Preliminary Results from a Phase I Study of HMPL-523, a Selective, Oral Syk Inhibitor, in Patients with Relapsed or Refractory Lymphoma

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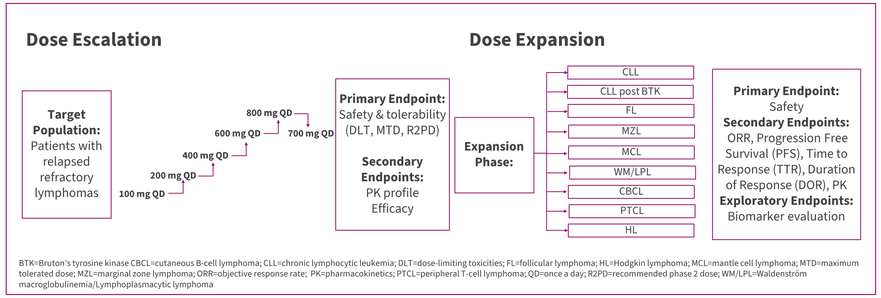
INTRODUCTION

- Spleen tyrosine kinase (Syk) plays an integral role in B-cell receptor signaling and is critical in the development and survival of several subtypes of lymphoma[1]
- HMPL-523 is a selective, oral Syk inhibitor that has shown strong anti-tumor efficacy in xenograft models of B and T-cell lymphoma[2]
- HMPL-523 had a manageable safety profile and demonstrated anti-tumor activity in a phase 1 study of lymphoma patients in China (NCT02857998).
- We report the safety and preliminary anti-tumor efficacy of HMPL-523 in the dose escalation phase of a phase 1 study of relapsed/refractory lymphoma patients in the United States and Europe (NCT03779113).

METHODS

- Ongoing phase 1, modified 3+3 dose escalation and dose expansion trial
- Primary objectives for dose escalation included safety and tolerability, and determination of the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D)
- Primary objectives for dose expansion included preliminary efficacy and safety at the RP2D
- Secondary objectives included assessment of pharmacokinetics (PK) and efficacy
- Key Eligibility Criteria:
  - ≥18 years of age, ECOG PS 0-1
  - Relapsed/refractory lymphoma, exhausted all approved therapies
  - Good organ function: creatinine clearance ≥40 mL/min, absolute neutrophil count ≥1000/μL, hemoglobin ≥8.0 g/dL
  - No serious comorbidities that would limit participation and compliance
- Treatment emergent adverse events (TEAEs) were assessed by NCI CTCAE v5.0
- Disease responses were evaluated by Lugano criteria at weeks 8, 16, 24, and then every 12 weeks
- Patients received HMPL-523 daily in 28-day cycles until disease progression or unacceptable toxicity

STUDY DESIGN



BTK=Bruton's tyrosine kinase CBCL=cutaneous B-cell lymphoma; CLL=chronic lymphocytic leukemia; DLT=dose-limiting toxicities; FL=follicular lymphoma; HL=Hodgkin lymphoma; MCL=mantle cell lymphoma; MTD=maximum tolerated dose; MZL=marginal zone lymphoma; ORR=objective response rate; PK=pharmacokinetics; PTCL=peripheral T-cell lymphoma; QD=once a day; R2PD=recommended phase 2 dose; WM/LPL=Waldenström macroglobulinemia/Lymphoplasmacytic lymphoma

BASELINE DEMOGRAPHICS

	(N=21)
Median age, years (min, max)	60.0 (26, 88)
Age group, n (%)	
<65 years	14 (66.7)
≥65 years	7 (33.3)
Gender, n (%)	
Male	15 (71.4)
Female	6 (28.6)
Race, n (%)	
Black or African American	2 (9.5)
White	19 (90.5)
Ethnicity, n (%)	
Hispanic or Latino	7 (33.3)
Not Hispanic or Latino	14 (66.7)
Baseline ECOG PS, n (%)	
0	6 (28.6)
1	15 (71.4)
Median number of prior systemic therapy (range)	4 (2, 17)
Number of lines of prior therapies, n (%)	
2	3 (14.3)
3	3 (14.3)
>3	15 (71.4)

	(N=21)
Tumor type, n (%)	
Hodgkin lymphoma (HL)	5 (23.8)
Diffuse large B-cell lymphoma (DLBCL)	4 (19.0)
Follicular lymphoma (FL)	4 (19.0)
Marginal zone lymphoma (MZL)	2 (9.5)
Mantle cell lymphoma (MCL)	1 (4.8)
Small cell lymphoma (SLL)	1 (4.8)
Peripheral T-cell lymphoma	1 (4.8)
Cutaneous T-cell lymphoma	1 (4.8)
Mixed HL/DLBCL	1 (4.8)
Richter's transformation	1 (4.8)
Prior therapies, n (%)	
Anti-CD20 antibody	15 (71.4)
BTK inhibitor	4 (19)
Lenalidomide	2 (9.5)
Venetoclax	1 (4.8)
PI3K inhibitor	2 (9.5)
Autologous Stem Cell Transplant (SCT)	5 (23.8)
Axicabtagene	1 (4.8)
Glofitamab	1 (4.8)

- Data cutoff of 25 August 2021
- As of the data cutoff, 4 patients remained on treatment (2 FL, 1 DLBCL, 1 HL)
- Median number of cycles received was 2 (range: 1,19)

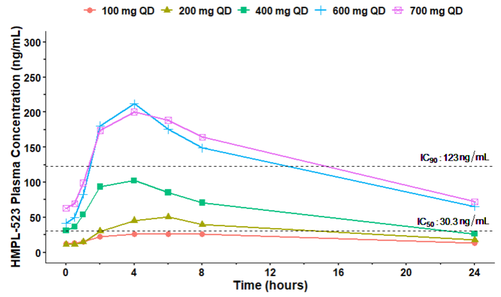
SAFETY

SOC Preferred Term	All Patients N=21			
	Treatment Emergent Adverse Events All TEAEs, n (%)		Treatment-Related Adverse Events (TRAEs), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	21 (100.0)	12 (57.1)	17 (81.0)	7 (33.3)
AST increased	6 (28.6)	0	5 (23.8)	0
Anemia	5 (23.8)	2 (9.5)	2 (9.5)	1 (4.8)
Infections	5 (23.8)	2 (9.5)	2 (9.5)	1 (4.8)
Neutropenia*	4 (19)	3 (14.3)	4 (19)	2 (9.5)
Hyponatremia	4 (19)	3 (14.3)	2 (9.5)	1 (4.8)
ALT increased	4 (19)	1 (4.8)	4 (19)	1 (4.8)
Nausea	4 (19)	0	4 (19)	0
Thrombocytopenia	3 (14.3)	1 (4.8)	1 (4.8)	0

ALT=alanine amino transferase; AST=aspartate amino transferase *Neutropenia includes terms neutropenia and neutrophil count decreased

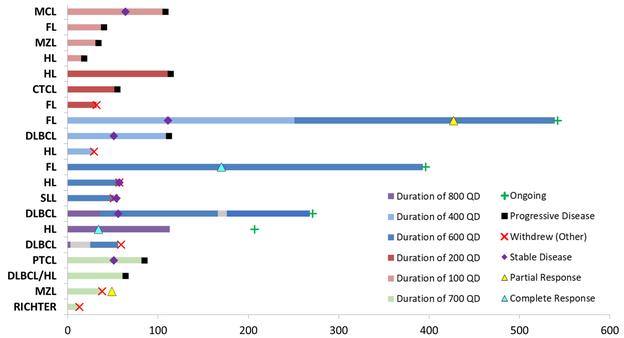
- 3 DLTs were observed: grade 3 confusion (100 mg cohort), grade 3 fever and grade 3 alanine aminotransferase elevation (800 mg cohort)
- Based on DLT evaluation, 800 mg dose was considered not tolerable; dose was de-escalated to 700 mg
- Serious adverse events occurred in 6 patients (28.6%)
- AEs leading to treatment discontinuation occurred in 2 patients (9.5%); dose reduction in 3 patients (14.3%); dose interruption in 10 patients (47.6%)

PHARMACOKINETICS



- At steady state, HMPL-523 showed approximately dose-proportional PK over the daily dose range (100-700 mg)

EFFICACY



- Out of 16 patients evaluable for response, 4 responses were noted in patients in the 400-800 mg cohorts
- Complete responses (CRs):
  - FL: 600 mg, 4 prior lines of therapy including autologous SCT and glofitamab
  - HL: 800 mg reduced to 600 mg due to toxicity, 4 prior lines of therapy including autologous SCT
- Partial responses (PRs):
  - FL: 400 mg increased to 600 mg, 2 prior lines
  - MZL: 700 mg, 2 prior lines including acalabrutinib

CONCLUSIONS

- **HMPL-523 was well tolerated at all dose levels within the range of 100 mg to 700 mg QD**
- **HMPL-523 demonstrated proof of activity at dose levels of 400 mg or higher in heavily pretreated patients**
- **The dose expansion phase of the study will evaluate safety and efficacy in multiple subtypes of B-cell and T-cell lymphoma at the R2PD of 700 mg**

For questions or comments please contact Dr. Paolo Strati PStrati@mdanderson.org

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REFERENCES
1. Geahlen. *Trends Pharmacol Sci*. 2014; 35(8): 414-22.
2. Yang et al. *Blood*. 2016; 128(22): 3970.

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