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Original Article

Safety and Clinical Activity of SHR7390 Monotherapy or Combined With Camrelizumab for Advanced Solid Tumor: Results From Two Phase I Trials

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Abstract

Background: SHR7390 is a novel, selective MEK1/2 inhibitor. Here, we report results from two phase I trials conducted to evaluate the tolerability, safety and antitumor activity of SHR7390 monotherapy for advanced solid tumors and SHR7390 plus camrelizumab for treatment-refractory advanced or metastatic colorectal cancer (CRC).

Patients and Methods: Patients received SHR7390 alone or combined with fixed-dose camrelizumab (200 mg every 2 weeks) in an accelerated titration scheme to determine the maximum tolerated dose (MTD). A recommended dose for expansion was determined based on the safety and tolerability of the dose-escalation stage. The primary endpoints were dose limiting toxicity (DLT) and MTD.

Results: In the SHR7390 monotherapy trial, 16 patients were enrolled. DLTs were reported in the 1.0 mg cohort, and the MTD was 0.75 mg. Grade ≥3 treatment-related adverse events (TRAEs) were recorded in 4 patients (25.0%). No patients achieved objective response. In the SHR7390 combination trial, 22 patients with CRC were enrolled. One DLT was reported in the 0.5 mg cohort and the MTD was not reached. Grade ≥3 TRAEs were observed in 8 patients (36.4%), with the most common being rash (n=4). One grade 5 TRAE (increased intracranial pressure) occurred. Five patients (22.7%) achieved partial response, including one of 3 patients with MSS/MSI-L and *BRAF* mutant tumors, one of 15 patients with MSS/MSI-L and *BRAF* wild type tumors, and all 3 patients with MSI-H tumors.

Conclusions: SHR7390 0.5 mg plus camrelizumab showed a manageable safety profile. Preliminary clinical activity was reported regardless of MSI and *BRAF* status.

Key words: SHR7390; camrelizumab; MEK inhibitor; anti-PD-1; colorectal cancer.

Implications for Practice

SHR7390 is a selective MEK 1/2 inhibitor. SHR7390 monotherapy had a maximum tolerated dose of 0.75 mg in patients with advanced solid tumors. Addition of MEK inhibitor to immunotherapy has been proposed to have potential synergistic therapeutic benefit. In phase I trial with SHR7390 plus camrelizumab in patients with advanced or metastatic colorectal cancer, SHR7390 0.5 mg plus camrelizumab showed a manageable safety profile and preliminary clinical benefits in patients with advanced or metastatic colorectal cancer regardless of MSI and *BRAF* status. Future research is warranted to further confirm these results.

Introduction

The RAS-RAF-MEK-ERK cascade is one of the critical pathways involved in the mitogen-activated protein kinase (MAPK) signaling transduction system, which functions in regulation of cell growth, differentiation, proliferation, and survival.[1,2] MEK (MEK1 and MEK2), a key enzyme in the

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RAS-RAF-MEK-ERK pathway, has been well characterized as an important therapeutic target for cancer treatment.[3] Inhibition of MEK provides clinical benefit for multiple solid tumors with activating mutations in upstream signaling proteins, including epidermal growth factor receptor (EGFR, an upstream effector of the RAS-RAF-MEK-ERK pathway), RAS, and RAF.[4-8] Trametinib, an inhibitor of MEK, was approved as single agent for the treatment of unresectable or metastatic melanoma with *BRAF V600E/K* mutations.[9] Due to the importance of this signaling pathway, MEK inhibitors have been extensively studied as monotherapy or combination therapy.[3,4,10-12]

Preclinical studies demonstrated that MEK inhibitors could increase T-cell infiltration into tumor and enhance the antitumor T-cell immunity.[13,14] Combination of MEK inhibitors with immunotherapy might exhibit synergistic and durable therapeutic benefit. For example, atezolizumab plus cobimetinib and vemurafenib significantly increased progression-free survival (PFS) in patients with *BRAF V600* mutation-positive advanced melanoma.[15] As a result, there is a growing interest in the combinatorial strategy.[15-17]

Colorectal cancer (CRC) accounts for approximately 10% of cancer-related deaths worldwide.[18] The 5-year overall survival (OS) of metastatic CRC is only 5-8%.[19] The standard of care in patients with refractory or metastatic CRC who failed previous systemic therapies (fluoropyrimidine, platinum and irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and, if the patient has *RAS* wild type tumors, anti-EGFR agents) is regorafenib or trifluridine/tiparacil.[20,21] However, these 2 regimens only provided a median PFS of 1.9-2.0 months, a median OS of 6.4-7.1 months, and an objective response rate (ORR) of 1%-1.6%.[22,23] Immune checkpoint inhibitors have shown unprecedented clinical activity in patients with microsatellite instability high (MSI-H) metastatic CRC, which accounts for only 3%-5% of patient with metastatic CRC.[24-28] However, compared to MSI-H disease, microsatellite instability low (MSI-L) or microsatellite stable (MSS) tumors derived much less benefit from immune checkpoint inhibitor monotherapy. Therefore, there is an urgent need for novel agents to augment the immune response of immune checkpoint inhibitor in patients with metastatic CRC.

SHR7390 is a novel, selective small molecular MEK1/2 inhibitor. Camrelizumab, a monoclonal antibody that targets programmed cell death-1, has shown clinical benefit both as monotherapy or combination treatment in multiple solid tumor types.[29-32] In this report, we present results from two phase I trials conducted to evaluate the tolerability, safety and preliminary antitumor activity of SHR7390 monotherapy in patients with advanced solid tumors (SHR7390 monotherapy trial) or SHR7390 in combination with camrelizumab in patients with treatment-refractory advanced or metastatic CRC (SHR7390 combination trial).

Patients and Methods

Study Design and Patients

This report presents data of 2 single-arm, open-label, phase I studies assessing the tolerability, safety, and preliminary antitumor activity of SHR7390 alone in patients with advanced solid tumors (ClinicalTrials.gov identifier, NCT02968485), or SHR7390 in combination with camrelizumab in patients with advanced CRC (ClinicalTrials.gov identifier, NCT03182673). Both the SHR7390 monotherapy trial and SHR7390 combination trial enrolled patients who failed upfront standard treatment or for whom no effective therapies were available. As per protocol, the SHR7390 combination trial also contains another part which assigned patients with advanced CRC to receive SHR7390 plus camrelizumab and fuzuloparib (a poly [ADP-ribose] polymerase inhibitor), and the data will be reported elsewhere.

The common eligibility criteria for both trials included aged 18-70 year; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; adequate organ function; adverse events from previous treatment for cancer resolved to grade ≤1 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03; an estimated life expectancy of at least 3 months. In the SHR7390 combination trial, patients need to provide fresh or archived tissues for mutational analysis of *BRAF*/*RAS* genes unless previous test results were provided. To investigate the clinical outcomes of the combination therapy for MSS/MSI-L CRC, patients enrolled in the dose-expansion phase must have MSS/MSI-L tumors. Key exclusion criteria included previous treatment with MEK inhibitors; involved in other interventional clinical trials within 4 weeks before enrollment; active central nervous system metastases or history of primary tumors in nervous system; evidence of retinopathy or a history of neurosensory retinal detachment; risk of retinal vein occlusion or central serous retinopathy; a history of or active autoimmune disease; known innate or acquired immunodeficiency disease; a history of organ transplantation; clinically significant cardiovascular disease; uncontrolled infections; or other uncontrolled chronic comorbidities. In the SHR7390 combination trial, patients who had received immune checkpoint inhibitors within 2 months before study treatment or had disease requiring the use of systemic steroids or other immunosuppressive medications were not permitted.

The two trials were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. The protocols were approved by the ethics committee of Sun Yat-sen University Cancer Center. All patients provided written informed consent before enrollment.

Treatment and Assessments

Both trials consisted of an initial dose-escalation phase and a subsequent expansion phase. The dose-escalation phase included an accelerated titration scheme with 1-2 patients enrolled at each dose level, followed by a standard 3+3 design (Supplementary Fig. S1, A and B).[33] In the accelerated titration scheme, patient received a single dose of SHR7390 orally at a starting dose of 0.125 mg at a 7-day run-in period, and then received continuous once daily SHR7390 alone (SHR7390 monotherapy trial) or SHR7390 plus camrelizumab (200 mg every 2 weeks intravenously; SHR7390 combination trial) in 28-day treatment cycles. At the second occurrence of a grade 2 treatment-related adverse event (TRAE), the first occurrence of a grade 3 TRAE or dose-limiting toxicity (DLT) during the first treatment cycle, a standard 3+3 design was introduced. If none of the above events occurred, dose was up-titrated to the next higher level. Intra-patient dose escalation was not allowed. In both trials, DLT was defined during the run-in period and the first cycle as follows: (1) grade 4 hematological toxicities, grade 3 neutropenia complicated with

≥38.5 °C fever, or grade 3 thrombocytopenia complicated with bleeding; (2) grade ≥3 non-hematological toxicities; (3) grade ≥2 retinal vein occlusion or other grade 2 or higher ocular toxicities at the discretion of investigator; (4) grade ≥2 decreased ventricular ejection fraction; (5) SHR7390 related adverse events resulted in treatment delay of ≥14 days. In the SHR7390 combination trial, the DLT also included grade ≥2 immune-related interstitial pneumonia. The maximum tolerated dose (MTD) was defined as the highest dose at which fewer than one third of patients had a DLT.

The MTD was selected for the expansion phase in the SHR7390 monotherapy trial, and a recommended phase II dose (RP2D) was determined by Safety Monitoring Committee (SMC) for expansion based on the safety and tolerability of the dose-escalation phase in the SHR7390 combination trial. In the dose-expansion phase, another 3 to 6 patients (SHR7390 monotherapy trial) or at least 12 patients (SHR7390 combination trial) were required to further analyze the safety and preliminary antitumor activity. Patients were treated until disease progression, intolerable toxicity, or withdrawal of consent. SHR7390 dose delay or modification were permitted for management of adverse events. Dose modification of camrelizumab was not allowed.

Adverse events were graded according to NCI-CTCAE version 4.03. Tumor response was assessed with RECIST version 1.1 at the end of the first and second cycle, then the assessment interval was at the investigators' discretion (SHR7390 monotherapy trial) or every 6 weeks (SHR7390 combination trial) thereafter. Patients who were assessed as complete response or partial response needed to be confirmed at least 4 weeks later. In both trials, ECOG performance status, vital signs, physical examination, laboratory tests, and 12-lead electrocardiograms were conducted at regular intervals. In addition, ophthalmologic examination, including fundoscopy, tonometry, and optical coherence tomography (only at screening), was performed at screening, the end of cycle 1, and study discontinuation/withdrawn. Echocardiogram was conducted at screening, the end of the run-in period, the end of each cycle, and study discontinuation/withdrawn.

Endpoints

In both trials, the primary endpoints were DLT and MTD, and the secondary endpoints included tolerability, safety, preliminary antitumor activity, and RP2D. In the SHR7390 monotherapy trial, the preliminary antitumor activity parameters included ORR (defined as the proportion of patients who achieved a confirmed complete response or partial response), and disease control rate (DCR, defined as the proportion of patients with a confirmed objective response or stable disease). In the SHR7390 combination trial, the preliminary antitumor activity parameters included ORR, best overall response (BOR, defined as the best response recorded from the start of the treatment until disease progression), duration of response (DoR, defined as the time from first documented objective response to disease progression or death, whichever occurred first), and DCR.

Statistical Analyses

No formal hypotheses were performed in the two studies. The sample size of dose-escalation phase in both trials were calculated based on the observed toxicities. The 95% CIs of ORR and DCR were calculated based on the Clopper-Pearson method. Time-to-event variables were estimated using the Kaplan-Meier method. Other parameters were summarized descriptively. In both trials, safety and activity were assessed in all patients who had at least one dose study treatment. All statistical analyses were done with SAS version 9.4.

Results

SHR7390 Monotherapy Trial

In the SHR7390 monotherapy trial, between December 20, 2016, and February 22, 2019, a total of 16 patients were enrolled and received study treatment. Therefore, 16 patients were included in the activity and safety analysis population. At data cutoff on November 26, 2019, all patients had discontinued study treatment, and the main reason was disease progression (*n* = 9, 56.3%). Median follow-up duration was 2.3 months (range 1.8-4.0 months). Baseline characteristics are summarized in Table 1. The predominant tumor type was CRC (n = 8, 50%), and the other tumor types were breast cancer (*n* = 4, 25.0%), gastric cancer (*n* = 3, 18.8%), and intrahepatic cholangiocarcinoma (*n* = 1, 6.3%).

Patients enrolled received the following doses: 0.125 mg (*n* = 1), 0.25 mg (*n* = 1), 0.5 mg (*n* = 1), 0.75 mg (*n* = 6), and 1.0 mg (*n* = 7). DLTs were reported in 3 patients with 1.0 mg SHR7390 (grade 3 stomatitis and grade 3 fatigue, grade 3 syncope, and grade 3 stomatitis; *n* = 1 each; Table 2), and the MTD was 0.75 mg.

All patients experienced adverse events, and grade 3 adverse events were noted in 7 patients (43.8%). No grade 4 or 5 adverse events were observed. TRAEs occurring in at least 15% of all patients are presented in Table 3. Separated by cohort, the most frequently observed TRAEs in the higher dose cohorts (0.75 and 1.0 mg) were rash (*n* = 6 [100%] in 0.75 mg cohort vs *n* = 5 [71.4%] in 1.0 mg cohort), increased aspartate aminotransferase (*n* = 5 [83.3%] vs *n* = 6 [85.7%]), increased alanine aminotransferase (*n* = 4 [66.7%] vs *n* = 6 [85.7%]), somnolence (*n* = 5 [83.3%] vs *n* = 3 [42.9%]), and stomatitis (*n* = 5 [83.3%] vs *n* = 3 [42.9%]; Supplementary Table S1). Grade 3 TRAEs were recorded in 4 patients (25.0%), including one patient in 0.75 mg cohort (anemia, hypoalbuminemia and incision site impaired healing; all occurred out of the DLTs observation window), and 3 patients in 1.0 mg cohort (syncope, increased lipase and stomatitis, stomatitis and fatigue; *n* = 1 each; increased lipase occurred out of the DLTs observation window). Two patients (12.5%) experienced treatment-related serious adverse events, with one patient in 0.75 mg cohort (grade 3 incision site impaired healing) and one in 1.0 mg cohort (grade 3 stomatitis and grade 3 fatigue). Five patients (31.3%) discontinued study treatment because of TRAEs, with one patient in 0.75 mg cohort (grade 3 incision site impaired healing), and 4 in 1.0 mg cohort (grade 3 syncope, grade 1 retinal disorder, grade 3 stomatitis and grade 3 fatigue, and grade 3 stomatitis; *n* = 1 each). Dose modification or delay occurred in one patient in 0.75 mg cohort (6.3%, grade 1 hallucination).

The class effects of MEK inhibitors included skin toxicities, gastrointestinal events, ocular events, and cardiac events. Rash was the most common TRAE, which occurred in 75.0% of all patients. Treatment-related gastrointestinal events were stomatitis (50.0%), diarrhea (18.8%), and constipation (18.8%). Treatment-related ocular events were retinal disorder (37.5%) and ocular hypertension (6.3%). All ocular events were grade 1 or 2. Cardiac toxicity (grade 1 myocardial ischemia) was reported in one patient. Among the most

Table 1. Baseline demographics and disease characteristics.

Characteristics	SHR7390 monotherapy trial (*n* = 16)	SHR7390 combination trial (*n* = 22)
Age, years		
Mean (SD)	47 (12)	44 (12)
Median (range)	51 (29-64)	43 (21-66)
Sex, *n* (%)		
Male	6 (37.5)	15 (68.2)
Female	10 (62.5)	7 (31.8)
ECOG performance status, *n* (%)		
0	7 (43.8)	14 (63.6)
1	9 (56.3)	8 (36.4)
Primary tumor type, *n* (%)		
Colorectal cancer	8 (50.0)	22 (100)
Breast cancer	4 (25.0)	—
Gastric cancer	3 (18.8)	—
Hepatobiliary cell carcinoma	1 (6.3)	—
Site of metastasis, *n* (%)		
Liver	9 (56.3)	15 (68.2)
Lung	5 (31.3)	12 (54.5)
Others	15 (93.8)	15 (68.2)
Site of primary tumor, *n* (%)		
Right	—	6 (27.3)
Left	—	7 (31.8)
Unknown	—	9 (40.9)
Microsatellite instability status, *n* (%)[a]		
Stable or low	—	18 (81.8)
High	—	3 (13.6)
Unknown	—	1 (4.5)
RAS mutation status, *n* (%)		
Mutant	3 (18.8)	8 (36.4)
Wild type	7 (43.8)	13 (59.1)
Unknown	6 (37.5)	1 (4.5)
BRAF V600E mutation status, *n* (%)		
Mutant	0	3 (13.6)
Wild type	10 (62.5)	18 (81.8)
Unknown	6 (37.5)	1 (4.5)
No. of prior lines of systemic therapy, *n* (%)		
0-1	1 (6.3)	1 (4.5)
2	8 (50.0)	14 (63.6)
≥3	7 (43.8)	7 (31.8)

[a]Microsatellite instability status were not collected in the SHR7390 monotherapy trial.
Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

common TRAEs, several neurologic toxicities were observed, including somnolence (50.0%) and dizziness (25.0%). The severity of all neurologic toxicities observed were grade 1 or grade 2, except one syncope (grade 3).

No patients achieved confirmed response, and one patient with CRC in 1.0 mg cohort had stable disease (Table 4). Four patients reached stable disease at the first post-baseline scan, with one patient in 0.25 mg cohort, one in 0.75 mg cohort, and 2 in 1.0 mg cohort. However, these patients discontinued study treatment before subsequent tumor assessments.

SHR7390 Combination Trial

In the SHR7390 combination trial, between August 8, 2017, and January 22, 2019, 22 patients with treatment-refractory advanced or metastatic CRC were enrolled and received study treatment (activity population and safety population). As of May 30, 2020, study treatment was ongoing in 3 patients (13.6%), and the main reason for study discontinuation was disease progression (*n* = 13, 59.1%). Median follow-up duration was 5.9 months (range 1.3-32.8 months). All patients enrolled had metastases, and all were diagnosed with stage IV disease (Table 1). No patients had received prior immune checkpoint inhibitor.

Although 0.75 mg was established as the MTD in the SHR7390 monotherapy trial, the safety profile suggested that 0.75 mg once daily was not well tolerated. Thus, on the basis of the tolerability and safety data of the SHR7390 monotherapy trial, the SMC chose 0.5 mg as the maximum dose in the dose-escalation phase. Among enrolled patients, 2 patients each received 0.125 or 0.25 mg SHR7390 plus 200 mg camrelizumab, respectively, and 18 patients received the RP2D of 0.5 mg. One DLT (grade 3 rash) was reported in a patient in 0.5 mg cohort, and the MTD was not reached (Table 2).

Adverse events were observed in all 22 patients, and 21 patients (95.5%) experienced adverse events that were considered to be related to the study drugs. TRAEs occurring in at least 15% of patients are listed in Table 3. Grade ≥ 3 TRAEs were observed in 8 patients (36.4%): 6 patients with grade 3 TRAEs (rash [*n* = 4], edema [*n* = 1], anemia [*n* = 1]), one patient with grade 4 increased lipase, and one patient with grade 5 increased intracranial pressure, which was deemed possibly related to the study treatment. Discontinuation of any study agent because of TRAEs was recorded in one patient (4.5%) in 0.5 mg cohort (grade 5 increased intracranial pressure). Nine patients (40.9%) required dose reduction or delay for any study agents, most commonly due to skin toxicity and gastrointestinal events.

Immune-related adverse events (irAEs) occurred in 10 patients (45.5%), being reactive capillary endothelial proliferation (40.9%), hypothyroidism, hyperthyroidism, increased intracranial pressure, and rash (4.5% each). All irAEs were grade 1 or 2 except the increased intracranial pressure (grade 5). Treatment-related rash occurred in 95.5% of all patients. The most common treatment-related gastrointestinal events were stomatitis (40.9%), diarrhea (27.3%), and gingival bleeding (18.2%). Treatment-related ocular events were observed in 7 patients (31.8%), with the most common being vision blurred (18.2%). All ocular events were grade 1. No cardiac toxicity was observed. The most frequently reported treatment-related neurologic toxicities included somnolence (54.5%), memory impairment (31.8%), hallucination (22.7%), and dizziness (18.2%). The neurologic toxicities were primarily grade 1 or 2.

Five patients (22.7% [95% CI 7.8 to 45.4]) in the activity population (*n* = 22) achieved confirmed response, all being partial response (*n* = 1 each in 0.125 and 0.25 mg cohorts,

Table 2. Dosing scheme and dose-limiting toxicities.

SHR7390 monotherapy trial			SHR7390 combination trial		
SHR7390 dose (mg)	Patients (*n*)	DLTs	SHR7390 + camrelizumab dose (mg)	Patients (*n*)	DLTs
0.125	1	No DLTs were observed	0.125 + 200	2	No DLTs were observed
0.25	1	No DLTs were observed	0.25 + 200	2	No DLTs were observed
0.5	1	No DLTs were observed	0.5 + 200	18	Grade 3 rash
0.75	6	No DLTs were observed	—	—	—
1.0	7	Grade 3 stomatitis, grade 3 fatigue, and grade 3 syncope	—	—	—

Abbreviations: DLTs, dose-limiting toxicities.

Table 3. Treatment-related adverse events occurring in ≥15% of patients in any study.

Term, *n* (%)	SHR7390 monotherapy trial (*n* = 16)		SHR7390 combination trial (*n* = 22)	
	All grade	Grade 3	All grade	Grade 3
Rash	12 (75.0)	0	21 (95.5)	4 (18.2)
Aspartate aminotransferase increased	11 (68.8)	0	15 (68.2)	0
Alanine aminotransferase increased	10 (62.5)	0	6 (27.3)	0
Somnolence	8 (50.0)	0	12 (54.5)	0
Stomatitis	8 (50.0)	2 (12.5)	9 (40.9)	0
Hypoalbuminemia	7 (43.8)	1 (6.3)	13 (59.1)	0
Anemia	6 (37.5)	1 (6.3)	12 (54.5)	1 (4.5)
Retinal disorder	6 (37.5)	0	1 (4.5)	0
Edema	6 (37.5)	0	20 (90.9)	1 (4.5)
Dizziness	4 (25.0)	0	4 (18.2)	0
Fatigue	3 (18.8)	1 (6.3)	3 (13.6)	0
Proteinuria	3 (18.8)	0	9 (40.9)	0
Diarrhea	3 (18.8)	0	6 (27.3)	0
Constipation	3 (18.8)	0	1 (4.5)	0
Lipase increased	2 (12.5)	1 (6.3)	7 (31.8)	0
Hallucination	1 (6.3)	0	5 (22.7)	0
Pruritus	0	0	14 (63.6)	0
RCCEP	0	0	10 (45.5)	0
Memory impairment	0	0	7 (31.8)	0
Hypothyroidism	0	0	5 (22.7)	0
Skin fissures	0	0	4 (18.2)	0
Gingival bleeding	0	0	4 (18.2)	0
Vision blurred	0	0	4 (18.2)	0
White blood cell count decreased	0	0	4 (18.2)	0

Abbreviations: RCCEP, reactive cutaneous capillary endothelial proliferation.

n = 3 in 0.5 mg cohort). The median DoR was 13.4 months (95% CI 8.1 to not reached). Three patients (13.6%) had stable disease, and 11 (50.0%) had disease progression (Table 4). The DCR reached 36.4% (95% CI 17.2 to 59.3). Reductions in tumor size are shown in Fig. 1. Median PFS was 2.0 months (95% CI 1.1 to 10.1), and median OS was not reached.

MSI status were available in 21 patients. All three patients with MSI-H and 2 of the 18 patients with MSS/MSI-L reached confirmed response. Three patients with MSS/MSI-L had *BRAF (V600E)* mutation and 15 patients had *BRAF* wild-type tumors. Partial responses were observed in one of 3 patients (33.3%) harboring MSS/MSI-L and *BRAF* mutant tumors and in one of 15 patients (6.7%) harboring MSS/MSI-L and *BRAF* wild-type tumors, with response lasting 13.4 and 8.1 months, respectively (Fig. 2). One of the 2 responders with MSS/MSI-L (*BRAF* wild type) discontinued

Table 4. Pooled clinical activity of SHR7390 monotherapy trial and SHR7390 combination trial.

Response	SHR7390 monotherapy trial (*n* = 16)	SHR7390 combination trial (*n* = 22)
Best overall response, *n* (%)		
Partial response	0	5 (22.7)
Stable disease	1 (6.3)	3 (13.6)
Progressive disease	11 (68.8)	11 (50.0)
Not evaluable	4 (25.0)[a]	3 (13.6)
ORR, % (95% CI)	0	22.7 (7.8-45.4)
DCR, *n* (%)	1 (6.3)	8 (36.4)
DoR (months), median (95% CI)	—	13.4 (8.1-NR)

[a]All 4 patients had stable disease at the first tumor assessment, and then discontinued study treatment due to adverse events without further evaluation.
Abbreviations: ORR, objective response rate; DCR, disease control rate; DoR, duration of response; NR, not reached.

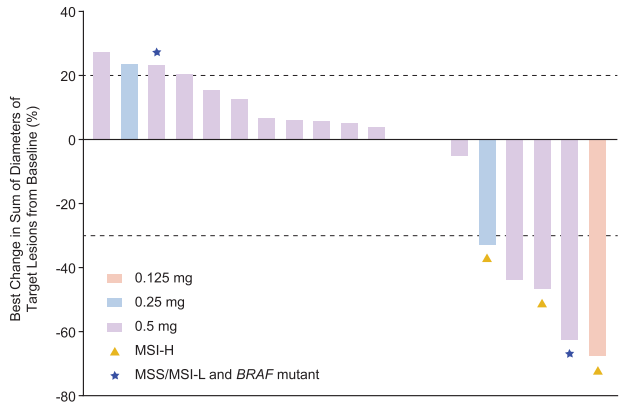

Figure 1. Best change from baseline in sum of diameters in individual patients in the SHR7390 combination trial. Patients with unknown best change from baseline are not included. Each bar represents one patient harboring MSS/MSI-L and *BRAF* wild-type tumors except those marked by asterisk or triangle. Abbreviations: MSI-H, microsatellite instability high; MSS/MSI-L, microsatellite stable or microsatellite instability low.

study treatment due to disease progression, and the other (*BRAF* mutant) discontinued due to grade 5 increased intracranial pressure. Eight patients with MSS/MSI-L harbored *RAS* mutation and 10 were *RAS* wild type. Both of the 2 responders with MSS/MSI-L had *RAS* wild type tumors. All 3 responders with MSI-H were *RAS*/*BRAF* wild type, with responses lasting 31.4+, 11.0+, and 10.1+ months (Fig. 2). All 3 patients with stable disease had MSS/MSI-L and *BRAF* wild-type CRC, with a PFS of 32.5, 20.4, and 29.7 months. One patient with stable disease had *RAS* wild type tumors, and the other 2 were *RAS* mutant.

Discussion

In this report, we assessed SHR7390 monotherapy in patients with advanced solid tumors and SHR7390 combined with camrelizumab in patients with treatment-refractory advanced or metastatic CRC in two phase I studies. In the SHR7390 monotherapy trial, 3 patients had DLTs, all in 1.0 mg cohort, and the MTD was 0.75 mg. The SHR7390 combination therapy showed tolerated safety profile, with one DLT (grade 3 rash) observed in 0.5 mg cohort, and the MTD was not reached. ORR was 22.7%, and DCR reached 36.4% in the SHR7390 combination trial.

The most common TRAEs in both the SHR7390 monotherapy trial and SHR7390 combination trial were skin toxicity, gastrointestinal events, and neurologic toxicity. Previous studies with MEK inhibitor have reported high occurrence of skin toxicity and gastrointestinal disorder, which are consistent with the findings of our study.[3,10,34] Of them, the most frequently reported events, including rash, diarrhea, stomatitis, were typical adverse events of MEK inhibitors.[3,10,34] In patients with advanced solid tumors who were administered trametinib, the incidence of treatment-related rash or dermatitis acneiform was 80%, diarrhea was 42%, nausea was 28%, and vomiting was 17%.[3] A phase I study with binimetinib in patients with advanced solid tumors showed that combined rash of any causality occurred in 81% of patients, 51% of patients had diarrhea, 56% had nausea, and 52% had vomiting.[10] Cobimetinib was associated with 54% of rash, 61% of diarrhea, 26% of nausea, and 23% of vomiting in patients with advanced solid tumors in a phase I trial.[6] In the present SHR7390 monotherapy trial, rash was still the most common TRAE, which occurred in 75.0% of patients. The incidence of diarrhea (18.8%) and vomiting (0%) was lower compared with other studies with MEK inhibitors. Laboratory abnormalities, increased aspartate aminotransferase (68.8%) and increased alanine aminotransferase (62.5%), which were less common with other MEK inhibitors, were among the most frequently reported TRAEs in the SHR7390 monotherapy trial.

In the present study, we noted a high incidence of SHR7390-related neurologic toxicities, including somnolence (50.0% in the SHR7390 monotherapy trial and 54.5% in the SHR7390 combination trial), dizziness (25.0% and 18.2%), hallucination (6.3% and 22.7%), delirium (12.5% and 0), insomnia (12.5% and 4.5%), and abnormal dreams (12.5% and 0). Neurologic toxicities were also observed in patients with other MEK inhibitors. In phase I dose-escalation and expansion study with binimetinib in patients who had advanced solid tumors, 15% of patients reported occurrence of dizziness.[10] Also, abnormal dreams, syncope, somnolence were noted in patients with advanced solid tumors who received refametinib, although the incidence was infrequent.[35] Notably, these neurologic events in our studies were mainly grade 1 or 2, and could be managed with early recognition and supportive treatment, except for one grade 5 increased intracranial pressure in the SHR7390 combination trial. To our knowledge, previous studies did not show any association between increased intracranial pressure and the combination therapy or either of the component agents. The mechanism of these neurologic events remains unknown and should be closely monitored in future studies.

Ocular toxic effects are considered a class effect of MEK inhibition.[36] During our studies, we observed drug-related retinal disorder in 6 patients in the SHR7390 monotherapy trial and one patient in the SHR7390 combination trial. Vision blurred was noted in four patients in the SHR7390 combination trial. The results further confirmed the prevalence of

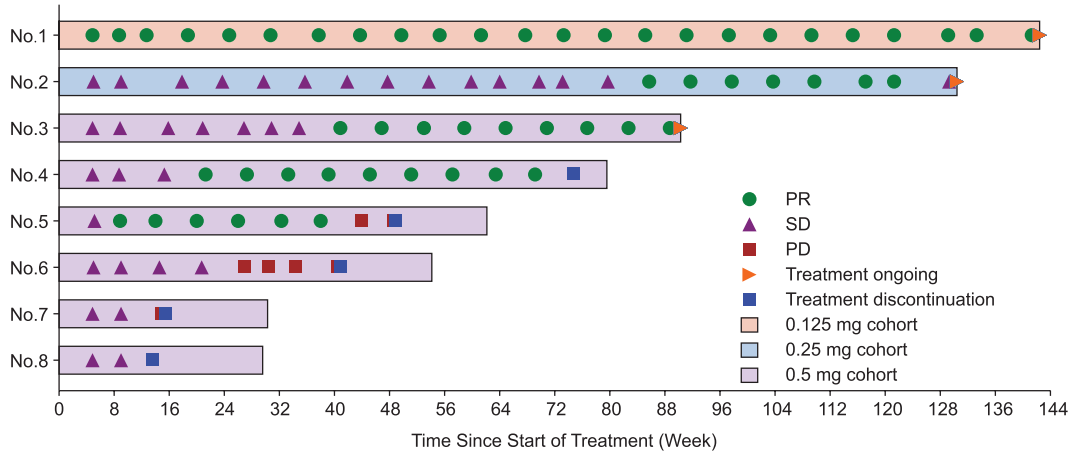

Figure 2. Tumor assessment and duration of follow-up in patients who had an objective response (Nos. 1-5) or stable disease (Nos. 6-8) in the SHR7390 combination trial. Patient No. 1: *RAS/BRAF* wild type, MSI-H, tumor sidedness unknown; patients No. 2: *RAS/BRAF* wild type, MSI-H, left-sided tumor; patient No. 3: *RAS/BRAF* wild type, MSI-H, left-sided tumor; patient No. 4: *RAS* wild type, *BRAF* mutant, MSS/MSI-L, tumor sidedness unknown; patient No. 5: *RAS/BRAF* wild type, MSS/MSI-L, right-sided tumor; patient No. 6: *RAS/BRAF* wild type, MSS/MSI-L, tumor sidedness unknown; patient No. 7: *RAS* mutant, *BRAF* wild type, MSS/MSI-L, left-sided tumor; patient No. 8: *RAS* mutant, *BRAF* wild type, MSS/MSI-L, tumor sidedness unknown. Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; MSI-H, microsatellite instability high; MSS/MSI-L, microsatellite stable or microsatellite instability low.

ocular toxicities with MEK inhibitors and necessity of attention in future studies. Cardiac toxic effects have been reported in several studies with MEK inhibitor.[3,35,37] Decreased left ventricular ejection fraction was noted in 8% of advanced solid tumor patients treated with trametinib, with 2 patients reporting grade 3 events.[3] Interestingly, there was scarcely any cardiac function disorder in our studies.

In the SHR7390 monotherapy trial, disappointingly, no responses were observed possibly because that clinically meaningful exposure of MEK inhibitor was not reached due to the rise of toxic effects. Moreover, there might be other resistance mechanisms to the MAPK pathway in these patients. Therefore, combination therapy might serve as a potential approach. MAPK signaling pathway was involved in immune escape by upregulation of multiple immunosuppressive cytokines.[38] Inhibition of the MAPK pathway with a MEK inhibitor could increase T-cell infiltration into tumors and induce synergistic antitumor activity with immune inhibitors.[13,14] In this study, SHR7390 in combination with camrelizumab showed evidence of clinical benefit in 5 of 22 patients (22.7%) with treatment-refractory advanced or metastatic CRC. Some durable responses were seen in this study, with responses lasting 8 to 31 months. Three patients with stable disease had long PFS, and DCR reached 36.4%.

Clinical benefits from immune checkpoint inhibitors are widely seen in patients with advanced MSI-H solid tumors,[39,40] especially in patients with MSI-H metastatic CRC.[24,27] By contrast, patients with MSS/MSI-L CRC, which constitutes the majority of patients with advanced or metastatic CRC, benefit little from immune checkpoint inhibitor monotherapy.[41] In our study, all 3 patients with MSI-H tumors responded to SHR7390 plus camrelizumab (response lasting 31.4+, 11.0+, and 10.1+ months), and importantly, 2 of 18 patients with MSS/MSI-L disease achieved partial response (11.1%; response lasting 13.4 and 8.1 months, respectively). In the IMblaze370 study, atezolizumab plus cobimetinib only provided an objective response in 3 of 180 patients with CRC (1.7%; 170 patients with MSS/MSI-L; 10 with missing MSI status).[42] *BRAF* mutations are reported in around 8% of patients with metastatic CRC, and patients with *BRAF* oncogene mutations are associated with poor prognosis.[43] In our SHR7390 combination trial, one of 3 patients with MSS/MSI-L and *BRAF* mutant tumors achieved partial response. Although the small sample size limited the possibility of drawing firm conclusions, our study demonstrated potential antitumor activity in patients with advanced CRC regardless of MSI and *BRAF* status. Metastatic CRC is a heterogeneous disease, and underlying mechanism of dual inhibition with immune checkpoint inhibitor and MEK inhibitor remains unclear. This study did not incorporate biomarker analysis, making it impossible to identify potential biomarkers for patient screening. Additional studies with large number of patients and biomarker analysis are warranted to further validate our results and to identify reliable predictive biomarkers to select patients who will benefit from this combination regimen.

Conclusion

SHR7390 (0.5 mg once daily) plus camrelizumab (200 mg every 2 weeks) showed a manageable safety profile in patients with treatment-refractory advanced or metastatic CRC. Preliminary clinical activity was reported regardless of MSI and *BRAF* status, and future studies are warranted to further evaluate these results.

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Conflict of Interest

Jie Xie, Chun-Lei Jin, and Xian-Feng Zhou are employees of Jiangsu Hengrui Pharmaceuticals. The other authors indicated no financial relationships.

Author Contributions

Conception/design: C.-L.J., R.-H.X. Provision of study material or patients: X.-L.W., Y.Z., H.-Y.Z., W.-F.F., H.-Y.L., M.-Z.Q., M.-M.H., B.-Y.Z., F.W., F.-H.W., Y.-H.L., Z.-Q.W., R.-H.X. Collection and/or assembly of data: X.-L.W., Y.Z., H.-Y.Z., W.-F.F., H.-Y.L., M.-Z.Q., M.-M.H., B.-Y.Z., F.W., F.-H.W., Y.-H.L., Z.-Q.W., R.-H.X. Data analysis and interpretation: X.-L.W., J.X., C.-L.J., X.-F.Z., R.-H.X. Manuscript writing: X.-L.W., J.X., C.-L.J. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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