(%)
Pneumonia	9 (16.1)
Neutropenia	6 (10.7)
Rash	3 (5.3)
Hypertension	3 (5.3)
Lipase increased	3 (5.3)
Amylase increased	2 (3.6)
Electrocardiogram QT prolonged	2 (3.6)
Leukopenia	2 (3.6)

Preferred terms of grade ≥3 TEAEs with 1 patient (1.8%): abdominal pain, acute kidney injury, ALT increased, AST increased, back pain, bilirubin conjugated increased, blood bilirubin increased, bronchitis, dermatitis allergic, dizziness, ejection fraction decreased, gingival pain, hypercalcemia, hypercholesterolemia, hypersensitivity, hypertriglyceridaemia, hyperuricemia, left ventricular dysfunction, leukocytosis, lymphocyte count decreased, lymphocyte percentage decreased, paronychia, respiratory tract infection, skin infection, and stomatitis.

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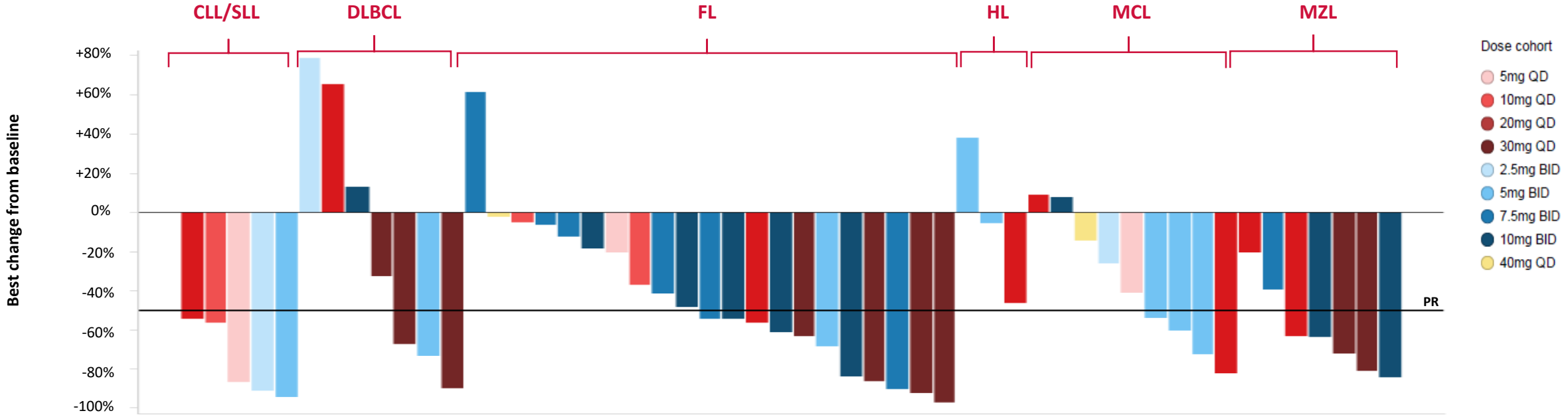
Preliminary efficacy (dose escalation)

- In the ITT population (N=56), ORR was 48.2% (34.7- 62.0), CR rate 10.7% (4.0- 21.9), PR 37.5%; CBR 82.1% (95%CI: 69.6- 91.1);
- The median time of treatment was 5.6 months (0.7- 23.2) ;
- The median time to response (TTR) and duration of response (DOR) were 1.8 months (1.8- 1.9) and 9.2 months (3.9- NA).
- Median PFS was 10.1 months (5.5- 15.7), 1 year PFS 40.0% (95%CI: 27.0- 57.0).

Best Response of Target Lesions in dose escalation stage (ITT population, N=56)



NE: 2 DLBCL patients were EOT due to AE (5mg BID) and voluntary withdraw (7.5 mg BID) , 1 FL was EOT due to AE (20 mg QD) before the first tumor evaluation.
1 CLL achieved PR base on target lesion, but was assessed as PD at C3D1 due to sustained lymphocytosis.

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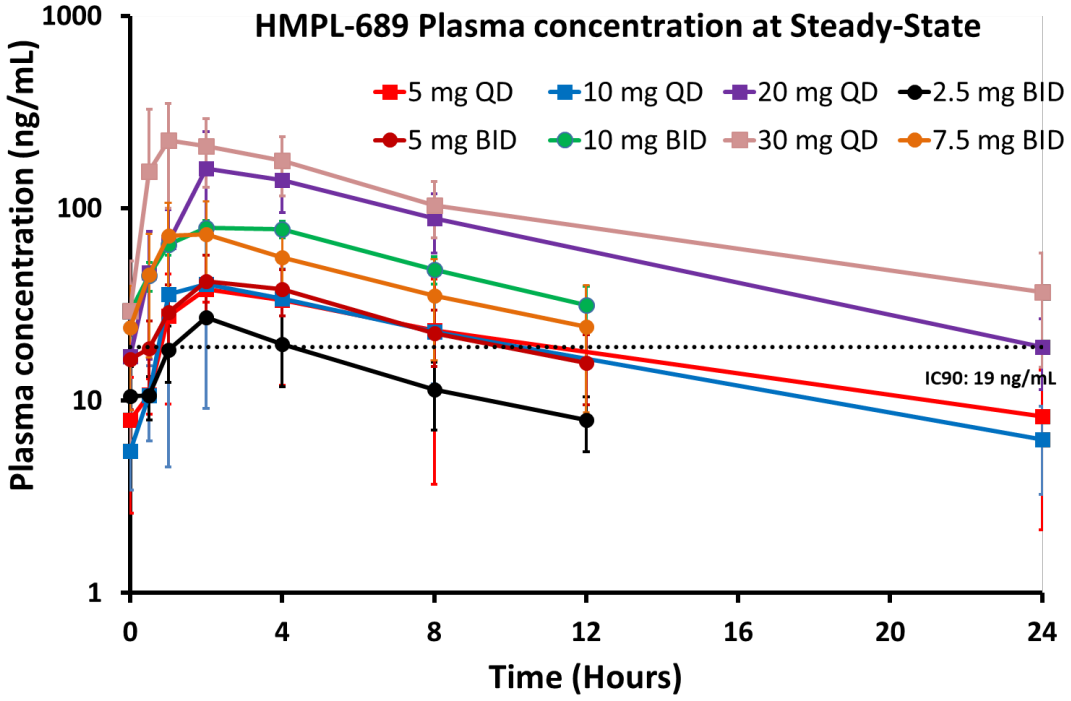
HMPL-689 in R/R lymphoma: PK profiles

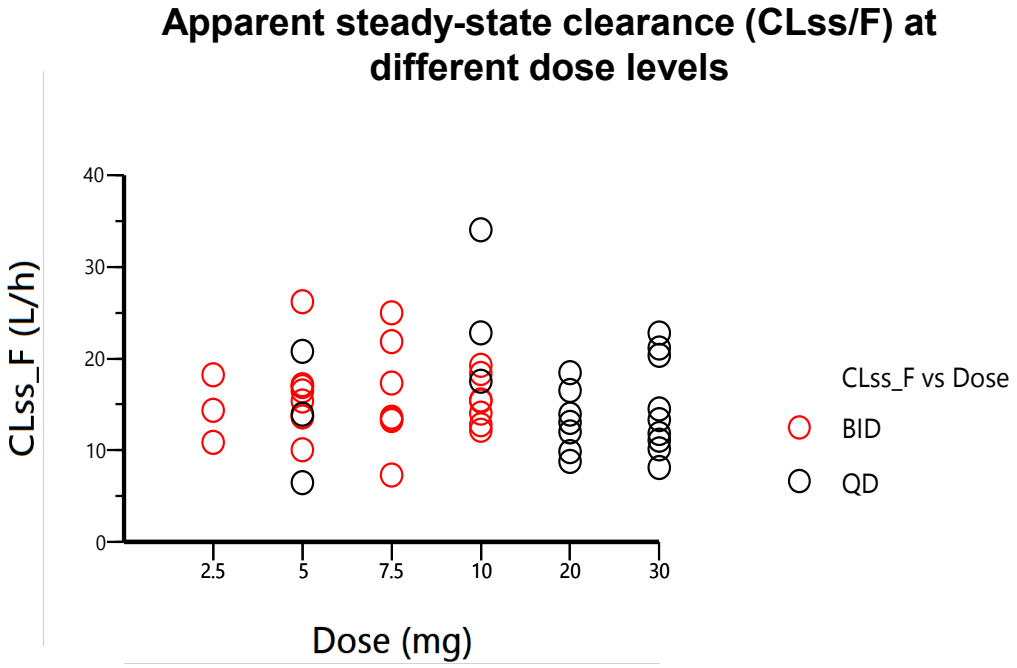
Plasma exposures: Dose-proportional increase from 5 to 30mg QD, and 2.5 to 10 mg BID, as reflected in AUC and C_{max}.

Median T_{max}: ~2 hours.

Arithmetic Mean $t_{1/2}$: 5 to 10 hours, consistent across all dose levels.

Target inhibition at RP2D (30 mg QD): complete target inhibition can be achieved and maintained for the entire dosing interval based on in vitro whole blood IC90 of 19 ng/mL.





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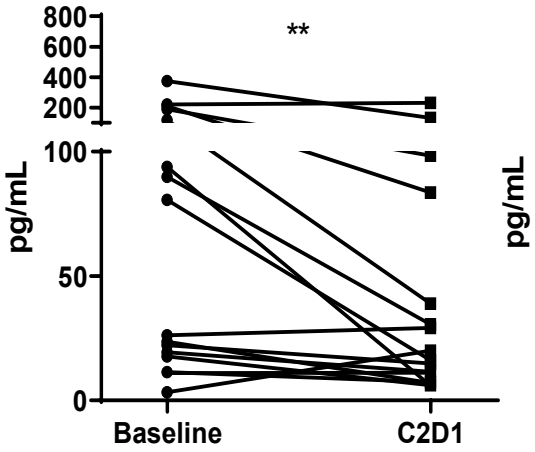
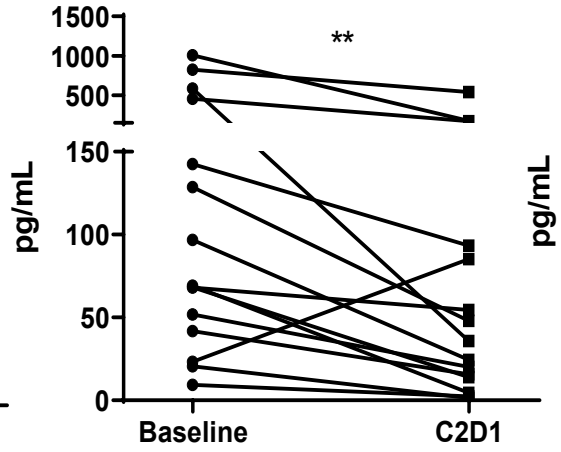
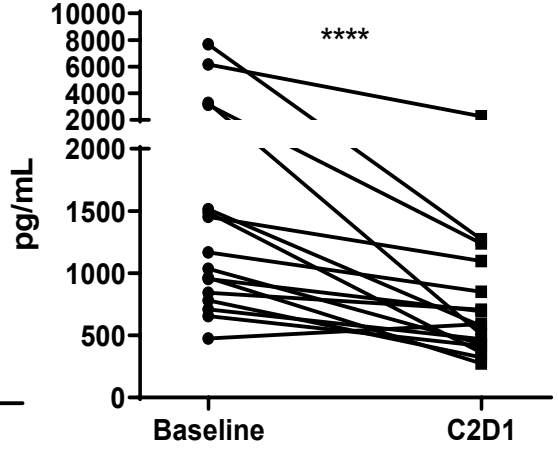
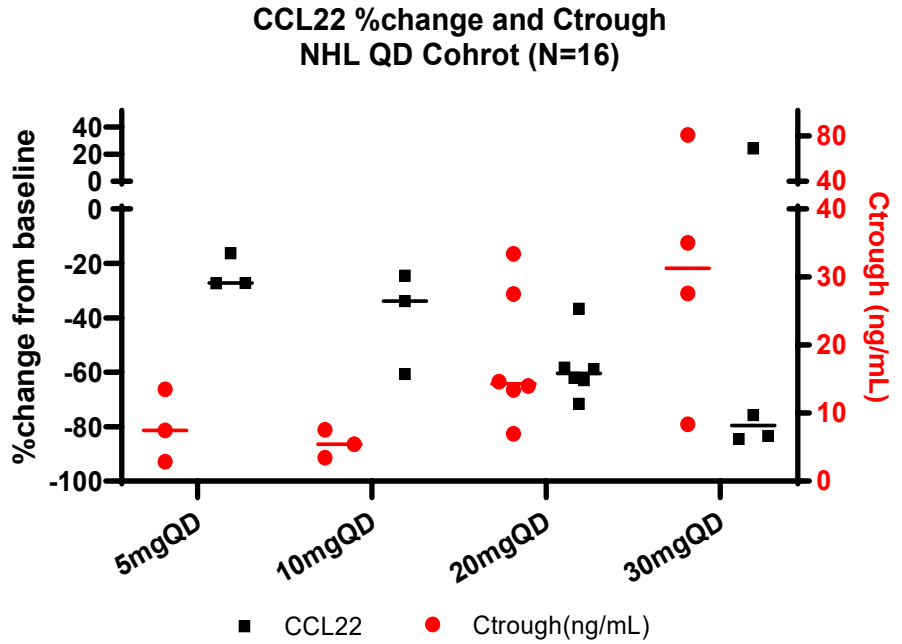
HMPL-689 treatment led to a significant decrease of CCL17, CXCL13 and CCL22 which correlated well with HMPL-689 trough plasma concentration









** P<0.01, *** p<0.001 was calculated by Wilcoxon matched-pairs signed rank test

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Conclusion

- HMPL-689 was well tolerated, with a manageable safety profile.
- HMPL-689 exposures increased dose-proportionally, with the trough following 30 mg QD estimated to fully cover the target.
- 30 mg QD orally was selected as the RP2D based on overall safety, preliminary efficacy and PK/PD data.
- Encouraging anti-tumor activity was seen across the dose-range against multiple sub-types of indolent NHL.
- A dose expansion study is ongoing evaluating the safety and efficacy of HMPL-689 in patients with R/R B-cell lymphoma.

Thank you!