Preliminary phase I/II study results of orelabrutinib combined with MIL62 in patients with relapsed or refractory B-cell non-Hodgkin lymphoma

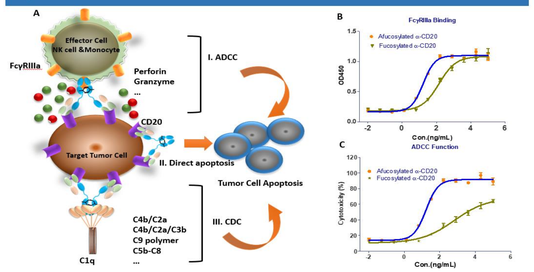
Yuankai Shi[1], Yan Qin[1], Weijing Zhang[2], Xinghe Wang[3], Hui Liu[4], Aimin Zang[5], Yanli Yang[6], Sijun Liu[7], Min Wei[7], Danhua Lin[7], Feng Li[7], Huaqiang Zhu[8], Renbin Zhao[8]

1 Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China. 2 Lymphoma Dept., Beijing Shijitan Hosptials, Beijing, China. 3 Phase I Clinical Trial Center, Beijing Shijitan Hosptials, Beijing, China.4 Hematology, Beijing Hospital, Beijing, China. 5 Oncology Department, Affiliated Hospital of Hebei University, Baoding, China. 6 Hematology, The first Affiliated Hospital of Bengbu Medical College, Bengbu, China. 7 Medical Research, Beijing Mabworks Biotech Co., Ltd, Beijing, China. 8 Medical Research, Beijing InnoCare Pharma Tech Co., Ltd, Beijing, China

Background

- MIL62 is a glycoengineered anti-CD20 antibody with a nearly completely afucosylated N-glycans in Fc region and enhanced ADCC function compared with wild type Fc anti-CD20 antibody（Figure 1). Single agent activity for MIL62 has demonstrated clinical activity in patients with r/r CD20-positive B-cell NHL which were heavily treated with prior therapies..
- Orelabrutinib (ICP-022) is a novel and highly selective irreversible Bruton's tyrosine kinase (BTK) inhibitor without inhibitory activity against IL2-associated tyrosine kinase (ITK). Orelabrutinib doesn't interfere with the antibody-dependent cellular cytotoxicity (ADCC) of CD20 antibody in combined therapy and is therefore an attractive candidate for combo studies.
- This ongoing study is to evaluate the safety, tolerability and preliminary anti-tumor activity of orelabrutinib in combination with MIL62 in patients with refractory or relapsed CD20 positive B cell NHL.

Figure 1. Mechanism of action of MIL62



Study Design

- This is a phase I/IIa dose escalation and dose expansion study (NCT 04304040). The study is divided into two parts, phase I is 3+3 Dose Escalation evaluating DLTs, phase IIa is dose expansion for NHLs.

Phase I: Dose-escalation

Part A		Part B			Phase IIa: Dose-expansion
MIL62, IV 800 mg*	Orelabrutinib 100 mg, QD, PO	MIL62, IV 1000 mg*	Orelabrutinib 150 mg, QD, PO	RP2D →	Relapsed or refractory NHLs
MIL62, IV 800 mg*	Orelabrutinib 150 mg, QD, PO	Part A: 28 days per cycle (except for cycle 1=35 days) Part B: 21 days per cycle (except for cycle 1=28 days) * MIL62: D8 and D15 for 1st cycle. D1 for cycle 2-6, and every 2 cycles for cycle 7-24.			NHLs: including DLBCL, MCL, FL/MZL and CLL/SLL group, 10~20 patients for each group, DLBCL group is up to 30 patients.
MIL62, IV 1000 mg*	Orelabrutinib 100 mg, QD, PO				
MIL62, IV 1000 mg*	Orelabrutinib 150 mg, QD, PO				

- Primary Objectives: Safety and Maximum Tolerated Dose (MTD), phase 2 dose (RP2D).
- Secondary Objective: To assess Efficacy (overall response rate) and PK.
- Key Eligibility Criteria
  - Histologically confirmed CD20 positive B-cell non-Hodgkin lymphoma (NHL)
  - Relapsed after, or refractory to, at least 1 prior treatment regimen
  - ECOG performance status ≤ 2
  - Adequate organ system function: ANC ≥1500/μL; platelets ≥ 75 K/μL

Patient Population

As of June 30, 2021, 25 patients with DLBCL (18 pts) and other B cell NHLs (7 pts) have been treated with orelabrutinib and MIL62 combination therapy. Baseline characteristics and demographic data are shown in Table 1.

Table 1: Baseline characteristics

Characteristics	N=25
Median age (range), yrs	67.0 (38, 77)
Male, n (%)	10 (40.0)
ECOG PS, n (%)	
0-1	9 (36.0)
2	14 (56.0)
3	2 (8.0)
Histology subtype, n (%)	
MZL(marginal zone lymphoma)	2 (8.0)
MCL (mantle cell lymphoma)	4 (16.0)
FL (follicular lymphoma)	1 (4.0)
DLBCL (diffuse large B-cell lymphoma)	18 (72.0)
Ann Arbor Stage, n (%)	
III-IV	14 (56.0)
Prior Therapies	
median (range)	2.0 (1, 7)
Previous CD20 antibody treated, n (%)	24 (96.0)

Safety

TRAEs, n (%)	All Patients (N=25)
Any grade	13 (52.0)
≥ 3 grade	3 (12.0)
Serious TRAE	2 (8.0)
Led to drug discontinuation	3 (12.0)
Led to dose reduction	3 (12.0)
Led to death	0

- No dose-limiting toxicity (DLT) or unexpected adverse events
- 12% (3/25) of patients reported grade ≥3 TRAEs.
- 12% (3/25) of patients TRAEs resulted in treatment discontinuation or dose reduction respectively.
- The most frequently (>10%) reported TRAEs were neutropenia (16%), leukopenia (12%), thrombocytopenia (28%), infusion related reaction (16%) and rash(12%).

Note: Cutoff date: Jun.30, 2021.

Efficacy

- Twenty patients are evaluable for antitumor activity with at least one post-treatment assessment, overall response rate was 65.0% (95%CI: 40.8, 84.6) and CR rate was 35.0% across all dose groups.

Best overall response, n (%)	M 800mg/ O 100mg (N=3)	M 800mg /O150mg (N=3)	M 1000mg/ O 100mg (N=4)	M 1000mg/ O 150mg (N=7)	M 1000mg/ O 150mg(B) (N=3)	Total (N=20)
CR	2 (66.7)	1 (33.3)	0	3 (42.9)	1 (33.3)	7 (35.0)
PR	1 (33.3)	2 (66.7)	1 (25.0)	1 (14.3)	1 (33.3)	6 (30.0)
SD	0	0	2 (50.0)	1 (14.3)	1 (33.3)	4 (20.0)
PD	0	0	1 (25.0)	2 (28.6)	0	3 (15.0)
NE	0	0	0	0	0	0
ORR	3 (100.0)	3 (100.0)	1 (25.0)	4 (57.1)	2 (66.7)	13 (65.0)
DCR	3 (100.0)	3 (100.0)	3 (75.0)	5 (71.4)	3 (100.0)	17 (85.0)

Note: Cutoff date: Aug. 4, 2021; M: MIL62; O: orelabrutinib

- Tumor responses in individual patients are shown in Figure 3, ORR was 61.5% (95%CI: 31.6, 86.1) for DLBCL, including 4 CR, 4 PR of 13 assessed patients. ORR was 71.4% including 3 CR, 2 PR of 7 other B-NHLs patients. ORR was 62.5% (5/8), including 2 CR, 3 PR in rituximab-refractory (rituximab-containing chemotherapy) DLBCL.

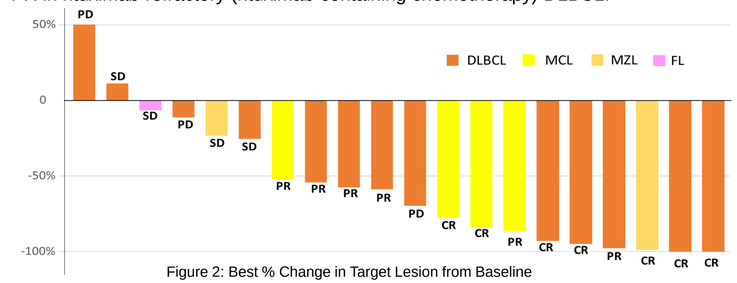
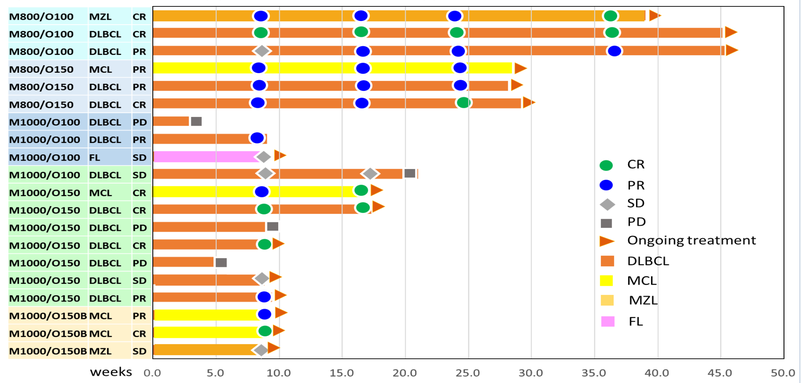


Figure 2: Best % Change in Target Lesion from Baseline

- Median duration of treatment is 2.4 months (range 0.03-10.4 months) for 20 assessed patients, 15/20 (75.0%) patients remain on therapy.



Note: Cutoff date: Aug. 4, 2021; M: MIL62; O: orelabrutinib; B: part B regimen.

Conclusions

- Orelabrutinib and MIL62 combination therapy was generally well tolerated, There is no reported DLT, unexpected toxicities or new safety signals. The safety profile of this study is consistent with previous results of orelabrutinib or MIL62.
- The combination therapy demonstrated encouraging antitumor activity, with ORR 65.0% and CR Rate 35.0% in R/R CD20-positive B-cell NHL.
- Phase IIa expansion groups of the study is ongoing.

Correspondence

Prof. Yuankai Shi, E-mail: syuankai@cicams.ac.cn

Disclosures

Feng Li, Danhua Lin and Min Wei are employees from Beijing Mabworks Biotech Co. Ltd.
Renbin Zhao and Huaqiang Zhu are employees from Beijing Innocare Pharma Tech Co., Ltd.
Other authors declared no conflicts of interest.

Acknowledgements

Study sponsored by Beijing Mabworks Biotech Co. Ltd. and Beijing Innocare Pharma Tech Co., Ltd.