Efficacy of PD-1 monoclonal antibody SHR-1210 plus apatinib in patients with advanced non-squamous NSCLC with wild-type EGFR and ALK

Caicun Zhou[1], Guanghui Gao[1], Shengxiang Ren[1], Yi Na Wang[2], Jun Zhao[3], Gongyan Chen[4], Zhihua Liu[5], Kangsheng Gu[6], Meijuan Huang[7], Jianxing He[8], Jianhua Chen[9], Zhiyong Ma[10], Jifeng Feng[11], Jianhua Shi[12], Xinmin Yu[13], Ying Cheng[14], Yu Yao[15] Ying Yang[16], Quanren Wang[17]

[1]Pulmonary Hospital of Tongji University, Shanghai, China; [2]The First Affiliated Hospital Zhejiang University, Hangzhou, China; [3]Beijing Cancer Hospital, Beijing, China; [4]Harbin Medical University Cancer Hospital, Harbin, China; [5]Jiangxi Cancer Hospital, Nanchang, China; [6]The First Affiliated Hospital of Anhui Medical University, He Fei, China; [7]West China Hospital, Sichuan Univeristy, Chengdu, China; [8]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [9]Hunan Cancer Hospital, Changsha, China; [10]Henan Cancer Hospital, Zhengzhou, China; [11]Jiangsu Cancer Hospital, Nanjing, China; [12]Shandong Linyi Tumor Hospital, Linyi, China; [13]Zhejiang Cancer Hospital, Hangzhou, China; [14]Jilin Province Cancer Hospital, Changchun, China; [15]The First Affiliated Hospital of Xi'an Jiaotong University, Xi''an, China, [16]BGI Genomics, Tianjin, China; [17]Jiangsu HengRui Medicine Co., Ltd., Shanghai, China

BACKGROUND

- Standard of care for previously treated advanced non-small-cell lung cancer (NSCLC) without treatable driver mutations includes chemotherapy and nivolumab in China, yet treatment options are still limited for a majority of patients who could not benefit from monotherapy.
- SHR-1210 is a high-affinity, fully humanized, IgG4-κ PD-1 monoclonal antibody that blocks binding of PD-1 to its ligands.
- Apatinib is a VEGFR 2 inhibitor that blocks the signal transduction of VEGF/VEGFR and then inhibits tumor angiogenesis.
- Our preclinical study suggested combination of SHR-1210 and apatinib significantly improved antitumor effects.
- We reported here the preliminary results of an open-label, multi-center, phase 1/2 study of SHR-1210 plus apatinib in patients with advanced non-squamous NSCLC with wild-type EGFR and ALK.

OBJECTIVES

- We sought to assess the tolerability and safety of SHR-1210 and Apatinib combination in the dose-escalation phase, and then the efficacy and safety in the dose-expansion phase.
- We sought to explore potential biomarker correlated to clinical response as well.

METHODS

Study Design

- This study utilizes an open-label, dose escalation and expansion two-phase design.
- In the dose-escalation phase, the starting dose of Apatinib was 250 mg, and would escalate up to maximal 500mg plus SHR-1210 200mg, with 10-12 patients per cohort .

  Dose-limited toxicities (DLTs) were assessed in the first cycle of treatment (4 weeks).
- In the dose-expansion phase and pharmacokinetic(PK) study, patients received Apatinib at recommended dose plus SHR-1210 200 mg.

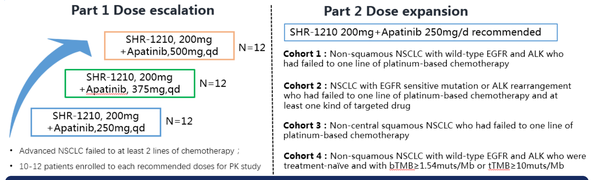
Procedures

- Apatinib was given orally once daily and SHR-1210 200 mg 30-minute intravenous infusion every 2 weeks. The treatment was continued until disease progression or intolerable toxicity.
- Radiographic tumor imaging was done at baseline and for every 8 weeks for the first 48 weeks, then every 12 weeks thereafter. Tumor response was assessed according to RECIST version 1.1.
- Adverse events were graded according to Common Terminology Criteria for Adverse Events CTCAE v4.03.
- During follow-up, patients were contacted every 2 months to assess survival.

Sample sizes

- In the dose-escalation phase, about 40-60 patients would be enrolled. Once the recommended dose of Apatinib was determined, 174 patients with advanced NSCLC would be enrolled in the expansion phase and assigned to four different cohorts due to tumor histology or EGFR/ALK status. In addition, 10-12 patients would be enrolled for PK study.

Study Design



BIOMARKER ASSESSMENTS

- Archived or fresh tumor tissues and matched peripheral blood samples were obtained prior to treatment for targeted capture sequencing on MGISEQ-2000 platform by OseqTM panel including 636 genes and 1.95Mb, which is developed by BGI Genomics Co., Ltd.
- Archived or fresh tumor tissues were obtained prior to treatment for IHC PD-L1 expression.
- Peripheral blood samples were collected prior to treatment for circulating tumor cells (CTCs) analysis.

KEY INCLUSION/EXCLUSION CRITERIA

Inclusion criteria

- Subjects aged ≥ 18 years and ≤ 70 years.
- Advanced recurrent or metastatic NSCLC with at least one measurable lesion per RECIST 1.1.
- Failure to at least two chemotherapy regimens (Part 1 and PK study); Failure to first-line chemotherapy (Part 2).
- ECOG performance status 0-1.

Exclusion criteria

- Subjects with active, known or suspected autoimmune disease.
- Subjects with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of first administration of study treatment.
- Subjects with untreated CNS metastases.
- Subjects with grade II or above myocardial ischemia or myocardial infarction, and uncontrolled arrhythmias .
- Subjects with coagulation disfunction, hemorrhagic tendency or receiving anticoagulant therapy.
- Subjects with previous and current objective evidence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonia, drug-related pneumonia, and severe impairment of lung function.

RESULTS

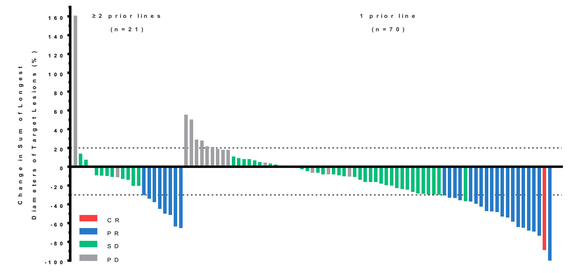
- As of Apr 30, 2019, a total of 23 patients in the dose-escalation phase and PK study who received SHR-1210 200mg + apatinib 250mg, and 73 patients in cohort 1 were enrolled. All 96 patients had non-squamous NSCLC with wild-type EGFR and ALK. Only the results of the 96 patients were reported here.
- Median follow-up time was 22.1 months for 23 patients in the dose-escalation phase and PK study, and 9.2 months for those in cohort 1.
- At the time of data cutoff, 4/23(17.4%) patients in the dose-escalation phase and PK study and 25/73(34.2%) patients in cohort 1 were still on treatment.
- Among 96 patients, 83 patients had blood samples for blood TMB(bTMB) testing, a cut-point of 1.54 muts/Mb as determined by receiver operating characteristic curve.
- Among 91 evaluable patients, overall response rate (ORR) was 30.8%(28/91), median progression-free survival 5.9 months, and overall survival not reached. In patients with high bTMB (bTMB-H, bTMB≥1.54 muts/Mb), ORR was 52.6%(20/38).

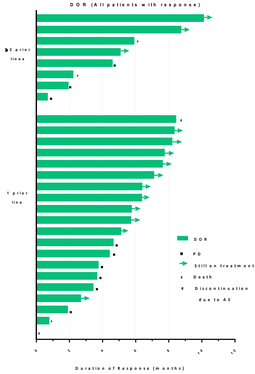
Baseline characteristics	NSCLC (n=96)
Age	
Median (range) , years	57 (35-70)
Gender, n(%)	
Male	76 (79.2%)
Female	20 (20.8%)
ECOG, n(%)	
0	14 (14.6%)
1	82 (85.4%)
Disease stage, n(%)	
IIIB	5 (5.2%)
IV	91 (94.8%)
Tumor histology, n(%)	
Non-squamous	90 (93.8%)
Other	6 (6.2%)
Smoking status, n(%)	
Current or former smoker	54 (56.3%)
Never smoked	31 (32.3%)
Unknown	11 (11.4%)
No. of prior systemic regimens, n(%)	
1	73 (76.0%)
2	23 (24.0%)
No. of organs of metastasis	
> 2	22 (22.9%)
≤ 2	74 (77.1%)

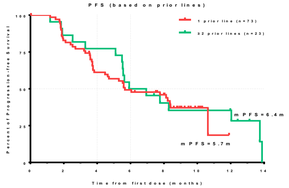
EFFICACY

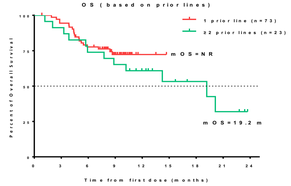
	≥2 prior lines (n=23)	1 prior line (n=73)	Overall (n=96)	Subgroup bTMB-H (n=40)	Subgroup bTMB-L (n=43)
Complete response	0	1 (1.4%)	1 (1.1%)	1 (2.5%)	0
Partial response	8 (34.8%)	19 (26.0%)	27 (28.1%)	19 (47.5%)	7 (16.3%)
Stable disease	11 (47.8%)	36 (49.3%)	47 (49.0%)	11(12.5%)	25 (58.1%)
Progressive disease	2 (8.7%)	14 (19.2%)	16 (16.7%)	7(17.5%)	9 (20.9%)
Not evaluable	2 (8.7%)	3 (4.1%)	5 (5.2%)	2 (5.0%)	2 (2.7%)
Evaluable patients	21	70	91	38	41
ORR in evaluable patients, 95% CI	38.1% (20.8%-59.1%)	28.6% (18.4%-40.6%)	30.8% (22.2%-40.9%)	52.6% (35.8%-69%)	17.1% (7.2%-32.1%)
DCR in evaluable patients, 95% CI	90.5% (71.1%-98.3%)	80.0% (68.7%-88.6%)	82.4% (73.3%-88.9%)	81.6% (65.7%-92.3%)	78% (62.4%-89.4%)
Time to response (m) Median(range)	3.7 (1.8-5.5)	1.8 (1.8-5.5)	1.8 (1.8-5.5)	1.8 (1.8-5.5)	1.8 (1.8-5.5)
Duration of response (m) Median	5.3	NR	NR	NR	NR
Ongoing, n/N (%)	3/8(37.5%)	12/20(60%)	15/28(53.6%)	12/20(60%)	4/7(57.1%)
PFS(m) Median (95% CI)	6.4 (5.1-12)	5.7 (4.7-10.3)	5.9 (5.5-10.3)	7.8 (5.3-12.0)	5.6 (3.7-8.2)
OS(m) Median (95% CI)	19.2 19.2-NR	NR	NR	NR	NR

Best Change of Target Lesions from Baseline (All evaluable patients)

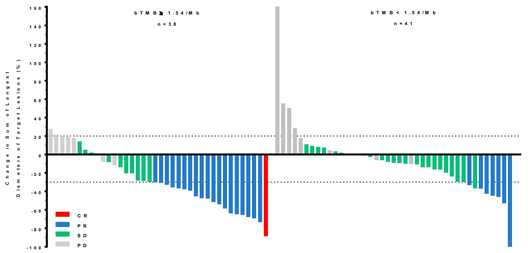








Best Change of Target Lesions from Baseline (All evaluable patients with bTMB value)



SAFETY

Adverse Events (any grade) occurring in ≥10% of Patients, n(%)

Any event	Any Grade	Grade 3-5
Investigations		
Aspartate aminotransferase increased	47(49.0%)	1(1%)
Alanine aminotransferase increased	37(38.5%)	3(3.1%)
Neutrophil count decreased	25(26.0%)	2(2.1%)
Blood bilirubin increased	24(25.0%)	1(1%)
White blood cell count decreased	22(22.9%)	1(1%)
Platelet count decreased	20(20.8%)	1(1%)
Bilirubin conjugated increased	19(19.8%)	1(1%)
Blood thyroid stimulating hormone increased	19(19.8%)	0
Blood creatinine increased	18(18.8%)	0
Gamma-glutamyltransferase increased	16(16.7%)	9(9.4%)
Weight decreased	13(13.5%)	1(1%)
Blood alkaline phosphatase increased	13(13.5%)	3(3.1%)
Renal and urinary disorders		
Proteinuria	59(61.5%)	6(6.3%)
Haematuria	10(10.4%)	0
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	43(44.8%)	11(11.5%)
Rash	35(36.5%)	1(1%)
Reactive capillary endothelial proliferation	15(15.6%)	0
Vascular disorders		
Hypertension	56(58.3%)	16(16.7%)
General disorders and administration site conditions		
Asthenia	33(34.4%)	0
Pyrexia	16(16.7%)	1(1%)
Gastrointestinal disorders		
Diarrhoea	21(21.9%)	0
Mouth ulceration	20(20.8%)	1(1%)
Metabolism and nutrition disorders		
Decreased appetite	31(32.3%)	0
Respiratory, thoracic and mediastinal disorders		
Dysphonia	16(16.7%)	0
Cough	10(10.4%)	0
Blood and lymphatic system disorders		
Anaemia	23(24.0%)	0
Hepatobiliary disorders		
Hepatic function abnormal	15(15.6%)	6(6.3%)
Endocrine disorders		
Hypothyroidism	12(12.5%)	1(1%)

CONCLUSIONS

- SHR-1210 200mg once every 2 weeks in combination with Apatinib 250mg once daily demonstrated promising anti-tumor activity with acceptable safety in patients with non-squamous NSCLC.
- Particularly encouraging clinical activity (ORR, 52.6%) was observed in those with high bTMB.
- A prospective study would be conducted to validate the results and predictive value of bTMB.

2019 ASCO Annual Meeting **Abstract No. 9112**

Contact: Caicun Zhou (caicunzhoudr@163.com)