Clinical Cancer Research

Anti-PD-1 Antibody SHR-1210 Combined with Apatinib for Advanced Hepatocellular Carcinoma, Gastric, or Esophagogastric Junction Cancer: An Open-label, Dose Escalation and Expansion Study

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Abstract

Purpose: This study assessed the safety and efficacy of SHR-1210 (anti-PD-1 antibody) and apatinib (VEGFR2 inhibitor) as combination therapy in patients with advanced hepatocellular carcinoma (HCC), gastric, or esophagogastric junction cancer (GC/EGJC).

Patients and Methods: This was an open-label, dose-escalation (phase Ia) and expansion study (phase Ib). In phase Ia, patients ($n = 15$) received SHR-1210 200 mg every 2 weeks and apatinib 125–500 mg once daily until unacceptable toxicity or disease progression. In phase Ib, patients ($n = 28$) received apatinib at the phase Ia–identified recommended phase II dose (RP2D) plus SHR-1210. The primary objectives were safety and tolerability and RP2D determination.

Results: At data cutoff, 43 patients were enrolled. In phase Ia, four dose-limiting toxicity events were observed (26.7%): one grade 3 lipase elevation (6.7%) in the apatinib 250 mg cohort and three grade 3 pneumonitis events (20%) in the apatinib 500 mg cohort. The maximum tolerated RP2D for apatinib was 250 mg. Of the 33 patients treated with the R2PD combination, 20 (60.6%) experienced a grade $\geq$3 treatment-related adverse event; adverse events in $\geq$10% of patients were hypertension (15.2%) and increased aspartate aminotransferase (15.2%). The objective response rate in 39 evaluable patients was 30.8% (95% CI: 17.0%–47.6%). Eight of 16 evaluable HCC patients achieved a partial response (50.0%, 95% CI: 24.7%–75.4%).

Conclusions: SHR-1210 and apatinib combination therapy demonstrated manageable toxicity in patients with HCC and GC/EGJC at recommended single-agent doses of both drugs. The RP2D for apatinib as combination therapy was 250 mg, which showed encouraging clinical activity in patients with advanced HCC.

Introduction

Hepatocellular carcinoma (HCC) and gastric or esophagogastric junction cancer (GC/EGJC) are among the second and third leading causes of cancer mortality worldwide, respectively (1). Despite multimodal therapy, systemic treatment options for patients with advanced HCC and GC/EGJC who progress after second-line therapy are limited. Clinical trials of sorafenib or lenvatinib as first-line therapy in patients with advanced HCC achieved an objective response rate (ORR) of 2%–19% and median time to progression of 3.7–8.9 months, respectively (2, 3). A study of regorafenib as second-line therapy in advanced HCC patients that regressed following treatment with sorafenib, reported an objective response of 11%, and progression-free survival (PFS) of 3.1 months (4). In patients with advanced GC/EGJC, ORRs following second-line therapy range from 17% to 28% and PFS from 4.4 to 5.5 months (5, 6). Therefore, there is an unmet need for effective systemic therapies for advanced HCC and GC/EGJC, particularly after failure of first-line therapy.

Anti-programmed death-1 (PD-1) antibodies and antibodies to its ligand, PD-L1, have shown antitumor efficacy in multiple cancers (7–9), including HCC and GC (10, 11). Of these, nivolumab and pembrolizumab have been approved as second-line

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Translational Relevance

PD-1/PD-L1 blockade immunotherapies are promising therapies for multiple cancers. However, a large proportion of patients with advanced hepatocellular carcinoma (HCC) or gastric cancer (GC) do not achieve durable responses with anti-PD-1/PD-L1 monotherapy. Combination therapies of anti-PD-1/PD-L1 treatments with antiangiogenic agents have demonstrated activation of immune checkpoints that result in more potent antitumor activity than anti-PD-1 monotherapy. Apatinib (VEGFR2 inhibitor) in combination with an anti-PD-L1 has demonstrated synergistic antitumor effects *in vivo*. Our study identified a recommended phase II dose of apatinib of 250 mg, with a median treatment duration of 5.1 months. Patients treated with this dose of apatinib and 200 mg of SHR-1210 demonstrated clinical benefit in patients with HCC and a well-tolerated adverse event profile in patients with HCC or GC/esophagogastric junction cancer (EGJC). A phase II trial is currently underway to confirm our early-stage results of apatinib and SHR-1210 combination therapy in patients with advanced HCC (NCT03463876).

treatment of advanced HCC and third-line therapy of advanced GC with PD-L1 expression, respectively (12, 13). Despite these advances, approximately 11%–20% (10–13) of unselected patients elicited tumor responses to these treatments (12, 13), emphasizing the need to explore strategies to increase the efficacy of immunotherapy.

In recent years, the efficacy of anti-PD-1 in combination with molecular antiangiogenic agents has attracted much interest (14). Although this approach has strong scientific rationale for additive or synergistic effects (15, 16), studies combining PD-1 blockade and multitargeted tyrosine kinase inhibitors (TKI) have shown unacceptable levels of toxicity (17, 18). Recently, promising antitumor activity and an acceptable safety profile was reported in a study of axitinib, a selective VEGFR1–3 inhibitor, in combination with pembrolizumab in patients with advanced renal cell carcinoma (19). Another study on anti-PD-L1 antibody and VEGF–antibody combination, atezolizumab and bevacizumab, also showed encouraging response rate with tolerated toxicities in patients with advanced HCC (20).

Apatinib, a selective VEGFR2 TKI, is approved for the treatment of advanced gastric cancer in China (21), and has demonstrated activity across a wide range of solid tumors, including HCC (22). In addition, in combination with anti-PD-L1, apatinib has shown synergistic antitumor effects *in vivo* (23). We therefore postulate that this combinatorial approach might improve the clinical efficacy of anti-PD-1 immunotherapy, while reducing the toxicity induced by off-target effects of multitargeted TKIs. Herein, we conducted a single-arm, phase I dose escalation and expansion study to assess the safety and efficacy of anti-PD-1 antibody SHR-1210 combined with apatinib as second-line, or later, therapy in patients with advanced HCC or GC/EGJC.

Patients and Methods

Eligibility criteria

Patients were aged $\geq$18 years with histologically confirmed HCC or GC/EGJC, and were refractory to at least the standard first-line of therapy. Patients with HCC had Child–Pugh Class A or B liver function status (score $\leq$7). Additional eligibility requirements included: $\geq$1 measurable disease at baseline per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1); Eastern Cooperative Oncology Group performance status of 0 or 1; or life expectancy of $\geq$3 months and adequate organ function. The main exclusion criteria were interstitial lung disease, pulmonary fibrosis, active or prior autoimmune disease or active hepatitis, or history of apatinib or any other PD-L1/PD-1 antagonist treatment. Patients with abdominal fistula, diverticulitis, gastrointestinal ulcerative disease or perforation, or abdominal abscess within the prior 4 weeks were also excluded. Further details are available in the Supplementary Data.

Study oversight

This study was approved by the Affiliated Hospital Institutional Review Board (IRB) and all patients provided written informed consent in accordance with Declaration of Helsinki principles. Patients were enrolled at Affiliated Hospital Cancer Center, Academy of Military Medical Sciences (Beijing, China).

Study design and treatment

This was a single-center, open-label, dose escalation (phase Ia) and expansion (phase 1b) study. The primary objective was to determine the efficacy and safety of once-daily, oral apatinib in combination with SHR-1210, administered intravenously every 2 weeks. Eligible patients were enrolled from October 25, 2016 to February 27, 2018. Phase Ia was designed to identify the MTD and recommended phase II dose (RP2D) of apatinib in combination with SHR-1210. Patients ($n = 5$ per cohort) received apatinib at doses of 125, 250, or 500 mg, in combination with SHR-1210 200 mg (24). Apatinib dose was escalated if $\leq$1 patient per cohort experienced dose-limiting toxicity (DLT) within the first 28 days treatment. If $\geq$2 patients experienced DLTs, the prior dose was considered the MTD. Once the MTD was established, additional patients were enrolled at that level in an RP2D expansion cohort (phase Ib, $n = 28$). Intrapatient dose escalation of apatinib was permitted during the expansion phase. All patients continued combination treatment until disease progression, unacceptable toxicity, death, or discontinuation for any reason.

DLT was defined as any grade $\geq$4 hematologic toxicity or any grade $\geq$3 nonhematologic toxicity occurring within the first 28 days of treatment, or any SHR-1210- or apatinib-related toxicity resulting in a treatment delay of >21 days. Patients who received $\geq$1 dose of SHR-1210 or apatinib were considered safety evaluable. Objective response was evaluated every 6 weeks until week 24 and every 12 weeks thereafter, using RECIST v1.1. Patients with progressive disease (PD) while still receiving clinical benefit (as determined by the investigator), could continue study treatment and were reevaluated after 4 weeks.

Study endpoints and assessments

The primary endpoints were safety and tolerability and RP2D determination of apatinib in combination with SHR-1210. Efficacy endpoints included investigator-assessed ORR, disease control rate (DCR), PFS, and overall survival (OS). Endpoint definitions are available in the Supplementary Data

Tumor tissue biopsies and peripheral blood samples were obtained from patients with informed consent for biomarker analyses. Tumor mutation burden (TMB) was assessed by sequencing. Hybridization capture of exonic regions from

1,021 cancer-related genes was applied. TMB analysis interrogated single-nucleotide variants, small insertions, and deletions (Supplementary Data).

Peripheral blood samples were collected prior to treatment (T0) for the analysis of PD-L1 levels on circulating tumor cells (CTC). CTC isolation and enumeration were performed using Pep@MNPs method (Nanopep Biotech) according to manufacturer's instructions. CTCs were characterized as $CK19^+$, $DAPI^+$, and $CD45^-$; PD-L1 expression was categorized as negative, low, medium, and high, based on mean fluorescence intensity (25).

Safety

Safety was monitored throughout the study for all patients. Adverse events (AE) and serious adverse events (SAE) occurring $\leq$30 days of the last dose were reported according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v4.03. A treatment-related AE (TRAE) was defined as an AE that first occurred or worsened in intensity after study drug administration and considered related to apatinib, SHR-1210, or both.

Apatinib or SHR-1210 treatment was suspended following any grade $\geq$3 TRAE until toxicity resolved to grade $\leq$1. Apatinib was discontinued if a >4-week treatment delay was required. SHR-1210 dose modification was prohibited.

Statistical analysis

The study was planned with five patients per cohort for safety evaluation. Sample size for the primary efficacy endpoint was estimated using a Simon Minmax two-stage design. The expansion phase Ib study aimed to rule out an unacceptably low ORR of 15% ($p0 = 0.15$) in favor of an improved ORR of 30% ($p1 = 0.30$). With a two-sided $\alpha = 0.10$ and 80% power, the trial was designed to enroll 18 evaluable patients in the first stage and, if at least three responses were noted, to enroll an additional 19 patients. If nine (24.3%) or more responses were noted, further study could be considered.

The distributions of OS and PFS were compared via a two-sided, log-rank test. PFS and OS curves were estimated using the Kaplan–Meier (KM) product-limit method. Two-sided, 95% confidence intervals (CI) for median OS and PFS were computed by the Brookmeyer and Crowley method.

ORR and DCR were calculated using the Clopper–Pearson method and compared in $PD\text{-}L1^+$ CDCs using a two-sided exact test. TMBs were compared by the Mann–Whitney test. Analyses were descriptive and $P < 0.05$ was considered significant. All data were analyzed using SAS version 9.4.

Results

Patient population and baseline characteristics

At data cutoff (June 15, 2018), 43 patients (18 HCC, 25 GC/EGJC) were enrolled. The median age was 53 years and 74.4% were male. Forty-one patients (95.3%) had stage IV disease at study entry and 25 patients (58.1%) had disease involvement at multiple sites; 39 patients (90.7%) had received prior systemic treatment. The median follow-up duration was 7.9 months (interquartile range, 5.1–12.2 months). Baseline characteristics for patients are presented in Table 1.

Of the 18 HCC patients, 13 had clinical cirrhosis with a median Child–Pugh score of six. All had inactive hepatitis B (HBV) infection (positive for HBsAg and HBV DNA <2,000 IU/mL) and were receiving antiviral medication at study enrollment; 17 patients (94%) were Barcelona Clinic Liver Cancer stage C, 89% had extrahepatic spread, and 33% had macrovascular invasion. Prior treatment included surgical resection (67%), transarterial chemoembolization (83%), and/or radiofrequency ablation (50%). A total of 15 patients (83%) had failed or were intolerant to sorafenib treatment. Of the 25 patients with GC/EGJC, 24 had metastatic disease and all had received prior chemotherapy for advanced disease.

Dose escalation, expansion, and safety

Fifteen patients were enrolled into the dose escalation phase (phase Ia), and 28 patients into the dose expansion phase (phase Ib; Fig. 1); all 43 patients were evaluated for safety. In phase Ia, no protocol-defined DLTs were reported in the apatinib 125 mg cohort. Within 28 days of treatment, one patient in the apatinib 250 mg cohort had a grade 3 DLT (lipase elevation with no clinical symptoms of pancreatitis) and three patients in the 500 mg cohort developed grade 3 immune-related pneumonitis.

The identified RP2D for apatinib was 250 mg (Fig. 1), which was well tolerated with a median treatment duration of 5.1 months (range, 1.3–15.7 months). In 33 patients receiving 250 mg apatinib, including those in phase Ia, the median number of SHR-1210 treatment cycles was 10.0 (interquartile range: 5.0–15.0) at a mean dose of 172.9 ± 26.5 mg. Twenty-six (78.8%) of 33 patients discontinued treatment, 22 patients (66.7%) due to progressive disease (PD), one patient (3.0%) withdrew consent and three patients (9.1%) due to AEs (two TRAEs and one unrelated AE). TRAEs were manageable (Table 2) and there were no treatment-related deaths. Grade $\geq$3 TRAEs that occurred in $\geq$10% were hypertension (15.2%) and elevated aspartate aminotransferase (AST; 15.2%). Among patients with HCC, no reactivation of HBV was observed.

Efficacy

Thirty-nine of 43 patients were evaluable by RECIST v1.1 criteria. Thirteen patients achieved PR (8 with HCC, 5 with GC/EGJC), 20 patients had stable disease (SD; 7 with HCC, 13 with GC/EGJC), and 6 patients had PD as best response. The ORR was 30.8% (95% CI: 17.0%–47.6%) and the DCR was 84.6% (95% CI: 69.5%–94.1%; Table 3). Notably, two patients with HCC in the apatinib 125 mg cohort had initial SD as best response and achieved PR after escalating to 250 mg (Supplementary Table S1). Therefore, 11 of 12 responses occurred at the apatinib 250 mg dose (Fig. 2A). Changes in tumor burden from baseline are shown in Fig. 2B and C; at data cutoff, 8 responders remained on treatment with ongoing responses.

Eight of 16 evaluable HCC patients achieved PR, including one in the apatinib 125 mg cohort and 7 receiving apatinib 250 mg. The ORR and DCR were 50.0% (95% CI: 24.7%–75.4%) and 93.8% (95% CI: 69.8%–99.8%), respectively (Table 3). Median time to response was 3.4 months (range, 1.4–9.7 months). The ORR for treatment with apatinib 250 mg was 53.8% (7/13 patients). Six of 7 patients with PR remained on treatment with ongoing responses; five responses lasted >49 weeks (Supplementary Fig. S1). During the median follow-up duration of 7.8 months (interquartile range, 4.2–14.9 months) the median PFS of patients with HCC was 5.8 months [95% CI: 2.6 to not reached (NR) months]. The 6-month PFS rate in patients receiving apatinib 250 mg was 51.3% (95% CI: 21.4%–74.9%) and the

Table 1. Patient baseline demographics and disease characteristics

Characteristics	*n* (%) or median (range) (*N* = 43)
Hepatocellular carcinoma, *n* (%)	18 (41.9%)
Age, years, median (range)	49 (29–64)
Gender, *n* (%)	
Male	17 (94.4%)
Female	1 (5.6%)
ECOG, *n* (%)	
0	10 (55.6%)
1	8 (44.4%)
Liver cirrhosis, *n* (%)	
Yes	13 (72.2%)
No	5 (27.8%)
Etiology of HCC, *n* (%)	
Hepatitis B	18 (100.0%)
Hepatitis C	0
Macrovascular invasion, *n* (%)	
Yes	6 (33.3%)
No	12 (66.7%)
Extrahepatic disease, *n* (%)	
Yes	16 (88.9%)
No	2 (11.1%)
Macrovascular invasion and/or extrahepatic disease, *n* (%)	
Yes	17 (94.4%)
No	1 (5.6%)
Baseline Child-Pugh score, *n* (%)	
5	8 (44.4%)
6	5 (27.8%)
7	5 (27.8%)
BCLC stage, *n* (%)	
A	0
B	1 (5.6%)
C	17 (94.4%)
Prior therapies (HCC), *n* (%)	
≥2 Locoregional procedures[a]	12 (66.7%)
Surgery	12 (66.7%)
Ablation	9 (50.0%)
TACE/TAE	15 (83.3%)
Sorafenib[b]	15 (83.3%)
GC and EGJC, *n* (%)	25 (58.1%)
Age, years, median (range)	54 (34–68)
Gender, *n* (%)	
Male	15 (60.0%)
Female	10 (40.0%)
ECOG, *n* (%)	
0	6 (24.0%)
1	19 (76.0%)
Histology subtype (Lauren classification), *n* (%)	
Intestinal	4 (16.0%)
Diffuse	6 (24.0%)
Mixed	4 (16.0%)
Unknown	11 (44.0%)
Extent of disease, *n* (%)	
Metastatic	24 (96.0%)
Locally advanced	1 (4.0%)
Number of metastatic sites, *n* (%)	
1–2	14 (56.0%)
≥3	11 (44.0%)
Prior therapies (GC/EGJC), *n* (%)	
Surgery	16 (64.0%)
First-line therapy[c]	9 (36.0%)
>First-line therapy[d]	16 (64.0%)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; TACE, transcatheter arterial chemoembolization; TAE, transcatheter embolization.

[a]Includes ablation, transcatheter arterial chemoembolization, and transcatheter embolization.

[b]Reasons for previous treatment failure with sorafenib therapy included disease progression [14 (93.3%)] and sorafenib intolerance [1 (6.7%)].

9-month PFS rate was 41.0% (95% CI, 13.8%–66.9%). The median OS was not reached (Fig. 3).

In 23 evaluable GC/EGJC patients, the ORR was 17.4% (95% CI: 5.0%–38.9%) and DCR was 78.3% (95% CI: 56.3%–92.5%; Table 3). During the median follow-up duration of 7.6 months (interquartile range, 5.1–11.3 months), the median PFS was 2.9 months (95% CI: 2.5–4.2 months) and the median OS was 11.4 months (95% CI: 8.6–NR months; Fig. 3).

Overall, 12 responders of a total of 39 evaluable patients (30.8%; 95% CI: 17.0%–47.6%) met the predetermined estimate for the primary efficacy endpoint.

Biomarker assessments

Eighteen patients had sufficient tumor samples for TMB analysis. Patients with PR/SD at the first response evaluation showed statistically significantly higher TMB than those with PD (mean, 8.53 vs. 1.44 mutations/MB; $P = 0.0002$; Supplementary Fig. S2A). The median PFS in patients with high TMB was 3.0 months (95% CI: 1.03–4.97 months), numerically longer than 2.1 months (95% CI: 1.86–2.27 months) for low TMB patients ($P = 0.063$; Supplementary Fig. S2B).

Next, we evaluated whether PD-L1 levels on CTCs could predict treatment efficacy. CTCs and PD-L1$^+$ CTCs were detected in 39 (95.1%) of 41 patients at T0; 29 (82.9%) of 35 evaluable patients had PD-L1^{high} CTCs (Supplementary Fig. S3A). In our prior study, PD-L1^{high} CTCs, rather than PD-L1$^+$ CTCs, correlated with therapeutic response (24). Therefore, we examined the proportion of PD-L1^{high} CTCs relative to total CTCs. The median proportion of PD-L1^{high} CTCs was 33.3%. Using a cutoff of 20%, which was determined in our previous study (25), the ORRs achieved in patients with PD-L1^{high} CTCs above and below this value were 47.8% (11/23 patients) and 0% (0/12 patients), respectively ($P = 0.002$; Supplementary Fig. S3B). Furthermore, patients with ≥20% PD-L1^{high} CTCs had a significantly longer PFS (median 6.1 vs. 2.9 months, HR: 0.28, 95% CI: 0.12–0.67; $P = 0.0002$; Supplementary Fig. S3C) and a longer OS (median NR vs. 8.9 months, HR: 0.40, 95% CI: 0.14–1.13; $P = 0.0601$) compared with patients who had <20% PD-L1^{high} CTCs (Supplementary Fig. S3D). Baseline PD-L1^{high} CTC levels might therefore represent a biomarker to identify patients who will benefit from anti-PD-1 therapy.

Discussion

In this study, we report the ORR and PFS following combination therapy of SHR-1210 and apatinib in patients with advanced HCC or GC/EGJC. Combination therapy showed modest clinical activity in GC/EGJC; however, encouraging signs of antitumor activity were observed in patients with HCC, regardless of extrahepatic disease and prior treatment failure with sorafenib. The difference in activity between GC/EGJC and HCC may, in part,

[c]First-line therapy included taxane and fluoropyrimidine [4 (44.4%)], platinum and fluoropyrimidine [3 (33.3%)], platinum and irinotecan [1 (11.1%)], fluoropyrimidine [1 (11.1%)].

[d]In patients who had received more than one line of therapy, first-line therapy included platinum and fluoropyrimidine [11 (68.8%)], taxane and fluoropyrimidine [2 (12.5%)], platinum and irinotecan [2 (12.5%)], fluoropyrimidine and adriamycin [1 (6.3%)]; second-line therapy included taxane and fluoropyrimidine [7 (43.8%)], taxane and platinum [2 (12.5%)], taxane and irinotecan [2 (12.5%)], platinum and fluoropyrimidine [1 (6.3%)], raltitrexed and irinotecan [1 (6.3%)], taxane [1 (6.3%)], fluoropyrimidine [1 (6.3%)], apatinib [1 (6.3%)].

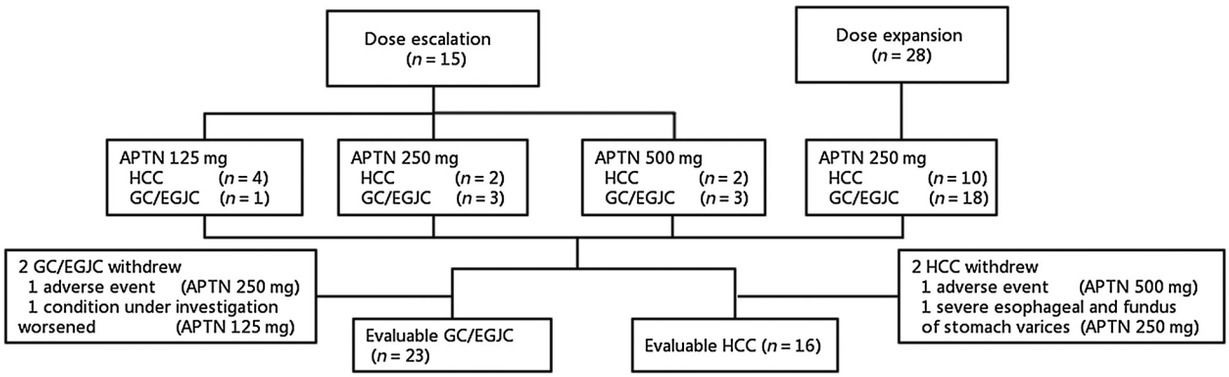

Figure 1.
Trial design. APTN, apatinib.

Table 2. Drug-related adverse events occurring in ≥5% of patients within dosage cohorts

	Apatinib 125 mg ($n = 5$)		Apatinib 250 mg ($n = 33$)		Apatinib 500 mg ($n = 5$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
General disorders						
Hypertension	3 (60.0%)	1 (20.0%)	14 (42.4%)	5 (15.2%)	4 (80.0%)	2 (40.0%)
Fatigue	2 (40.0%)	0	13 (39.4%)	0	1 (20.0%)	0
Proteinuria	1 (20.0%)	0	12 (36.4%)	0	2 (40.0%)	0
Pyrexia	1 (20.0%)	0	5 (15.2%)	0	1 (20.0%)	0
Hand–foot syndrome	2 (40.0%)	0	4 (12.1%)	1 (3.0%)	0	0
Pruritus	1 (20.0%)	0	4 (12.1%)	0	1 (20.0%)	0
Pneumonia	1 (20.0%)	0	1 (3.0%)	0	4 (80.0%)	3 (60.0%)
Rash	0	0	4 (12.1%)	1 (3.0%)	1 (20.0%)	1 (20.0%)
Cherry hemangioma	0	0	4 (12.1%)	0	0	0
Cough	0	0	4 (12.1%)	0	0	0
Gastrointestinal disorders						
Nausea	1 (20.0%)	0	8 (24.2%)	0	1 (20.0%)	0
Abdominal discomfort	1 (20.0%)	0	8 (24.2%)	0	0	0
Decreased appetite	1 (20.0%)	0	6 (18.2%)	0	0	0
Abdominal pain	0	0	6 (18.2%)	0	2 (40.0%)	0
Vomiting	0	0	6 (18.2%)	0	1 (20.0%)	0
Abdominal distention	0	0	5 (15.2%)	0	2 (40.0%)	0
Diarrhea	1 (20.0%)	0	4 (12.1%)	0	0	0
Hepatic function abnormal						
AST increase	3 (60.0%)	0	17 (51.5%)	5 (15.2%)	3 (60.0%)	1 (20.0%)
Blood bilirubin increase	3 (60.0%)	0	16 (48.5%)	3 (9.1%)	3 (60.0%)	1 (20.0%)
ALT increase	3 (60.0%)	0	13 (39.4%)	3 (9.1%)	2 (40.0%)	1 (20.0%)
Hematologic AE						
Platelet count decrease	3 (60.0%)	1 (20.0%)	15 (45.5%)	2 (6.1%)	3 (60.0%)	1 (20.0%)
Leukopenia decrease	4 (80.0%)	1 (20.0%)	11 (33.3%)	3 (9.1%)	2 (40.0%)	0
Neutropenia decrease	4 (80.0%)	1 (20.0%)	12 (36.4%)	2 (6.1%)	2 (40.0%)	0
Hemoglobin decrease	3 (60.0%)	0	11 (33.3%)	2 (6.1%)	2 (40.0%)	0
Biochemistry						
Hypoalbuminaemia	0	0	12 (36.4%)	0	4 (80.0%)	0
Hypertriglyceridaemia	1 (20.0%)	0	5 (15.2%)	0	0	0
Uric Acid increase	1 (20.0%)	0	4 (12.1%)	1 (3.0%)	0	0
Lipase increase	0	0	4 (12.1%)	1 (3.0%)	0	0
Hypophosphatemia	0	0	3 (8.8%)	0	2 (40.0%)	1 (20.0%)
Hypokalemia	1 (20.0%)	0	2 (6.1%)	0	1 (20.0%)	0
Estradiol increase	2 (40.0%)	0	7(21.2%)	0	0	0
Thyroid function test abnormal	0	0	5 (15.2%)	0	1 (20.0%)	0
Blood gonadotrophin abnormal	2 (40.0%)	0	3 (9.1%)	0	1 (20.0%)	0
LH increase	1 (20.0%)	0	4 (12.1%)	0	0	0
Progesterone decrease	0	0	4 (12.1%)	0	0	0
Blood testosterone decrease	1 (20.0%)	0	3 (9.1%)	0	0	0

NOTE: Data are *n* (%) of all 43 participants. There were no treatment-related deaths.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LH, Luteotropic hormone.

Table 3. Efficacy of SHR-1210 and apatinib combination treatment in patients with HCC or GC/EGJC

	HCC ($n = 18$)	GC/EGJC ($n = 25$)	Overall ($n = 43$)
Confirmed objective response[a]	8 (44.4%)	4 (16.0%)	12 (27.9%)
Complete response	0	0	0
Partial response	8 (44.4%)	5 (20.0%)	12 (27.9%)
Stable disease ≥6 weeks	7(38.9%)	13 (52.0%)	21 (48.8%)
Progressive disease	1 (5.6%)	5 (20.0%)	6 (14.0%)
Not evaluable	2 (11.1%)	2 (8.0%)	4 (9.3%)
ORR in evaluable patients	50.0% (24.7%, 75.4%)	17.4% (5.0%, 38.9%)	30.8% (17.0%, 47.6%)
DCR in evaluable patients	93.8% (69.8%, 99.8%)	78.3% (56.3%, 92.5%)	84.6% (69.5%, 94.1%)
Median time to response	3.4 (1.4∼9.7)	2.8 (1.4∼6.0)	3.45 (1.4∼9.7)
Duration of response			
KM median	NR	4.7	NR
Ongoing, n/N (%)	7/8 (87.5%)	1/4 (25%)	8/12 (66.7%)
PFS			
KM median	5.8 (2.6,NR)	2.9 (2.5, 4.2)	4.2 (2.8, 5.8)
6 months	45.4% (20.9%, 67.1%)	25.3% (9.7%, 44.4%)	33.9% (19.5%, 48.9%)
9 months	37.8% (15.0%, 60.7%)	12.6% (2.4%, 31.7%)	23.7% (11.2%, 38.8%)
APTN-250 mg/day	7.2 (4.1, NR)	2.9 (2.5, 6.1)	4.4 (2.9, 6.6)
OS			
KM median	NR (4.0, NR)	11.4 (8.6, NR)	12.6 (8.6, NR)
APTN-250 mg/day	NR (8.2, NR)	11.4(8.9, NR)	NR (9.9, NR)

NOTE: Data are *n* (%); % (95% CI) or months (95% CI).
[a]Response was assessed in all enrolled patients.

be attributed to the fact that HCC is an immunogenic tumor (26), while GC/EGJC tumors, especially in late-stage disease, are less immunogenic (27, 28). All patients with HCC enrolled in the study were infected by HBV; despite this status, combination therapy resulted in confirmed PRs in 8 of 16 (50.0%) evaluable patients, irrespective of the line of therapy. Compared with a recent study of regorafenib, ORR and PFS were substantially increased (4). Durable responses were achieved, with the duration of treatment in 8 responders >28 weeks (Supplementary Fig. S1). Notably, disease control was observed in 93.8% of patients, and the 6- and 9-month PFS were 51.3% and 41.0%, respectively; these results are higher than the rates of 64%, 37%, and 28% achieved following nivolumab (anti-PD-1) monotherapy (12). The enhanced and durable clinical

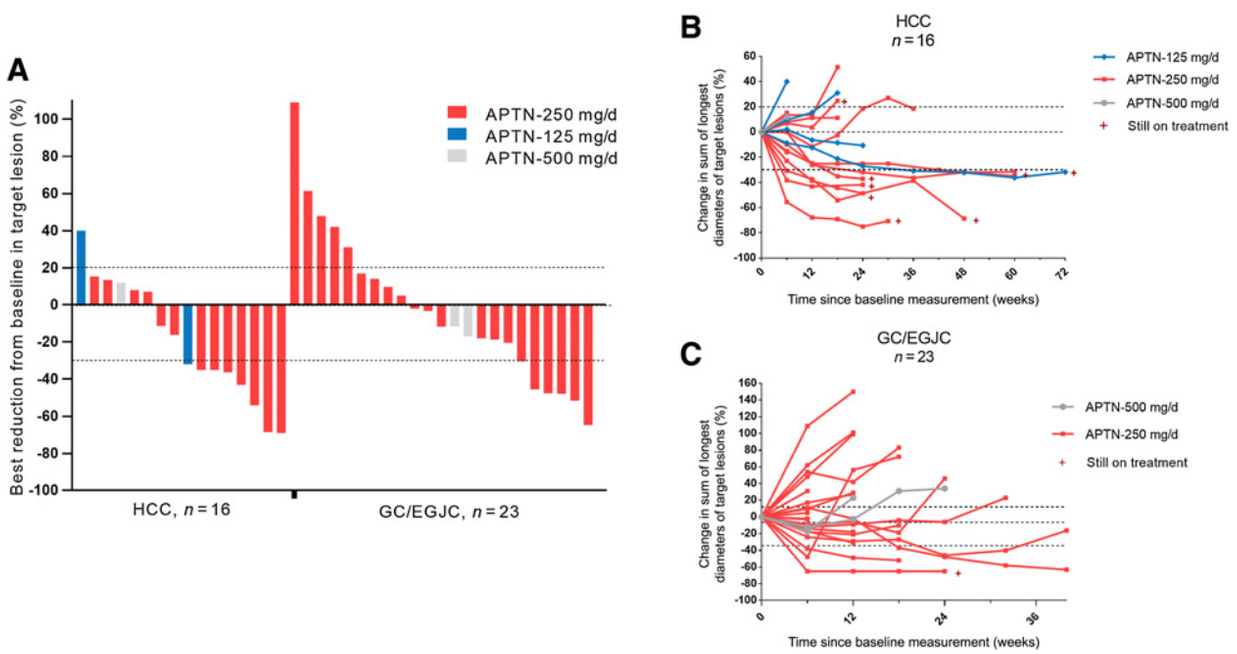

Figure 2.
Best percentage change in tumor burden and lesion diameters over time. **A,** Waterfall plot of best percentage change from baseline in size of target tumor lesion. Color code defines different doses of apatinib treatment. Two patients with HCC represented by red bars (apatinib 250 mg) were initiated on the 125 mg dose and achieved a PR after dose escalation. **B,** Percentage change in HCC lesion diameters over time. **C,** Percentage change in GC/EGJC lesion diameters over time.

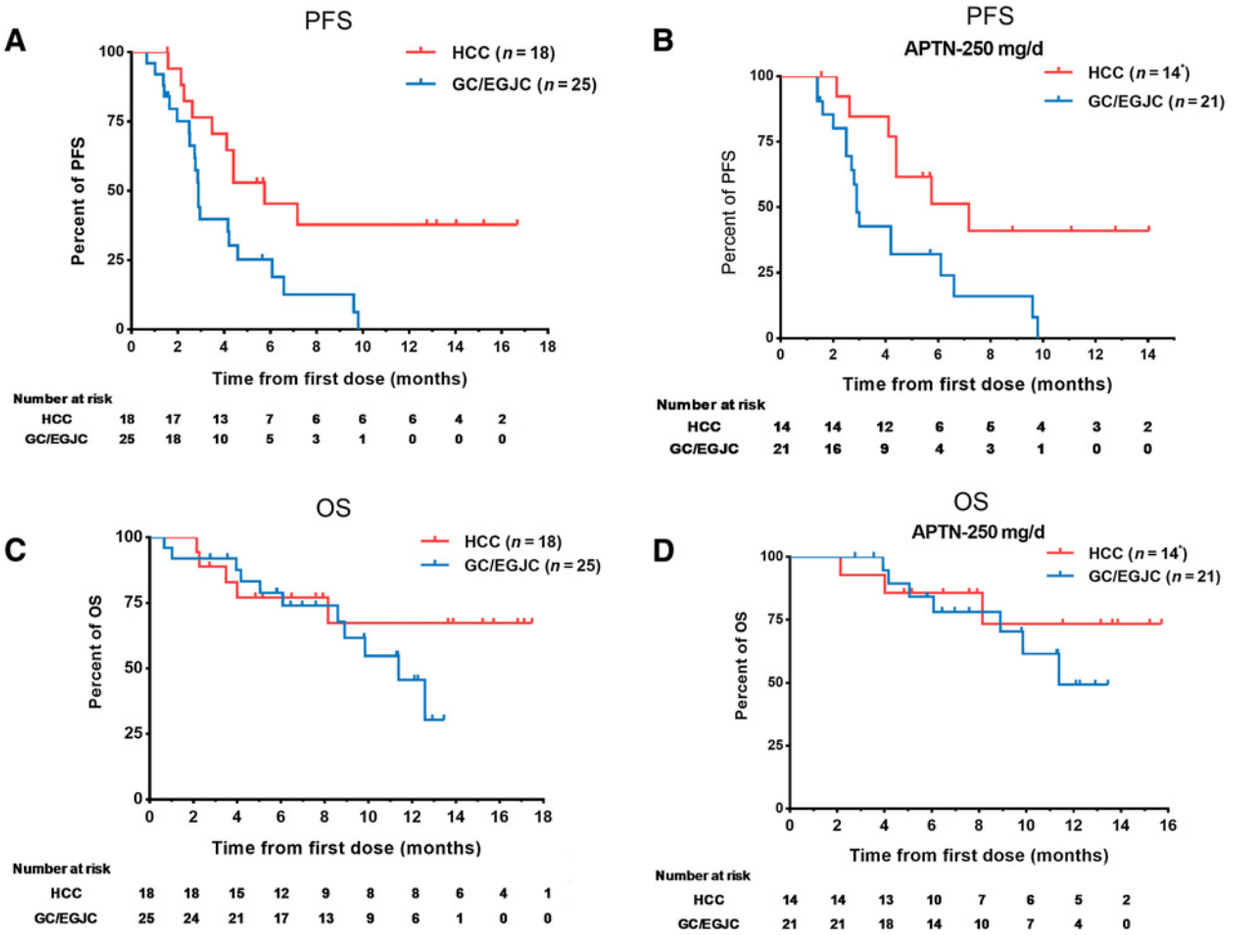

Figure 3.

PFS and OS of all patients and of patients in the apatinib 250 mg cohort. Kaplan–Meier PFS curves of all patients (**A**) and of patients in the apatinib 250 mg cohort (**B**). Kaplan–Meier overall survival curves of all patients (**C**) and of patients in the apatinib 250 mg cohort (**D**). Points on the curves represent censored patients. **B** and **D** include two patients initiated on the 125 mg dose and then escalated to 250 mg dose. PFS and OS for these two patients were calculated from the first dose of 250 mg.

efficacy achieved in this study was also higher than for apatinib treatment alone (29).

Nivolumab and pembrolizumab have both received FDA approval for second-line treatment of advanced HCC and third-line treatment of advanced GC with PD-L1 expression, respectively (12, 30). Although both agents achieved durable responses in some patients, the ORRs following monotherapy were approximately 11%–20%, highlighting that PD-1 blockade alone is insufficient in most patients. The results of this study agree with previous studies that have achieved a synergistic effect between antiangiogenic agents and immunotherapy (14, 15, 31, 32). Indeed, combined antiangiogenic and anti-PD-1/PD-L1 therapy has been shown to elicit T-cell function and drive tumor cells to activate immune checkpoints, resulting in greater antitumor immunity than anti-PD-1 treatment alone (22, 32, 33). In addition, some studies have demonstrated that low doses of anti-VEGF therapy can induce vascular normalization and improve antitumor immunity, and that high dose or prolonged treatment promotes hypoxia and immunosuppression in the tumor microenvironment (34, 35). The apatinib dose used in this study might induce prolonged vessel normalization, thereby reducing tumor hypoxia and acidosis and improving the anticancer activity of infiltrating immune cells. Although obviously synergy was observed in HCC, this efficacy was not observed in GC/EGJC. Several factors may contribute to this observation including innate immunogenicity difference between HCC and GC/EGJC (27, 28), 48.0% of enrolled GC/EGJC (12/25) patients with liver metastasis, which is associated with reduced $CD8^+$ T-cell infiltration (36), and relatively lower antiangiogenic activity in GC/EGJC. Treatment efficacy in this study was higher than reported for regorafenib or nivolumab in patients with advanced HCC (4, 12); however, direct comparisons between studies should be cautiously interpreted. There were some limitations in our study, including the small number of patients evaluated. Nevertheless, our results suggest that combination therapy with SHR-1210 and apatinib may provide synergistic effects by improving the tumor-induced immunosuppressive microenvironment.

Despite the dose escalation of apatinib in combination with SHR-1210, the safety profile of combination therapy was similar to previous reports for the component monotherapies (21, 24). One exception was three patients in the apatinib 500 mg cohort developed grade 3 immune-related pneumonitis during DLT evaluation period. This indicated that the tolerability of SHR-1210 was remarkably influenced by the addition of high dose of apatinib. Overall, AEs that occurred at the RP2D were relatively well tolerated, with transaminase elevation and hypertension most commonly reported. Hypertension, proteinuria, and hand–foot syndrome are associated with apatinib treatment, while lung infection and pneumonitis are associated with SHR-1210 treatment. Other AEs might be associated with both treatment components, and the prolonged exposure to the combination therapy might account for the increase in these events. The apatinib dose used in this study was <30% of a phase III study dose for gastric cancer (21). Nevertheless, combination therapy resulted in a slightly increased occurrence of some apatinib-related AEs or SAEs, including hypertension and increased levels of ALT and AST. As reported by Atkins and colleagues, these AEs might be enhanced by SHR-1210 (19). The rates of immune-related AEs were similar to those observed with anti-PD-1 treatment alone (24), thus SHR-1210 tolerability was likely unaffected by apatinib. Lung infection, pneumonitis, and hypophysitis (part of the checkpoint inhibitor syndrome; refs. 12, 37, 38), are the main toxicities associated with SHR-1210, and occurred at a similar incidence to a phase I study of SHR-1210 alone (24). Reactive capillary hemangiomas, previously the most common SHR-1210–related AE (24), were reduced in this study.

Several studies have demonstrated the importance of PD-L1 expression as a biomarker to identify patients who will most likely benefit from checkpoint blockade; however, the absence of PD-L1 expression is not an absolute indicator of the lack of clinical response (39, 40). This discrepancy could be explained by multiple factors, including heterogeneous expression within tumors, and dynamic changes in PD-L1 expression at different tumor stages (41, 42). Therefore, there remains an urgent need for the identification of reliable biomarkers to predict treatment response. The clinical significance of CTCs has been clearly demonstrated (43, 44). Furthermore, PD-L1 expression on CTCs may serve as a predictor to clinical outcome following PD-1 blockade (25, 42). In this study, the PFS in patients with $\geq$20% PD-L1^{high} CTCs at baseline was significantly longer than in patients with <20% PD-L1^{high} CTCs. These results suggest that monitoring for the presence of PD-L1^{high} CTCs prior to commencing therapy may be a promising prognostic approach.

In conclusion, this phase I study of SHR-1210 and apatinib combination therapy has shown promising efficacy in patients with advanced HCC. Furthermore, treatment was well tolerated in patients with advanced HCC or GC/EGJC. A multicenter, phase II clinical trial is underway in China to confirm these encouraging early indications of efficacy in patients with advanced HCC (NCT03463876).

Disclosure of Potential Conflicts of Interest

Q.R. Wang is an associate medical director at Jiangsu Hengrui Medicine co., LTD. No potential conflicts of interest were disclosed by the other authors.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.M. Xu
Study supervision: J.J. Zou

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