SHR-1701, a novel bifunctional anti-PD-L1/TGF-βRII agent, for pretreated recurrent/refractory (r/r) gastric cancer (GC): data from a first-in-human phase 1 study

2021 ESMO congress

#1375P

Dan Liu[1], Suxia Luo[2], MingJun Li[3], Tianshu Liu[4], Minghua Ge[5], Ying Wang[6], Haiping Jiang[7], Yunpeng Liu[8], Xiaojun Xiang[9], Xiaojing Zhang[10], Linna Wang[10], Pan Liu[10], Lin Shen[11]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Early Drug Development Center, Peking University Cancer Hospital & Institute, Beijing, China; [2]Medical oncology, Henan Cancer Hospital , Zhengzhou, China; [3]Department of Oncology, The First Affiliated Hospital of Zhengzhou Unversity, Zhengzhou, China; [4]Medical oncology, Zhongshan Hospital Fudan University, Shanghai, China; [5]Head and Neck Surgery, Zhejiang Provincial People's hospital, Hangzhou, China; [6]Phase I Clinical Trial Ward, Zhejiang Provincial People's hospital, Hangzhou, China; [7]Medical oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; [8]Medical oncology, The First Hospital of China Medical University, Shengyang, China; [9]Medical oncology, The First Affiliated Hospital of Nanchang University, Nanchang, China; [10]Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd, Shanghai, China; [11]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Oncology/Early Drug Development Center, Peking University Cancer Hospital & Institute, Beijing, China.

BACKGROUND

- Advanced gastric cancer (GC) pts have limited treatment options and poor prognosis.
- Immune checkpoint inhibitors (ICIs) showed promising activities in pretreated pts, especially for those with a high PD-L1 expression[1-2].
- Blockade of TGF-β pathway may enhance the tumor response to ICIs[3-5].
- SHR-1701 is a novel bifunctional anti-PD-L1/TGF-βRII agent.

METHODS

Study design

- This was a multicenter, open-label, first-in-human phase 1 trial of SHR-1701 composed of a dose-escalation phase and a dose-expansion phase in advanced solid tumors, followed by multiple clinical expansion cohorts (NCT03710265; Figure 1A).
- Based on findings of the dose-escalation and dose-expansion phases, 30 mg/kg q3w was determined as RP2D[6].
- Here, we report the results from the GC clinical expansion cohort (Figure 1B).

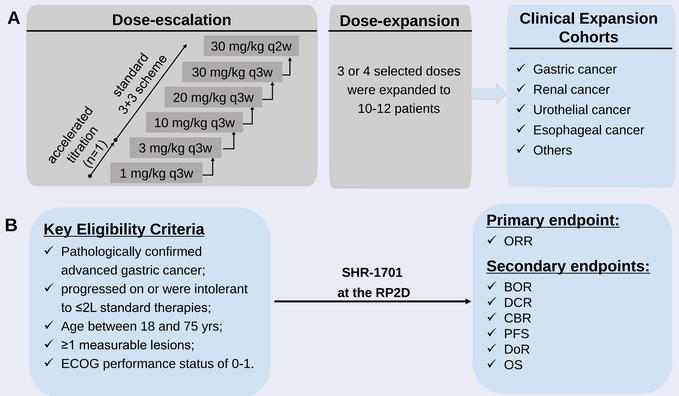

Figure 1. Study design

A. Whole study; B. Gastric cancer clinical expansion cohort.

Tumor response was assessed by investigators according to RECIST v1.1.
Continuation of study treatment beyond the initial RECIST v1.1-defined progression was permitted, if the patient had no investigator-assessed clinical deterioration and tolerated study treatment as agreed by the investigator.

RESULTS

Patients

- Between Dec 26, 2019 and Mar 9, 2021, 35 GC pts were recruited from 8 hospitals in China. 91.4% of pts had stage IV disease, and 54.3% of pts were heavily pretreated with 2 lines of prior systemic therapies (Table 1).
- By Apr 6, 2021, the median SHR-1701 exposure was 12.0 wk (range 3.0-64.9). Fourteen (40.0%) pts remained on study treatment, and 21 (60.0%) pts discontinued treatment mainly due to radiographical progression.

Table 1. Patient characteristics

		GC pts (N=35)
Age, median (range), yrs		61 (31-74)
Male, n (%)		28 (80.0%)
ECOG performance status, n (%)	0 / 1	4 (11.4%) / 31 (88.6%)
Metastases disease*		34 (97.1%)
No. of organs of metastases*, n (%)	<2 / ≥2	14 (40.0%) / 20 (57.1%)
Lines of prior therapies, n (%)	1 / 2	16 (45.7%) / 19 (54.3%)

*Including regional lymph node involvement.

Efficacy outcomes

- Of the 31 pts with post-baseline scan(s), 16 (51.6%) showed tumor shrinkage (Figure 2 and 3).
- One CR and 7 PR were achieved (Figure 4), and the ORR was 25.8% (95% CI 11.9-44.6).
- Two PR were not confirmed yet as there was no consequent scan after first PR as of data cutoff. Thus, the confirmed ORR was 19.4% (95% CI 7.5-37.5; 1 CR + 5 PR).
- Responses were ongoing in 66.7% (4/6) of the responders (Figure 4). The median DoR was not reached yet.
- DCR was 41.9% (95% CI 24.5-60.9).
- CBR (CR + PR + SD≥23 wk) was 25.8% (95% CI 11.9-44.6).
- Median PFS was 1.4 mo (95% CI 1.3-9.6), and 6-mo PFS rate was 38.7% (95% CI 22.0-55.1) (Figure 5).
- Median OS was not reached yet.

RESULTS

Figure 2. Best change from baseline in target lesions.

* represent patients with confirmed CR/PR

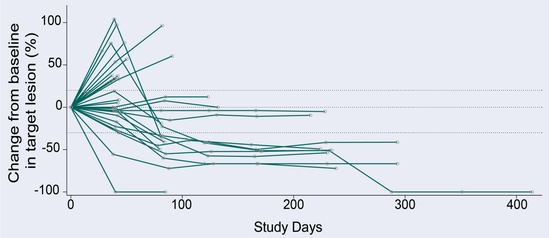

Figure 3. Percentage change from baseline in target lesion tumor burden over time

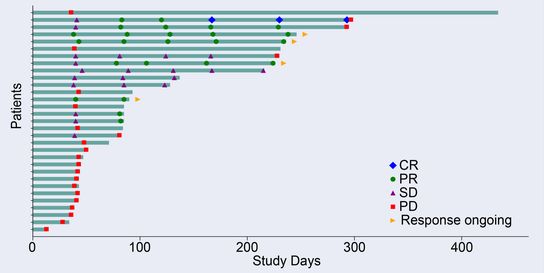

Figure 4. Tumor responses per RECIST v1.1 over time.

RESULTS

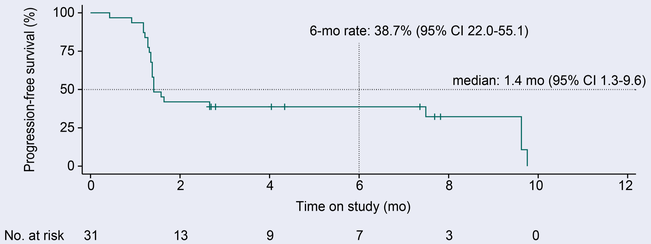

Figure 5. Progression-free survival

- Exploratory analyses showed a trend towards favorable responses for pts with a PD-L1 CPS ≥5 (Table 2).

Table 2. Efficacy outcomes* in subgroups by PD-L1 expression.

	PD-L1 CPS	
	<5 (N=10)	≥5 (N=9)
ORR, n (%; 95% CI)	1 (10.0%; 0.3-44.5)	4 (44.4%; 13.7-78.8)
DCR, n (%; 95% CI)	3 (30.0%; 6.7-65.2)	4 (44.4%; 13.7-78.8)
CBR, n (%; 95% CI)	2 (20.0%; 2.5-55.6)	4 (44.4%; 13.7-78.8)
Median PFS (95% CI), mo	1.4 (1.2-7.5)	1.4 (0.4-9.8)
6-mo PFS rate, % (95% CI)	30.0% (7.1-57.8)	44.4% (13.6-71.9)

* CR and PR were confirmed.

Safety outcomes

- TRAEs occurred in 21 (60.0%) pts (Table 3). Grade 3 or 4 TRAEs occurred in 17.1% of pts, and no pts died due to TRAEs.
- irAEs occurred in 16 (45.7%) pts. Four (11.4%) pts experienced grade ≥3 irAEs.

Table 3. TRAEs with an incidence of ≥5%

	Any grade, n (%)		Any grade, n (%)
Rash	6 (17.1%)	Protein urine present	2 (5.7%)
AST increased	5 (14.3%)	Blood corticotrophin increased	2 (5.7%)
TF3 decreased	5 (14.3%)	Cortisol decreased	2 (5.7%)
ALT increased	4 (11.4%)	Blood TSH increased	2 (5.7%)
Pruritus	4 (11.4%)	Pyrexia	2 (5.7%)
Anemia	3 (8.6%)	Hypothyroidism	2 (5.7%)

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; FT3, Tri-iodothyronine free; TSH thyroid stimulating hormone.

CONCLUSIONS

SHR-1701 showed encouraging antitumor activity and manageable safety profile in pretreated r/r GC pts. PD-L1 might be a prognostic factor for SHR-1701, which needs further investigation.

Reference: [1]Janjigian YY, et al. Lancet. 2021;398:27-40. [2]Chung HC, et al. Future Oncol. 2021 Feb;17(5):491-501. [3]Mariathasan S, et al. Nature. 2018;554:544-8.
[4]Okazaki T, et al. Nat Immunol. 2013;14:1212-8. [5]Huang CY, et al. Biomed Pharmacother. 2021;134:111046. [6]Liu D, et al. J Clin Oncol. 2021;39: 2503. Oral presentation.

Funding: Jiangsu Hengrui Pharmaceuticals Co. Ltd, China

Declaration of interests: The presenter declares no competing interests.

Contact:
Dr. Dan Liu (13521396535@163.com) or Dr. Lin Shen (linshenpku@163.com)