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Efficacy and Safety of SHR7390 Alone or in Combination with Camrelizumab in Advanced Solid Tumors: Findings from Two Phase I Studies

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ABSTRACT

SHR7390 represents an innovative and highly specific inhibitor targeting MEK1/2. The findings presented here stem from a pair of early-stage clinical studies aimed at assessing the safety, tolerability, and potential anticancer effects of SHR7390 used alone in cases of progressed solid malignancies, as well as in conjunction with camrelizumab for individuals with heavily pretreated advanced or metastatic colorectal cancer (CRC). Participants were administered SHR7390 either as a single agent or alongside a standard dose of camrelizumab (200 mg intravenously biweekly) through an accelerated dose-escalation approach to identify the maximum tolerated dose (MTD). A suitable dose for further evaluation was selected based on tolerability and safety observed during escalation. Key objectives focused on dose-limiting toxicities (DLTs) and determination of the MTD. In the study evaluating SHR7390 alone, a total of 16 individuals were included. DLTs emerged at the 1.0 mg level, leading to an MTD of 0.75 mg. Severe (grade ≥3) treatment-emergent adverse events linked to the drug occurred in 4 cases (25.0%). None of the participants experienced an objective tumor response. For the combination study involving SHR7390 and camrelizumab, 22 CRC patients were recruited. A single DLT was noted at the 0.5 mg dose, with no MTD established. Serious (grade ≥3) drug-related adverse events affected 8 patients (36.4%), predominantly skin rash (observed in 4 individuals). One fatal (grade 5) event involving elevated intracranial pressure was recorded. Partial responses were seen in 5 patients (22.7%), comprising one out of three with MSS/MSI-low and BRAF-mutated disease, one out of 15 with MSS/MSI-low and BRAF wild-type tumors, and all three with MSI-high profiles. The regimen of SHR7390 at 0.5 mg combined with camrelizumab exhibited an acceptable safety profile. Early signs of therapeutic efficacy were observed independent of microsatellite instability or BRAF mutation status.

Keywords: Colorectal cancer, SHR7390, Camrelizumab, Anti-PD-1, MEK inhibitor

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Introduction

The RAS-RAF-MEK-ERK signaling pathway plays a pivotal role in the broader mitogen-activated protein kinase (MAPK) network, influencing processes such as cellular proliferation, differentiation, growth, and survival [1, 2]. MEK1 and MEK2 serve as central components in this cascade and have emerged as promising targets for oncology therapeutics [3]. Blocking MEK activity has yielded therapeutic gains in various malignancies harboring upstream alterations, including those in EGFR (a regulator upstream of RAS-RAF-MEK-ERK), RAS, or RAF itself [4-8]. For instance, trametinib, a MEK blocker, gained approval for standalone use in BRAF V600E/K-mutated unresectable or metastatic melanoma [9]. Given the pathway's significance, extensive research has explored MEK inhibitors both singly and in combinations [3, 4, 10-12].

Evidence from preclinical models indicates that MEK suppression can promote greater T-cell presence within tumors and bolster antitumor immune responses [13, 14]. Pairing MEK inhibitors with immunotherapeutic agents may thus produce enhanced and sustained outcomes. One notable example is the triplet of atezolizumab,

cobimetinib, and vemurafenib, which markedly improved progression-free survival in advanced melanoma with BRAF V600 mutations [15]. This has fueled increasing exploration of such integrated approaches [15-17].

Colorectal cancer contributes to roughly 10% of global cancer fatalities [18]. Five-year survival for metastatic cases remains low, at 5-8% [19]. For patients with disease refractory to prior lines—including fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens, anti-VEGF therapies, and (in RAS wild-type cases) anti-EGFR antibodies—options like regorafenib or trifluridine-tipiracil represent standards, yet these yield modest median progression-free survival (1.9-2.0 months), overall survival (6.4-7.1 months), and response rates (1%-1.6%) [20-23]. PD-1/PD-L1 inhibitors have transformed management of MSI-high metastatic CRC (comprising 3%-5% of cases), delivering robust responses [24-28]. In contrast, MSS or MSI-low tumors show limited gains from checkpoint inhibition alone. Hence, new strategies to potentiate immunotherapy in this population are critically needed.

SHR7390 is an original oral agent that potently and selectively inhibits MEK1/2. Camrelizumab, an anti-PD-1 monoclonal antibody, has evidenced efficacy alone or combined across diverse cancers [29-32]. Herein, we describe data from two phase I studies assessing the safety, tolerability, and early efficacy of SHR7390 alone in advanced solid malignancies or combined with camrelizumab in treatment-resistant advanced or metastatic CRC.

Materials and Methods

Study design and participants

The current analysis integrates findings from two single-arm, open-label, phase I investigations designed to examine the safety, tolerability, and early signs of anticancer efficacy of SHR7390 administered as a single agent in individuals with progressed solid malignancies (ClinicalTrials.gov identifier: NCT02968485) or combined with camrelizumab in those with advanced colorectal cancer (ClinicalTrials.gov identifier: NCT03182673). Enrollment in both the monotherapy and combination studies was restricted to patients who had progressed after standard frontline therapies or lacked viable treatment alternatives. Notably, the combination study protocol included an additional cohort evaluating SHR7390 together with camrelizumab and fuzuloparib (a PARP inhibitor) in advanced CRC patients; results from that segment will be presented separately.

Shared inclusion requirements across the two studies encompassed age between 18 and 70 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; presence of at least one evaluable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; sufficient organ function; resolution of prior anticancer treatment toxicities to grade ≤1 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03; and anticipated survival of ≥3 months. For the combination trial, participants were required to submit fresh or archival tumor samples for BRAF and RAS mutation testing, unless prior results were available. To specifically evaluate outcomes in microsatellite stable (MSS) or microsatellite instability-low (MSI-L) CRC, enrollment during the dose-expansion stage was limited to patients with MSS/MSI-L disease.

Major exclusion factors included prior exposure to MEK inhibitors; participation in another investigational trial within the preceding 4 weeks; active brain metastases or primary central nervous system malignancies; documented retinopathy or prior neurosensory retinal detachment; predisposition to retinal vein occlusion or central serous retinopathy; active or historical autoimmune conditions; known congenital or acquired immunodeficiency; prior organ transplantation; significant cardiovascular disorders; ongoing uncontrolled infections; or other unmanaged chronic illnesses. In the combination study, additional exclusions applied to individuals who had received PD-1/PD-L1 inhibitors within 2 months prior to initiation or required ongoing systemic corticosteroids or immunosuppressants.

Both studies adhered to the principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. Protocols received approval from the institutional ethics committee at Sun Yat-sen University Cancer Center, and all participants gave informed written consent prior to study entry.

Treatment and evaluations

Each trial featured a dose-escalation stage followed by a dose-expansion stage. Escalation employed an initial accelerated titration approach involving 1–2 patients per cohort, transitioning to a conventional 3+3 design as needed [33]. During accelerated escalation, participants received a single oral dose of SHR7390 starting at 0.125 mg during a 7-day lead-in phase, followed by daily continuous dosing of SHR7390 alone (monotherapy trial) or

in combination with fixed-dose intravenous camrelizumab (200 mg every 2 weeks; combination trial) in 28-day cycles. Transition to the 3+3 schema occurred upon the second instance of grade 2 treatment-related toxicity, the first grade 3 event, or any dose-limiting toxicity (DLT) in cycle 1. Absent such events, escalation proceeded to the next dose level. No intra-patient dose increases were permitted.

Dose-limiting toxicities were assessed during the lead-in period and cycle 1, defined as: (1) grade 4 hematologic events, grade 3 neutropenia with fever ≥38.5°C, or grade 3 thrombocytopenia with hemorrhage; (2) grade ≥3 non-hematologic toxicities; (3) grade ≥2 retinal vein occlusion or other ocular toxicities ≥grade 2 deemed significant by the investigator; (4) grade ≥2 reduction in left ventricular ejection fraction; (5) SHR7390-attributable events causing treatment interruption ≥14 days. In the combination arm, grade ≥2 immune-mediated pneumonitis was also considered a DLT. The maximum tolerated dose (MTD) was established as the highest level at which <1/3 of patients experienced a DLT.

For the monotherapy study, the identified MTD advanced to expansion. In the combination study, a recommended phase II dose (RP2D) was designated by the Safety Monitoring Committee based on overall escalation-phase safety and tolerability. The expansion cohorts enrolled an additional 3–6 patients (monotherapy) or a minimum of 12 patients (combination) to further characterize safety and early efficacy signals. Treatment continued until documented progression, unacceptable toxicity, or patient withdrawal. Dose interruptions or reductions of SHR7390 were allowed for toxicity management, whereas camrelizumab dosing remained fixed without modification.

Adverse events were classified using NCI-CTCAE version 4.03. Antitumor responses were evaluated according to RECIST version 1.1, with imaging performed after cycles 1 and 2, then at investigator discretion (monotherapy) or every 6 weeks (combination). Confirmed complete or partial responses required verification ≥4 weeks later. Routine monitoring included ECOG status, vital signs, physical exams, laboratory parameters, and 12-lead electrocardiograms. Ophthalmologic assessments (fundoscopy, tonometry, and optical coherence tomography at baseline only) were conducted at screening, end of cycle 1, and treatment discontinuation. Echocardiograms were obtained at baseline, completion of the lead-in phase, end of each cycle, and study exit.

Endpoints

Across both studies, the primary objectives centered on dose-limiting toxicity (DLT) and maximum tolerated dose (MTD). Secondary objectives encompassed overall tolerability, safety profile, early indicators of anticancer efficacy, and identification of a recommended phase II dose (RP2D).

In the monotherapy study with SHR7390, measures of early efficacy included objective response rate (ORR), calculated as the percentage of patients achieving confirmed complete or partial response, and disease control rate (DCR), defined as the percentage with confirmed response or stable disease.

In the combination study of SHR7390 plus camrelizumab, early efficacy assessments comprised ORR, best overall response (BOR; the optimal response documented from treatment initiation until progression), duration of response (DoR; interval from initial confirmed response to progression or death, whichever came first), and DCR.

Statistical analyses

Neither trial involved formal hypothesis testing. Sample sizes for the dose-escalation stages were driven by observed adverse events. Ninety-five percent confidence intervals for ORR and DCR were derived using the Clopper-Pearson exact method. Time-to-event endpoints were analyzed via Kaplan-Meier estimation. Remaining variables were presented through descriptive summaries. Safety and efficacy evaluations included all participants who received at least one dose of investigational therapy. Analyses were performed using SAS software, version 9.4.

Results and Discussion

SHR7390 monotherapy trial

From December 20, 2016, to February 22, 2019, 16 patients with advanced solid tumors were enrolled and treated with SHR7390 alone. All 16 were evaluable for both safety and efficacy. As of the data cutoff date of November 26, 2019, every patient had discontinued treatment, primarily due to progressive disease (n=9, 56.3 percent). The median duration of follow-up was 2.3 months (range: 1.8–4.0 months). Patient demographics and baseline features are outlined in **Table 1.** Colorectal cancer was the most common malignancy (n=8, 50 percent), followed by breast

cancer (n=4, 25.0 percent), gastric cancer (n=3, 18.8 percent), and intrahepatic cholangiocarcinoma (n=1, 6.3 percent).

Table 1. Baseline Demographics and Disease Characteristics

Characteristics	SHR7390 Combination Trial (n = 22)	SHR7390 Monotherapy Trial (n = 16)
Age, years		
Mean (SD)	44 (12)	47 (12)
Median (range)	43 (21-66)	51 (29-64)
Sex, n (%)		
Male	15 (68.2)	6 (37.5)
Female	7 (31.8)	10 (62.5)
ECOG Performance Status, n (%)		
0	14 (63.6)	7 (43.8)
1	8 (36.4)	9 (56.3)
Primary Tumor Type, n (%)		
Colorectal cancer	22 (100)	8 (50.0)
Breast cancer	—	4 (25.0)
Gastric cancer	—	3 (18.8)
Hepatobiliary cell carcinoma	—	1 (6.3)
Site of Metastasis, n (%)		
Liver	15 (68.2)	9 (56.3)
Lung	12 (54.5)	5 (31.3)
Others	15 (68.2)	15 (93.8)
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	8 (36.4)	3 (18.8)
Wild type	13 (59.1)	7 (43.8)
Unknown	1 (4.5)	6 (37.5)
BRAF V600E Mutation Status, n (%)		
Mutant	3 (13.6)	0
Wild type	18 (81.8)	10 (62.5)
Unknown	1 (4.5)	6 (37.5)
No. of Prior Lines of Systemic Therapy, n (%)		
0-1	1 (4.5)	1 (6.3)
2	14 (63.6)	8 (50.0)
≥3	7 (31.8)	7 (43.8)

[a] Microsatellite instability status was not collected in the SHR7390 monotherapy trial.

Abbreviations**:** SD = standard deviation; ECOG = Eastern Cooperative Oncology Group.

Participants in the monotherapy arm were allocated to the following dose levels: 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).

Dose-limiting toxicities occurred in three individuals receiving 1.0 mg SHR7390 (one case each of grade 3 stomatitis accompanied by grade 3 fatigue, grade 3 syncope, and isolated grade 3 stomatitis); **(Table 2).** Consequently, the maximum tolerated dose was determined to be 0.75 mg.

Table 2. Dosing Scheme and Dose-Limiting Toxicities

SHR7390 + Camrelizumab Dose (mg)	Patients (n)	DLTs	SHR7390 Monotherapy Trial	Patients (n)	DLTs
0.125 + 200	2	No dose-limiting toxicities noted	0.125	1	No dose-limiting toxicities noted
0.25 + 200	2	No dose-limiting toxicities noted	0.25	1	No dose-limiting toxicities noted
0.5 + 200	18	Grade 3 rash	0.5	1	No dose-limiting toxicities noted
—	—	—	0.75	6	No dose-limiting toxicities noted
—	—	—	1.0	7	Grade 3 stomatitis, grade 3 fatigue, and grade 3 syncope

Abbreviations: DLTs = dose-limiting toxicities.

Every participant encountered at least one adverse event, with grade 3 events affecting 7 individuals (43.8 percent). No grade 4 or 5 events were recorded. Treatment-related adverse events (TRAEs) that occurred in ≥15% of the overall population are detailed in **Table 3.**

When examined by dose level, the most common TRAEs in the higher-dose groups (0.75 mg and 1.0 mg) included rash (n=6 [100%] in the 0.75 mg group versus n=5 [71.4%] in the 1.0 mg group), elevated aspartate aminotransferase (n=5 [83.3%] versus n=6 [85.7%]), elevated alanine aminotransferase (n=4 [66.7%] versus n=6 [85.7%]), somnolence (n=5 [83.3%] versus n=3 [42.9%]), and stomatitis (n=5 [83.3%] versus n=3 [42.9%]).

Severe (grade 3) TRAEs were observed in 4 patients (25.0 percent): one in the 0.75 mg group (anemia, hypoalbuminemia, and impaired healing at incision site; all outside the DLT evaluation period) and three in the 1.0 mg group (syncope, elevated lipase, and stomatitis; stomatitis with fatigue; n=1 each; elevated lipase outside the DLT period).

Treatment-related serious adverse events occurred in two patients (12.5%): one in the 0.75 mg group (grade 3 impaired incision site healing) and one in the 1.0 mg group (grade 3 stomatitis and grade 3 fatigue).

Five patients (31.3 percent) permanently discontinued therapy due to TRAEs: one in the 0.75 mg group (grade 3 impaired incision site healing) and four in the 1.0 mg group (grade 3 syncope, grade 1 retinal disorder, grade 3 stomatitis with grade 3 fatigue, and grade 3 stomatitis; n=1 each).

Dose adjustments or interruptions were required in one patient in the 0.75 mg group (6.3%; due to grade 1 hallucination).

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

Adverse event term, n (%)	SHR7390 combination therapy (n=22)		SHR7390 monotherapy (n=16)	
	All grades	Grade 3	All grades	Grade 3
Rash	21 (95.5)	4 (18.2)	12 (75.0)	0
Increased aspartate aminotransferase	15 (68.2)	0	11 (68.8)	0
Increased alanine aminotransferase	6 (27.3)	0	10 (62.5)	0
Somnolence	12 (54.5)	0	8 (50.0)	0
Stomatitis	9 (40.9)	0	8 (50.0)	2 (12.5)
Hypoalbuminemia	13 (59.1)	0	7 (43.8)	1 (6.3)
Anemia	12 (54.5)	1 (4.5)	6 (37.5)	1 (6.3)
Retinal disorder	1 (4.5)	0	6 (37.5)	0
Edema	20 (90.9)	1 (4.5)	6 (37.5)	0
Dizziness	4 (18.2)	0	4 (25.0)	0
Fatigue	3 (13.6)	0	3 (18.8)	1 (6.3)
Proteinuria	9 (40.9)	0	3 (18.8)	0
Diarrhea	6 (27.3)	0	3 (18.8)	0

Constipation	1 (4.5)	0	3 (18.8)	0
Increased lipase	7 (31.8)	0	2 (12.5)	1 (6.3)
Hallucination	5 (22.7)	0	1 (6.3)	0
Pruritus	14 (63.6)	0	0	0
Reactive cutaneous capillary endothelial proliferation (RCCEP)	10 (45.5)	0	0	0
Memory impairment	7 (31.8)	0	0	0
Hypothyroidism	5 (22.7)	0	0	0
Skin fissures	4 (18.2)	0	0	0
Gingival bleeding	4 (18.2)	0	0	0
Blurred vision	4 (18.2)	0	0	0
Decreased white blood cell count	4 (18.2)	0	0	0

Abbreviation: RCCEP, reactive cutaneous capillary endothelial proliferation.

The adverse events associated with MEK inhibitor treatment primarily involved dermatologic, gastrointestinal, ocular, and cardiac effects. The most frequently reported treatment-related adverse event (TRAE) was rash, affecting 75.0% of patients overall. Common treatment-related gastrointestinal toxicities included stomatitis (50.0 percent), diarrhea (18.8 percent), and constipation (18.8 percent). Ocular toxicities related to treatment consisted of retinal abnormalities (37.5%) and elevated intraocular pressure (6.3%), all of which were limited to grade 1 or 2 severity. A single instance of cardiac toxicity (grade 1 myocardial ischemia) occurred in one patient.

Additionally, among frequently observed TRAEs, various neurological effects were noted, such as somnolence (50.0 percent) and dizziness (25.0 percent). All neurological adverse events were grade 1 or 2, with the exception of one case of syncope graded as 3.

No patients experienced a confirmed objective response. One patient with colorectal cancer in the 1.0 mg dose group achieved stable disease **(Table 4).** At the initial post-baseline evaluation, four patients demonstrated stable disease—one in the 0.25 mg cohort, one in the 0.75 mg cohort, and two in the 1.0 mg cohort—although these individuals discontinued treatment prior to any follow-up tumor assessments.

Table 4. Combined clinical efficacy results from the SHR7390 monotherapy study and the SHR7390 combination therapy study.

	SHR7390 combination therapy study (n = 22)	**SHR7390 monotherapy study (n = 16)**
Best overall response, n (%)		
Partial response	5 (22.7)	0
Stable disease	3 (13.6)	1 (6.3)
Progressive disease	11 (50.0)	11 (68.8)
Not evaluable	3 (13.6)	4 (25.0)[a]
Objective response rate (ORR), % (95% CI)	22.7 (7.8–45.4)	0
Disease control rate (DCR), n (%)	8 (36.4)	1 (6.3)
Median duration of response (DoR), months (95% CI)	13.4 (8.1–NR)	—

[a]All four patients showed stable disease on their initial post-baseline tumor assessment but withdrew from the study due to adverse events before any subsequent evaluations could be performed.

Abbreviations: ORR= objective response rate; DCR= disease control rate; DoR= duration of response; NR= not reached.

SHR7390 combination therapy study

In the SHR7390 combination therapy trial, conducted between August 8, 2017, and January 22, 2019, a total of 22 patients with heavily pretreated advanced or metastatic colorectal cancer (CRC) were enrolled and treated (comprising both the safety and efficacy evaluable populations). As of the data cutoff on May 30, 2020, three patients (13.6%) remained on treatment, while the primary cause of discontinuation was progressive disease (n = 13, 59.1 percent). The median duration of follow-up was 5.9 months (range: 1.3–32.8 months). Every enrolled

patient presented with metastatic disease and stage IV diagnosis **(Table 1).** None had previously received immune checkpoint inhibitors.

Despite 0.75 mg being identified as the maximum tolerated dose (MTD) in the monotherapy study, its tolerability profile indicated that this dose administered once daily was poorly tolerated. Accordingly, based on safety and tolerability findings from the monotherapy trial, the safety monitoring committee selected 0.5 mg as the highest dose for the dose-escalation portion. Of the enrolled patients, two each were treated with 0.125 mg or 0.25 mg SHR7390 in combination with 200 mg camrelizumab, while 18 received the recommended phase 2 dose (RP2D) of 0.5 mg. A single dose-limiting toxicity (grade 3 rash) occurred in the 0.5 mg group, and the MTD was not reached **(Table 2).**

All 22 patients experienced adverse events, with 21 (95.5%) having events judged related to the investigational drugs. Treatment-related adverse events (TRAEs) affecting ≥15% of patients are summarized in **Table 3**. Grade ≥3 TRAEs occurred in 8 patients (36.4 percent), including grade 3 events in 6 patients (rash [n = 4], edema [n = 1], anemia [n = 1]), one case of grade 4 lipase elevation, and one fatal (grade 5) event of elevated intracranial pressure considered possibly treatment-related. One patient (4.5 percent) in the 0.5 mg group permanently discontinued a study drug due to a TRAE (the grade 5 intracranial pressure event). Dose reductions or interruptions of any study drug were required in 9 patients (40.9%), predominantly because of dermatologic and gastrointestinal toxicities.

Immune-related adverse events (irAEs) were reported in 10 patients (45.5 percent), most commonly reactive capillary endothelial proliferation (40.9 percent), followed by hypothyroidism, hyperthyroidism, elevated intracranial pressure, and rash (4.5 percent each). All irAEs were grade 1 or 2 except for the grade 5 intracranial pressure event. Rash related to treatment was observed in 95.5% of patients. Frequent treatment-related gastrointestinal toxicities included stomatitis (40.9 percent), diarrhea (27.3 percent), and gingival bleeding (18.2 percent). Ocular toxicities attributed to treatment affected 7 patients (31.8%), primarily blurred vision (18.2%), and all were grade 1. No treatment-related cardiac events were recorded. Common neurologic TRAEs comprised somnolence (54.5 percent), memory impairment (31.8 percent), hallucinations (22.7 percent), and dizziness (18.2 percent), with most being grade 1 or 2.

In the efficacy-evaluable population (n = 22), five patients achieved a confirmed partial response (22.7% [95% CI 7.8–45.4]), distributed as one each in the 0.125 mg and 0.25 mg cohorts and three in the 0.5 mg cohort. The median duration of response was 13.4 months (95 percent CI 8.1–not reached). Stable disease was seen in three patients (13.6%), and progressive disease in 11 (50.0%) **(Table 4).** The disease control rate was 36.4% (95% CI 17.2–59.3). Tumor shrinkage is depicted in **Figure 1**. Median progression-free survival was 2.0 months (95 percent CI 1.1–10.1), while median overall survival was not reached.

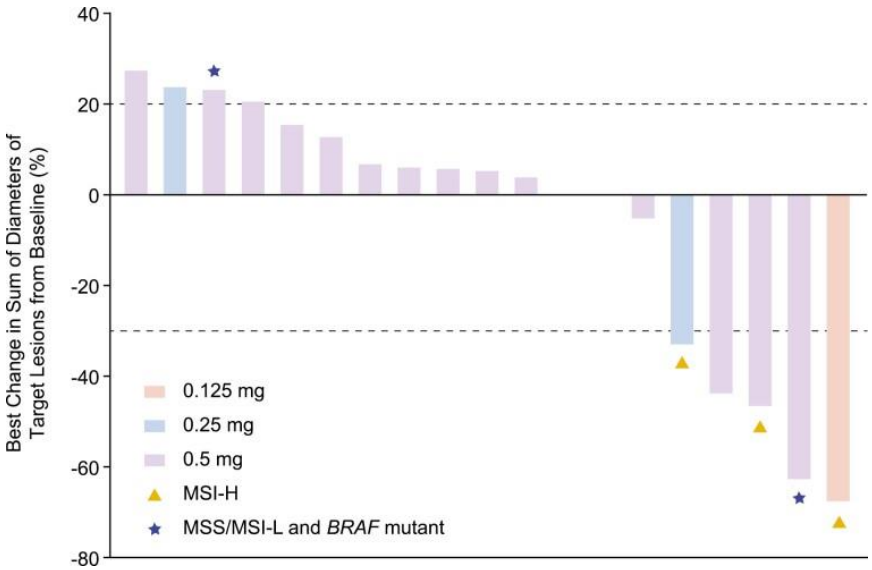

Figure 1.

In the SHR7390 combination trial, the best change from baseline in the sum of diameters for individual patients is presented, excluding those with unknown results. Each bar represents a patient with either MSS/MSI-L or

BRAF wild-type tumors, except for those marked with an asterisk or triangle. MSI status was determined for 21 patients, of whom all three with MSI-H and two of the 18 with MSS/MSI-L tumors achieved a confirmed response. Among the MSS/MSI-L group, three patients had a BRAF (V600E) mutation, while the remaining 15 had BRAF wild-type tumors. Partial responses were seen in one of three (33.3%) patients with MSS/MSI-L and BRAF mutant tumors, and one of 15 (6.7%) patients with MSS/MSI-L and BRAF wild-type tumors, with the response durations of 13.4 and 8.1 months, respectively **(Figure 2).** One of the responders with MSS/MSI-L and BRAF wild-type tumor discontinued treatment due to disease progression, while the BRAF mutant responder stopped treatment due to grade 5 increased intracranial pressure. Eight patients had MSS/MSI-L tumors with RAS mutations, while 10 had RAS wild-type tumors. Both of the responders with MSS/MSI-L had RAS wild-type tumors. The three MSI-H responders all had RAS/BRAF wild-type tumors, with responses lasting over 31.4, 11.0, and 10.1 months **(Figure 2).** Three patients with stable disease all had MSS/MSI-L and BRAF wild-type colorectal cancer, with progression-free survival (PFS) durations of 32.5, 20.4, and 29.7 months. One of the stable disease patients had RAS wild-type tumors, while the other two were RAS mutant.

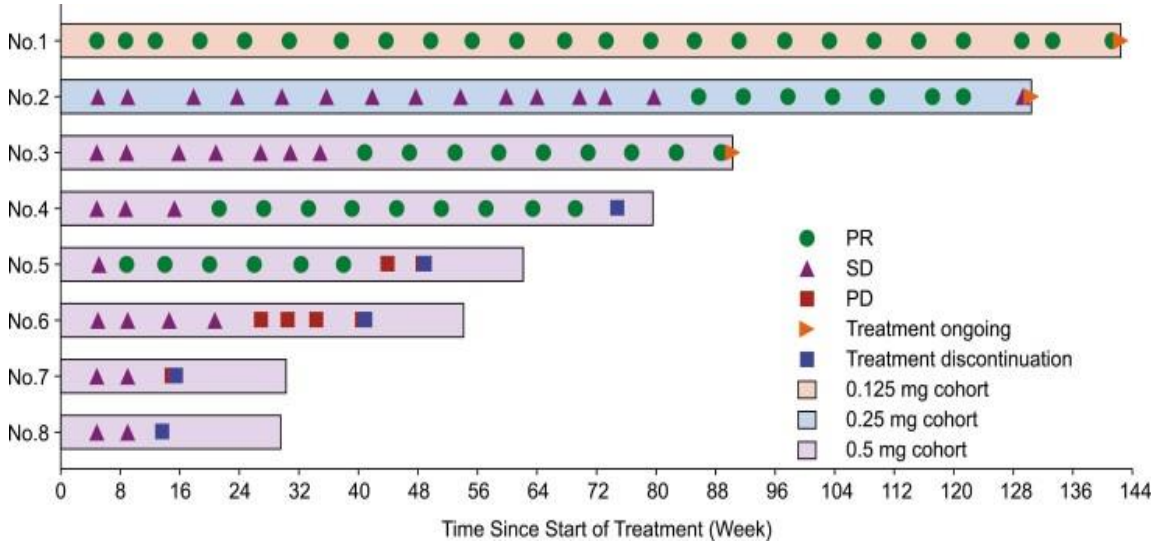

Figure 2.

The tumor evaluation and follow-up duration for patients showing either an objective response (Nos. 1-5) or stable disease (Nos. 6-8) in the SHR7390 combination trial are as follows: Patient 1, with RAS/BRAF wild type, MSI-H, and unknown tumor sidedness; Patient 2, with RAS/BRAF wild type, MSI-H, and a left-sided tumor; Patient 3, with RAS/BRAF wild type, MSI-H, and a left-sided tumor; Patient 4, with RAS wild type, BRAF mutant, MSS/MSI-L, and unknown tumor sidedness; Patient 5, with RAS/BRAF wild type, MSS/MSI-L, and a right-sided tumor; Patient 6, with RAS/BRAF wild type, MSS/MSI-L, and unknown tumor sidedness; Patient 7, with RAS mutant, BRAF wild type, MSS/MSI-L, and a left-sided tumor; Patient 8, with RAS mutant, BRAF wild type, MSS/MSI-L, and unknown tumor sidedness. Abbreviations used include PR (partial response), SD (stable disease), PD (progressive disease), MSI-H (microsatellite instability high), and MSS/MSI-L (microsatellite stable or microsatellite instability low).

In this report, we evaluated SHR7390 as monotherapy in patients with advanced solid tumors and in combination with camrelizumab in patients with treatment-refractory advanced or metastatic colorectal cancer (CRC) across two phase I trials. In the monotherapy study, three patients experienced dose-limiting toxicities (DLTs), all in the 1.0 mg cohort, leading to a maximum tolerated dose (MTD) of 0.75 mg. The combination regimen demonstrated a tolerable safety profile, with one DLT (grade 3 rash) in the 0.5 mg cohort and no MTD reached. The objective response rate (ORR) was 22.7%, and the disease control rate (DCR) was 36.4% in the combination trial.

The predominant treatment-related adverse events (TRAEs) in both trials included skin toxicities, gastrointestinal issues, and neurologic effects. Prior investigations of MEK inhibitors have documented frequent skin toxicities and gastrointestinal disturbances, aligning with our observations [3, 10, 34]. Common events such as rash, diarrhea, and stomatitis represent characteristic MEK inhibitor toxicities [3, 10, 34]. For instance, in patients with advanced solid tumors treated with trametinib, treatment-related rash or acneiform dermatitis occurred in 80%,

diarrhea in 42%, nausea in 28%, and vomiting in 17% [3]. A phase I trial of binimetinib in advanced solid tumors reported combined rash (any cause) in 81%, diarrhea in 51%, nausea in 56%, and vomiting in 52% [10]. Cobimetinib was linked to rash in 54%, diarrhea in 61%, nausea in 26%, and vomiting in 23% in a phase I study of advanced solid tumors [6]. In our SHR7390 monotherapy trial, rash remained the most prevalent TRAE (75.0%). However, diarrhea (18.8%) and vomiting (0%) rates were lower than those in other MEK inhibitor studies. Laboratory abnormalities, including elevated aspartate aminotransferase (68.8%) and alanine aminotransferase (62.5%)—less frequently seen with other MEK inhibitors—ranked among the common TRAEs in the monotherapy trial.

We observed notable SHR7390-associated neurologic toxicities, such as somnolence (50.0% in monotherapy and 54.5% in combination), dizziness (25.0% and 18.2%), hallucinations (6.3% and 22.7%), delirium (12.5% and 0%), insomnia (12.5% and 4.5%), and abnormal dreams (12.5% and 0%). Similar neurologic effects have been reported with other MEK inhibitors, including dizziness in 15% of patients in a binimetinib phase I dose-escalation study [10], and infrequent abnormal dreams, syncope, and somnolence with refametinib [35]. Most neurologic events in our trials were grade 1 or 2 and manageable with early intervention and supportive care, except for one grade 5 increased intracranial pressure in the combination trial. To date, no prior reports link increased intracranial pressure to this combination or its individual agents. The underlying mechanism of these neurologic toxicities is unclear and warrants close monitoring in subsequent trials.

Ocular toxicities are recognized as a class effect of MEK inhibition [36]. In our studies, drug-related retinal disorders affected six patients in monotherapy and one in combination, with blurred vision in four combination patients. These findings reinforce the common occurrence of ocular toxicities with MEK inhibitors and the need for vigilance in future research. Cardiac toxicities have appeared in multiple MEK inhibitor studies [3, 35, 37], including decreased left ventricular ejection fraction in 8% of trametinib-treated patients (with 2% grade 3) [3]. Notably, cardiac dysfunction was rare in our trials.

In the monotherapy trial, no objective responses occurred, likely due to insufficient clinically effective MEK inhibitor exposure amid rising toxicities, alongside potential MAPK pathway resistance mechanisms. Combination strategies may thus offer promise. The MAPK pathway contributes to immune evasion via upregulation of immunosuppressive cytokines [38]. MEK inhibition can enhance tumor T-cell infiltration and synergize with immune checkpoint inhibitors [13, 14]. Here, SHR7390 plus camrelizumab yielded clinical benefit in 5 of 22 patients (22.7%) with treatment-refractory advanced or metastatic CRC, including durable responses of 8 to 31 months. Three patients with stable disease achieved prolonged progression-free survival, contributing to a DCR of 36.4%.

Immune checkpoint inhibitors provide substantial benefit in microsatellite instability-high (MSI-H) advanced solid tumors [39, 40], particularly MSI-H metastatic CRC [24, 27]. In contrast, microsatellite-stable (MSS)/MSI-low CRC—the majority of cases—responds poorly to checkpoint inhibitor monotherapy [41]. In our trial, all three MSI-H patients responded to the combination (durations 31.4+, 11.0+, and 10.1+ months), and crucially, 2 of 18 MSS/MSI-low patients achieved partial response (11.1%; durations 13.4 and 8.1 months). The IMblaze370 trial of atezolizumab plus cobimetinib reported objective responses in only 3 of 180 CRC patients (1.7%; mostly MSS/MSI-low or unknown MSI) [42]. BRAF mutations occur in ~8% of metastatic CRC cases and portend poor prognosis [43]. One of three MSS/MSI-low BRAF-mutant patients in our combination trial attained partial response. Despite limited sample size precluding definitive conclusions, these data suggest potential antitumor activity independent of MSI or BRAF status. Metastatic CRC is heterogeneous, and the mechanisms underlying dual MEK and checkpoint inhibition remain incompletely understood. Absence of biomarker assessment in this study prevented identification of predictive markers. Larger trials incorporating biomarker analyses are needed to confirm these findings and select patients likely to benefit from this regimen.

Conclusion

SHR7390 (0.5 mg once daily) combined with camrelizumab (200 mg every 2 weeks) exhibited a manageable safety profile in treatment-refractory advanced or metastatic CRC. Early evidence of clinical activity emerged irrespective of MSI and BRAF status, supporting further investigation in future studies.

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