A Phase 1 Study of SHR6390, A Cyclin-dependent Kinase 4/6 Inhibitor in Patients with Advanced Breast Cancer

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Abstract

Background: SHR6390 is a novel inhibitor of cyclin-dependent kinase 4/6 which demonstrated promising anti-tumor potency in preclinical models. This first-in-human study was conducted to evaluate the tolerability, pharmacokinetics, safety, and preliminary antitumor activity of SHR6390 in patients with advanced breast cancer (ABC).

Methods: In this open-label, phase 1 study, patients who had failed standard therapy were enrolled to receive oral SHR6390 in 3 + 3 dose-escalation pattern at doses of 25–175 mg. Eligible patients were given a single-dose of SHR6390 in week 1, followed by once daily continuous doses for three weeks, and one week off in 28-day cycles. Based on the tolerability, pharmacokinetics, and activity data revealed from the dose-escalation phase, three dose cohorts were selected to expand to 8–10 patients. The primary endpoints were maximum tolerated dose (MTD) and pharmacokinetics.

Results: Between Apr 15, 2016 and Dec 21, 2018, 40 patients were enrolled; all were diagnosed of hormone receptor-positive and HER2-negative ABC. SHR6390 100 mg, 125 mg, and 150 mg cohorts were expanded to 10 patients. No dose limiting toxicity was observed and the MTD was not reached. Adverse events (AEs) of grade 3 or 4 were observed in 22 (55.0%) of 40 patients, being neutropenia (52.5%), leukopenia (35.0%), thrombocytopenia (5.0%), and hypertension (2.5%). No serious AEs were reported. At the doses of 50–175 mg, steady state areas under the concentration-time curve and peak concentration increased almost proportionally with dose. The disease control rate (DCR) was 62.5% (25/40, 95% CI: 45.8–77.3). Two patients (5%; 125 mg and 150 mg cohorts) achieved partial response, with responses lasting 169 and 356+ days, respectively. Among the three expansion cohorts, the 150 mg cohort had the numerically highest DCR of 80.0% (95% CI: 44.4—97.5) and longest median progression-free survival of 8.4 months (95% CI: 2.1—not reached).

Conclusions: SHR6390 showed acceptable safety profile and dose-dependent plasma exposure in patients with ABC. The recommended phase 2 dose was 150 mg. Preliminary evidence of clinical activity was observed, which warrants further validation.

Trial registration: ClinicalTrials.gov identifier: NCT02684266. Registered Feb 17, 2016. https://clinicaltrials.gov/ct2/show/NCT02684266.

Background

Cell cycle dysregulation and aberrant cell proliferation are a hallmark of cancer [1]. The cyclin D (CCND)–cyclin-dependent kinases 4/6 axis (CDK 4/6), which modulates the transition through the G_1 phase to S phase of the cell cycle, plays a key role in the pathological process of many cancer types [2]. CDK 4 and 6 can interact with CCNDs to promote the phosphorylation of the tumor-suppressor retinoblastoma protein (Rb) and the release of Rb-bound E2F transcription factor, enabling cell cycle progression from G_1 [3]. In

addition, selective CDK 4/6 inhibition allows preferential inhibition of oncogenic events while sparing toxicity in normal tissues and therefore represents an appealing therapeutic strategy for cancer [3,4].

Endocrine therapy is the cornerstone in the treatment of hormone receptor (HR)-positive advanced breast cancer (ABC). Nevertheless, acquired resistance to endocrine therapy inevitably develops during the course of treatment [5]. Estrogen-mediated hyperactivity of the CCND–CDK4/6 axis is a central feature of HR-positive breast cancer, and the tumors usually retain a functional Rb [6], which can be targeted by CDK 4/6 inhibitors. To date, three CDK 4/6 inhibitors including palbociclib, ribociclib, and abemaciclib have been approved by the US Food and Drug Administration in combination with endocrine therapy as the first- and second-line treatment for HR-positive and human epidermal growth factor receptor 2 (HER2)-negative ABC. In pivotal trials, the addition of these CDK 4/6 inhibitors to standard endocrine therapy substantially improved progression-free survival (PFS) and overall survival [7–15]. Abemaciclib has also been approved as a monotherapy for HR-positive and HER2-negative breast cancer progressing on prior endocrine therapy or chemotherapy in the metastatic setting [11].

SHR6390 is a novel, highly selective, small molecule CDK4/6 inhibitor that demonstrated anti-tumor activity in a variety of in-vitro and xenograft models primarily via Rb-dependent cytostasis [16,17]. In vivo xenografts, SHR6390 generally showed similar or slightly better anti-tumor potency compared with palbociclib, without inducing noticeable toxicity [17]. Moreover, in HR-positive breast cancer cell lines and xenografts, SHR6390 could overcome acquired drug resistance to endocrine therapy [17]. Based on these preclinical evidences, we conducted a first-in-human, phase 1 trial to assess the safety, tolerability, pharmacokinetics (PK) and preliminary efficacy of oral SHR6390 in patients with HR-positive and HER2-negative ABC.

Methods

Study design

This open-label, phase 1 trial in patients with ABC was conducted in China (ClinicalTrials.gov identifier: NCT02684266). The study consisted of dose-escalation and dose-expansion phases. In the dose-escalation phase, the primary objective was to establish the maximum tolerated dose (MTD) for oral SHR6390. In the dose-expansion phase, three selected dose cohorts were expanded to further characterize the safety profile, tolerability, PK parameters and preliminary anti-tumor activity of SHR6390.

Patients

Eligible patients were aged 18-65 years, with histologically confirmed ABC who failed standard therapy. Other inclusion criteria included Eastern Cooperative Oncology Group performance status 0-1, life expectancy ≥ 3 months, adequate bone marrow function (hemoglobin > 110 g/L, neutrophils > 2.0×10^9 per L and platelets > 100×10^9 per L), adequate liver or renal function (total bilirubin < 1.5 times the upper

limit of normal [ULN], alanine transaminase [ALT] and aspartate aminotransferase [AST] ≤ 1.5 times ULN [≤ 5 times ULN in the presence of liver metastases] and creatinine ≤ 1 ULN), and adequate cardiac function (left ventricular ejection fraction ≥ 50% and Fridericia corrected-QT interval < 450 ms in males or < 470 ms in females). The key exclusion criteria were prior or current treatment with CDK4/6 targeted therapy, cytotoxic chemotherapy within three weeks (six weeks for mitomycin C or nitrosamine) or any other anti-tumor therapy within three weeks (except for endocrine therapy, which had to be discontinued before the time of informed consent), untreated or uncontrolled/unstable brain metastases (as judged by the investigator) or requirement of long-term use of steroids.

Procedures

For dose escalation, a traditional 3 + 3 design was used with three to six patients enrolled per dose level and the escalation continued until two or more patients had dose-limiting toxicities (DLTs) in one dose cohort during the DLT assessment period (from the administration of the first study dose to the end of the first cycle). The starting dose of SHR6390 was 25 mg and was escalated by 25 mg increments up to 175 mg (25 mg, 50 mg, 75 mg, 100mg, 125 mg, 150 mg and 175 mg) in a modified Fibonacci schema. At 25 mg dose level, one patient was enrolled as a sentinel; if no grade ≥ 2 toxicity was observed during the sentinel patient's DLT assessment period, escalation could proceed to 50 mg dose level immediately. DLT was defined as an adverse event (AE) that met any of the following criteria: grade 4 hematologic toxicity, grade 3 neutropenia with infection or fever ≥ 38.5℃, grade 3 thrombocytopenia with apparent clinical bleeding tendency, grade ≥ 3 non-hematologic toxicity (excluding untreated nausea, vomiting, and diarrhea or AEs considered tolerable by the patients, such as alopecia) or grade ≥ 2 cardiac or renal toxicity. Based on the tolerability, PK, and anti-tumor activity revealed from dose-escalation phase, three dose cohorts were selected to expand to 8—10 patients.

All patients were first given a single dose of oral SHR6390. After a ≥ 7-day washout period, the patient was then administered once-daily continuous doses of SHR6390 for three weeks in 28-day cycles. Dose interruption or reduction was permitted after the initiation of the second cycle of treatment. Patients who achieved complete response [CR], partial response [PR] or stable disease [SD]) at first efficacy assessment after receiving two cycles of SHR6390 could continue treatment until disease progression, intolerable toxicity, withdrawal of patient consent or investigator decision.

Endpoint

The primary endpoint was MTD of oral SHR6390 and pharmacokinetic parameters in patients with ABC. MTD was the highest dose level at which <33% of the patients reported a DLT within the first cycle of multiple dosing. The secondary endpoints included safety and the investigator-assessed objective response rate (ORR, defined as the proportion of patients with CR and PR as the best overall response) and disease control rate (DCR, defined as the proportion of patients with CR, PR or SD ≥ 6 weeks) per RECIST v1.1.

Assessment

Safety was regularly monitored from the time of informed consent until 30 days after the last dose of study drug. AEs were graded according to Common Terminology Criteria for Adverse Events v4.0. Tumor response was assessed using computerized tomography or magnetic resonance imaging at baseline and every two cycles after the start of multiple once-daily dosing. The response was classified as CR, PR, SD or progressive disease (PD) according to RECIST v1.1 by the investigators [18]. A CR or PR was required to be confirmed with a subsequent scan four weeks after the initial assessment.

For PK analysis, blood samples were collected in all enrolled patients from predose and at intervals up to 24 h (0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h and 24 h) on day 1 and every 24 h thereafter through day 6 at a single dose stage; and on day 1 (predose), day 8 (predose), day 15 (predose), day 21 (predose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 10 h postdose) and day 22 through day 26 (every 24 h) of cycle 1 at the multiple-dose stage. The plasma concentrations of SHR6390 were measured by liquid chromatography with tandem mass spectrometry.

Statistics

The DLT analysis set included all patients who received at least one dose of the study drug and completed the first cycle of treatment or discontinued study drug due to AE during the first cycle of treatment. PK was analyzed in patients who received at least one dose of the study drug and had evaluable post-treatment PK data. Safety and efficacy were analyzed in all patients who received at least one dose of the study drug. Descriptive statistics were reported for the safety and efficacy outcomes and PK parameters. The ORR and DCR were calculated, with the corresponding 95% Clopper-Pearson confidence intervals (CIs) provided. The Kaplan-Meier method was used to analyze PFS, and the median PFS (month) was estimated. The two-sided 95% CI of the median PFS was calculated by the Brookmeyer Crowley method. PK parameters were analyzed using the non-compartmental model with WinNonlin 7.0 (Pharsight, Mountain View, CA). Statistical analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics and deposition

Between Apr 15, 2016 and Dec 21, 2018, 58 patients were screened. Among them, 40 patients were enrolled and received SHR6390. All patients were diagnosed of HR-positive and HER2-negative stage IV ABC. 45.0% of patients had at least three lines of prior chemotherapies and 55.0% had at least two prior endocrine therapies (Table 1). The median follow-up was 7.0 months (range, 2.7 − 35.0). The main reason for treatment discontinuation was disease progression (28 patients, 70.0%). At data cutoff (Jun 28, 2019), treatment was still on-going in 10 patients (25.0%). No deaths were reported.

Table 1
Demographics and baseline disease characteristics.

	25 mg (n = 1)	50 mg (n = 3)	75 mg (n = 3)	100 mg (n = 10)	125 mg (n = 10)	150 mg (n = 10)	175 mg (n = 3)	All patients (n = 40)
Age, years	50 (50–50)	52 (51–64)	53 (48–63)	58 (39–65)	54 (26–63)	55 (39–65)	51 (51–64)	54 (26–65)
Sex								
Female	1 (100)	3 (100)	3 (100)	10 (100)	10 (100)	10 (100)	3 (100)	40 (100)
ECOG performance status								
0	1 (100)	3 (100)	2 (66.7)	4 (40.0)	10 (100)	9 (90.0)	3 (100)	32 (80.0)
1	0	0	1 (33.3)	6 (60.0)	0	1 (10.0)	0	8 (20.0)
Time since first diagnosis, years	10.9 (10.9–10.9)	5.2 (1.7–11.9)	5.9 (2.4–12.0)	9.6 (4.9–20.3)	6.8 (1.4–20.1)	11.3 (1.0–19.6)	8.2 (8.2–10.5)	8.8 (1.0–20.3)
Tumor stage at study entry								
IV	1 (100)	3 (100)	3 (100)	10 (100)	10 (100)	10 (100)	3 (100)	40 (100)
Previous therapy								
Surgery	1 (100)	3 (100)	3 (100)	10 (100)	10 (100)	10 (100)	3 (100)	40 (100)
Radiotherapy	1 (100)	3 (100)	3 (100)	8 (80.0)	5 (50.0)	8 (80.0)	3 (100)	31 (77.5)
Chemotherapy								
1–2 regimens	0	0	2 (66.7)	2 (20.0)	4 (40.0)	3 (30.0)	2 (66.7)	13 (32.5)
3–6 regimens	1 (100)	0	1 (33.3)	6 (60.0)	4 (40.0)	5 (50.0)	1 (33.3)	18 (45.0)

Data are n (%) or median (range).

ECOG, Eastern Cooperative Oncology Group.

	25 mg (n = 1)	50 mg (n = 3)	75 mg (n = 3)	100 mg (n = 10)	125 mg (n = 10)	150 mg (n = 10)	175 mg (n = 3)	All patients (n = 40)
Endocrine therapy								
1–2 regimens	0	1 (33.3)	2 (66.7)	4 (40.0)	4 (40.0)	6 (60.0)	3 (100)	20 (50.0)
3–6 regimens	1 (100)	0	1 (33.3)	3 (30.0)	3 (30.0)	3 (30.0)	0	11 (27.5)
Data are n (%) or median (range).								
ECOG, Eastern Cooperative Oncology Group.								

Safety and tolerability

SHR6390 was dose escalated from 25 mg QD to 175 mg QD. No DLT was observed in all dose cohorts within the first cycle of treatment and MTD was not reached. With PK analysis showing increased exposure (C_{max}, C_{min}, AUC_{ss}) of SHR6390 and increased occurrence of neutropenia and leukopenia within first cycle (indicator of pharmacodynamics) at doses of 50 − 150 mg, and the best overall response of SD or better for all patients at 100 − 150 mg (4/7 PD at 25 − 75 mg and 1/3 PD at 175 mg), 150 mg was first selected for expansion. Then with safety as a main consideration (8/10 with grade 3 and 1/10 with grade 4 neutropenia for the 150 mg cohort), the 125 mg and 100 mg cohorts were subsequently expanded to 10 patients. Overall, no DLT was observed in the expansion cohorts within the pre-specified assessment window. With extended exposure beyond cycle 1 of treatment, a total of two cases of DLTs (grade 4 neutropenia; one in 100 mg and one in 150 mg cohort) were reported.

The median duration of treatment exposure was 123 days (range, 56 − 1063). No patients discontinued treatment due to AEs. All patients in the study had at least one treatment-emergent AE (TEAE) and the majority were transient laboratory abnormalities and low grade non-hematologic AEs (Table 2). TEAEs of grade 3 or 4 were observed in 22 (55.0%) of 40 patients, being neutropenia (52.5%), leukopenia (35.0%), thrombocytopenia (5.0%), and hypertension (2.5%). No serious AEs or grade 5 AEs were reported.

Table 2
Treatment-emergent adverse events occurring in ≥ 20% of patients.

	All patients (n = 40)	
	Any grade	Grade 3 or 4
Neutropenia	40 (100)	21 (52.5)
Leukopenia	40 (100)	14 (35.0)
AST increased	16 (40.0)	0
Fatigue	15 (37.5)	0
Blood creatinine increased	14 (35.0)	0
Anemia	13 (32.5)	0
ALT increased	13 (32.5)	0
Headache	13 (32.5)	0
Thrombocytopenia	11 (27.5)	2 (5.0)
Alopecia	11 (27.5)	0
Bilirubin conjugated increased	10 (25.0)	0
Decreased appetite	9 (22.5)	0
Constipation	8 (20.0)	0
Dyspnoea	8 (20.0)	0
Data are n (%). No grade 5 adverse events occurred.		
ALT, alanine aminotransferase; AST, aspartate aminotransferase.		

PK

PK parameters following single and multiple dosing of SHR6390 are presented in Table 3 and the plasma concentration-time curves are shown in Figure S1. At the doses of 50 − 175 mg, median time to peak concentration was 2.5 − 4.0 h, and geometric mean terminal half-life was 40.3 − 51.4 h after a single dose of SHR6390. Following multiple dosing, steady state SHR6390 was observed on day 8. The median time to peak concentration was 3.0 − 4.0 h, and geometric mean terminal half-life was 44.9 − 52.3 h at steady state on day 21 and the mean accumulation ratio for area under the concentration-time curve was 1.9 − 3.4 across the doses of 50 − 175 mg. The area under the concentration-time curve at steady state and peak concentration increased almost proportionally with dose increase over the dosing range of 50 −

175 mg, with steady state C_{max} at day 21 of 41.1, 53.4, 87.0, 115.0, 126.0, and 155.0 ng/mL in 50, 75, 100, 125, 150, and 175 mg cohorts, respectively (Table 3).

Table 3
Plasma pharmacokinetics of single and multiple dosing of SHR6390.

	50 mg QD	75 mg QD	100 mg QD	125 mg QD	150 mg QD	175 mg QD
Single dosing	n = 3	n = 3	n = 10	n = 10	n = 10	n = 3
T_{max}, h	3.0 (2.0–4.0)	3.0 (3.0–3.0)	2.5 (2.0–4.0)	3.5 (2.0–6.0)	3.5 (2.0–4.0)	4.0 (3.0–4.0)
C_{max}, ng/mL	12.2 (57.3)	20.3 (37.3)	46.8 (27.5)	46.6 (56.8)	63.6 (64.4)	114.0 (37.8)
AUC_{0-t}, h*ng/mL	482 (40)	572 (13)	1170 (20)	1480 (38)	1880 (57)	3080 (24)
$t_{1/2z}$, h	51.0 (13.6)	46.9 (8.0)	49.7 (16.6)	43.7 (23.5)	51.4 (23.2)	40.3 (22.4)
CL/F, L/h	89.8 (39.2)	117.0 (15.7)	76.1 (20.7)	76.6 (37.8)	70.5 (51.9)	52.8 (21.8)
V_z/F, L	6610 (40)	7900 (12)	5450 (25)	4830 (45)	5230 (71)	3080 (39)
Multiple dosing	n = 3	n = 3	n = 9	n = 9	n = 9	n = 3
T_{max}, h	4.0 (4.0–6.0)	3.0 (3.0–4.0)	3.00 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–8.0)	3.0 (3.0–3.0)
C_{max}, ng/mL	41.1 (23.9)	53.4 (9.4)	87.0 (48.5)	115.0 (28.7)	126.0 (30.0)	155.0 (57.8)
AUC_{ss}, h*ng/mL	615 (27)	792 (18)	1410 (53)	2020 (32)	2230 (24)	2730 (48)
$t_{1/2z}$, h	46.9 (11.9)	52.3 (6.3)	48.2 (20.3)	44.9 (21.2)	44.9 (17.5)	45.1 (6.6)
CL_{ss}/F, L/h	81.4 (26.9)	94.7 (18.0)	71.0 (52.5)	62.0 (31.8)	67.2 (23.9)	64.1(47.8)
V_z/F, L	5510 (35)	6920 (31)	4930 (67)	4010 (30)	4350 (32)	4170 (48)
$R_{acc(AUC)}$	3.4 (41.3)	3.0 (22.1)	2.7 (35.9)	3.3 (60)	2.7 (52.8)	1.9 (37.7)

Data are median (range) for T_{max} and geometric mean (coefficient of variation%) for others.

T_{max}, time to reach C_{max}; C_{max}, peak plasma concentration; AUC_{0-t}, area under the curve from time 0 to the last measurable concentration; AUC_{ss}: area under the curve for dose interval; $t_{1/2}$, terminal half-life; CL/F, apparent clearance; V_z/F, apparent volume of distribution; $R_{ac\ (AUC)}$, accumulation ratio for AUC.

Efficacy

All 40 patients with HR-positive and HER2-negative ABC were evaluable for tumor response. Of those, two patients (5%) achieved PR: one patient (125 mg cohort) had previously received two lines of chemotherapy for ABC and partial response was initially observed at cycle-8 tumor assessment visit and lasted for 169 days; the other patient (150 mg cohort) had previously received six regimens of endocrine therapy and partial response was initially documented at cycle-4 tumor assessment visit and lasted for 356 + days. A total of 23 (57.5%) patients across 50 – 175 mg dose cohorts had best overall response with stable disease and the median duration was 4.0 month (inter-quartile range, 2.1—7.6). The overall DCR was 62.5% (95% CI: 45.8—77.3) in all patients (Table 4). By data cutoff, a total of 26 disease progression events occurred. Median PFS was 4.0 month (95% CI: 2.4—9.1) in all 40 patients and 5.9 months (95% CI: 2.4—9.1) in 30 patients at three dose levels with expansion cohorts. Among the three dose cohorts with expansion, the 150 mg cohort had the numerically highest DCR of 80.0% (95% CI: 44.4—97.5) and longest median progression-free survival of 8.4 months (95% CI: 2.1—not reached).

Table 4
Tumor response per RECIST v1.1.

	25 mg (n = 1)	50 mg (n = 3)	75 mg (n = 3)	100 mg (n = 10)	125 mg (n = 10)	150 mg (n = 10)	175 mg (n = 3)	All patients (n = 40)
Best overall response, n (%)								
Complete response	0	0	0	0	0	0	0	0
Partial response	0	0	0	0	1 (10.0)	1 (10.0)	0	2 (5.0)
Stable disease	0	2 (66.7)	1 (33.3)	7 (70.0)	4 (40.0)	7 (70.0)	2 (66.7)	23 (57.5)
Progressive disease	1	1 (33.3)	2 (66.7)	3 (30.0)	5 (50.0)	2 (20.0)	1 (33.3)	15 (37.5)
DCR, % (95% CI)	0 (NR)	66.7 (9.4–99.2)	33.3 (0.8–90.6)	70.0 (34.8–93.3)	50.0 (18.7–81.3)	80.0 (44.4–97.5)	66.7 (9.4–99.2)	62.5 (45.8–77.3)

DCR, disease control rate; NR, not reached; RECIST, response evaluation criteria in solid tumors.

Discussion

The findings from this first-in-human, phase 1 trial showed that oral SHR6390 with a 3-week on and 1-week off dosing regimen was well-tolerated in patients with ABC, with no MTD observed up to the highest dose tested. TEAEs were generally manageable with no treatment discontinuation due to AEs or serious AEs documented. At doses of 50–175 mg, plasma exposure increased almost proportionally with dose. Preliminary evidence of clinical activity of SHR6390 in HR-positive and HER2-negative ABC was also observed, with a DCR of 62.5%.

During dose-escalation and expansion, no DLT was observed in all patients within the first cycle of treatment. With extended exposure beyond cycle 1 of treatment, a total of two cases of grade 4 hematologic AEs (neutropenia; one in 100 mg and one in 150 mg cohort) were observed, suggesting a general low rate of late onset severe toxicity. Consistent with the safety profile of other CDK 4/6 inhibitors (palbociclib and ribociclib) [19–21], the most frequent grade 3 or 4 AEs of SHR6390 were neutropenia and leukopenia, observed in 52.5% and 35.0% of patients respectively. All the hematologic AEs were managed with dose interruption and/or reduction and standard supportive care (granulocyte colony-stimulating factor etc.) and the abnormalities resolved immediately with no related complications such as fever or infection. The myelosuppressive effects of SHR6390 were considered an on-target effect due to the involvement of CDK6 in the proliferation of hematological precursors [22] and the cytostasis induced in G_1 phase by SHR6390 was reversible when the drug was held. Other frequent AEs included liver function test abnormalities and systemic symptoms such as fatigue, headache and alopecia; all were of grade 1–2 severity. Taken together, SHR6390 with a 3-week on/1-week off dosing regimen is well-tolerated with a manageable safety profile in patients with ABC.

Despite the initial success of endocrine therapy in the treatment of HR-positive and HER2-negative ABC, nearly all patients will develop acquired drug resistance with prolonged treatment [5]. In this phase 1 trial, our study subjects represented a heavily pretreated population with 55.0% receiving at least two prior endocrine therapies and 45.0% receiving at least three lines of prior chemotherapies. Clinical activity of single agent SHR6390 in HR-positive and HER2-negative ABC was demonstrated with an overall DCR of 62.5% (95% CI: 45.8–77.3) across all dose levels, consistent with the preclinical evidence that SHR6390 could overcome the resistance to an endocrine agent (tamoxifen) [17]. Despite the modest ORR rate (5%), SHR6390 was notable for the durable disease control, with a median duration of 4.0 months. Among all therapeutic dose levels with an expansion cohort (100–150 mg), patients treated with 150 mg QD SHR6390 appeared to derive the greatest clinical benefit, with a DCR of 80.0% (95% CI: 44.4–97.5) and a median PFS of 8.4 months. Taken together with the dose-dependent increase in systemic exposure of SHR6390 (C_{max}, C_{min}, AUC_{ss}) and the overall tolerability at doses of 100–150 mg, 150 mg QD was selected as the recommended phase 2 dose for ABC. In previous phase 2 trials of CDK 4/6 inhibitors on HR-positive, and HER2-negative metastatic breast cancer, treatment with single agent abemaciclib yielded a DCR of 66.7% and a median PFS of 5.9 months in a heavily pretreated population (median prior lines of therapy, two for endocrine agents, one for chemotherapy) whereas single agent palbociclib yielded a similar DCR of 63.8% and a median PFS of 6.5 months in a moderately pretreated population (69% with one line of prior endocrine therapy, 28% with prior chemotherapy) [20,23]. Within the limitations of cross-trial

comparison, the anti-tumor activity of single agent SHR6390 reported in this trial was comparable to abemaciclib and palbociclib in treatment of ABC. In general, our results were encouraging considering that the efficacy data of SHR6390 were derived from a heavily pre-treated population with refractory disease and from single agent treatment. Given the established synergic effects of SHR6390 with letrozole, anastrozole and fulvestrant in a phase Ib trial (NCT03481998, Hengrui data on file) and the purpose to further improve anti-tumor activities, SHR6390 is currently under evaluation in combination with endocrine therapy for HR-positive, and HER2-negative ABC in two phase 3 trials: one in combination with letrozole or anastrozole in the frontline setting (NCT03966898) and one in combination with fulvestrant in the later-line setting (NCT03927456).

In summary, SHR6390 showed acceptable safety profile and dose-dependent plasma exposure in patients with ABC. The recommended phase 2 dose was determined to be 150 mg QD. Preliminary evidence of clinical activity of SHR6390 was observed.

List Of Abbreviations

ABC, advanced breast cancer; AE, adverse events; ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval; CCND, cyclin D; CDK 4/6, cyclin-dependent kinases 4/6; CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; Rb, retinoblastoma protein; SD, stable disease; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Declarations

Ethics approval and consent to participate

This trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the ethics committee of the Cancer Hospital of the Chinese Academy of Medical Sciences (Beijing, China) and regulatory authorities. All patients provided written informed consent before enrollment.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Disclosure

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Authors' contributions

Concept and design: BX, PZ, and JZ. Acquisition of data: BX, PZ, LG, WW, and MX. Data analysis: XZhang and GS. Interpretation of data: all authors. Drafting of the manuscript: BX, PZ, XZhang, GS, and XZhu. Critical revision of the manuscript for important intellectual content: all authors. Approval of the final manuscript: all authors.

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