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Phase 1b study of first-line fuzuloparib combined with modified FOLFIRINOX followed by fuzuloparib maintenance monotherapy in pancreatic adenocarcinoma

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Abstract

Background Chemotherapy remains the standard first-line treatment for pancreatic adenocarcinoma, but with limited efficacy. We aimed to explore the feasibility of adding the PARP inhibitor fuzuloparib to mFOLFIRINOX in the locally advanced/metastatic (LA/M) setting.

Methods This was the dose-escalation and -expansion, phase 1b portion of a phase 1b/2 study. Patients were given oral fuzuloparib at escalating doses starting at 30 mg twice daily (BID) plus intravenous mFOLFIRINOX q2w for 8–12 cycles, followed by maintenance fuzuloparib at 150 mg BID. Cohorts at the maximal tolerated dose (MTD) and lower dose of fuzuloparib were expanded. Primary endpoints were dose-limiting toxicity (DLT), MTD, and recommended phase 2 dose (RP2D).

Results As of data cutoff on Jan 15, 2023, 39 patients were recruited. 12 patients were enrolled during dose escalation (30 mg [$n=4$]; 60 mg [$n=6$]; 100 mg [$n=2$]). DLT occurred in 1 patient in 60 mg cohort and 1 patient in 100 mg cohort. 60 mg BID was determined to be the MTD, and then 60 and 30 mg cohorts were expanded to 22 and 15 patients, respectively. The most common grade ≥ 3 treatment-related adverse events were hematologic toxicities. Efficacy in 60 mg cohort seemed to be most favorable, with an objective response rate of 50.0% (95% CI, 26.0–74.0) and disease control rate of 94.4% (95% CI, 72.7–99.9).

Conclusions First-line fuzuloparib plus mFOLFIRINOX followed by maintenance fuzuloparib was generally safe and showed encouraging anti-tumor activity in patients with LA/M pancreatic adenocarcinoma. The RP2D of fuzuloparib combination was 60 mg BID.

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Keywords Pancreatic cancer, Fuzuloparib, Chemotherapy, First-line, Maintenance

Background

Pancreatic cancer is a highly lethal malignant tumor and ranks as the seventh leading cause of cancer-related deaths worldwide for both men and women [1]. It is often asymptomatic at the early stage, and the deep-seated location of the pancreas makes it difficult to detect tumors in this organ. As a result, a large proportion of patients present with advanced (30–35%) or metastatic (50–55%) disease at diagnosis, which unfortunately eliminates the possibility of surgical resection [2–6]. Chemotherapy remains the standard first-line systemic treatment for pancreatic cancer, including AG (nab-paclitaxel plus gemcitabine), FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and fluorouracil), and modified FOLFIRINOX (mFOLFIRINOX) with reduced drug doses. However, only 23–35% of unresectable patients could achieve a response to these chemotherapy regimens, and the progression-free survival (PFS) and overall survival (OS) benefits are far from satisfactory [7–9]. Additional effective treatment strategies are urgently needed.

Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors have been developed with the concept of synthetic lethality, by targeting tumor cells with a homologous recombination repair (HRR) deficiency. Mutations in genes involved in HRR pathway have been identified in pancreatic cancer, such as *BRCA1*, *BRCA2*, *ATM*, and *PALB2* [10–13], providing a strong rationale for the clinical investigation of PARP inhibitors for the treatment of pancreatic cancer. In fact, olaparib has been approved as maintenance therapy in patients with *BRCA*-mutated metastatic pancreatic cancer who have response or stable disease after 4–6 months of first-line platinum-based chemotherapy. Several single-agent PARP inhibitors demonstrated modest activity in the later-line setting, with an objective response rate (ORR) ranging from 16% to 22% [14–16]. However, mutations in the *BRCA1/2* genes are present in only 5–9% of patients with pancreatic cancer [3, 17]. It has been reported that in other specific cancers, some patients without *BRCA1/2* mutations also could respond to PARP inhibitors [18, 19]. Our efforts are underway to ascertain the broad applicability of PARP inhibitors in pancreatic cancer.

Fuzuloparib, an orally administered PARP inhibitor, demonstrated almost complete inhibitor of PAR formation and potent anti-tumor activity in preclinical models [20]. It has been approved in China as monotherapy for patients with germline *BRCA*-mutated platinum-sensitive recurrent ovarian cancer and as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer regardless of *BRCA* mutational status [18, 21]. Given the potential synergistic effect between DNA-damaging agents and PARP inhibitors as well as the effectiveness of PARP inhibitors as maintenance treatment in multiple cancer types [22–25], we initiated this study to explore the feasibility of fuzuloparib in combination with first-line mFOLFIRINOX followed by fuzuloparib maintenance in patients with genetically unselected, locally advanced or metastatic pancreatic adenocarcinoma.

Methods

Study design and treatment

This multicenter, phase 1b/2 study consisted of an open-label, dose-escalation and -expansion, phase 1b portion and a randomized, double-blind, placebo-controlled, phase 2 portion (ClinicalTrials.gov, NCT04228601). Here, we reported the findings of the phase 1b portion.

In the dose-escalation phase, a standard 3 + 3 design was adopted to assess the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of fuzuloparib, when combined with mFOLFIRINOX. Patients were given fuzuloparib (planned escalating doses, 30, 60, 100, and 150 mg; orally twice daily [BID]) in combination with mFOLFIRINOX regimen (oxaliplatin, 85 mg/m^2, D1; leucovorin, 400 mg/m^2, D1; irinotecan, 150 mg/m^2, D1; and fluorouracil, 2400 mg/m^2 given as a 46-h continuous infusion; every 2 weeks) for 8 to 12 cycles, followed by maintenance with fuzuloparib monotherapy at 150 mg BID. Fixed dose of fuzuloparib was used for maintenance, as the MTD of single-agent fuzuloparib was determined to be 150 mg BID, based on the results of the phase 1 clinical study of fuzuloparib in advanced solid tumors [26]. A treatment cycle was defined 2 weeks for both the combination and maintenance therapy. DLTs were observed during the first 2 treatment cycles. During the observation period, primary prophylaxis of neutropenia with granulocyte colony-stimulating factor (G-CSF) was not permitted. However, if grade ≥ 3 decreased neutrophil count occurred, administration of G-CSF (5 μg/kg/day) was recommended for symptomatic management, as well as for prophylactic use in subsequent chemotherapy cycles.

In the dose-expansion phase, cohorts with the MTD and lower dose of fuzuloparib would be expanded to

further collect safety, pharmacokinetics, and efficacy data for the determination of recommended phase 2 dose (RP2D). Primary prophylactic use of G-CSF was allowed. The study treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal by patient or investigator, whichever occurred first. Treatment interruptions and dose reduction of fuzuloparib and mFOLFIRINOX were allowed to manage toxicities. For fuzuloparib, each interruption should not exceed 14 days. For mFOLFIRINOX, resumption of treatment within 7 days after interruption was recommended; if the interruption lasted for more than 14 days, the investigator would judge, based on the benefit to the patient, whether the patient should continue with the combination therapy or enter into the maintenance therapy with fuzuloparib alone.

Patient eligibility

Eligible patients were aged ≥ 18 years and had pathologically confirmed pancreatic adenocarcinoma with distant metastatic or locally advanced disease that was not amenable to surgery, regardless of the mutation status of homologous recombination and DNA damage response gene. Prior systemic anticancer therapies for pancreatic adenocarcinoma were not permitted, with the exception of previous neoadjuvant or adjuvant chemotherapy completed at least 12 months before recurrence. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), a life expectancy of at least 6 months, and adequate organ function. Key exclusion criteria included prior PARP inhibitors; radiotherapy, investigational agents, or cellular therapies within 4 weeks prior to the start of study treatment; radiological evidence of brain metastases; and active hepatitis B or C virus infection.

Outcomes

Primary endpoints were DLT, MTD, and RP2D as determined by the safety monitoring committee and the sponsor. Secondary endpoints were safety, ORR, duration of response (DoR), disease control rate (DCR), PFS, OS, and pharmacokinetic parameters. Exploratory endpoint was carbohydrate antigen 19-9 (CA19-9) response rate.

Assessments

DLTs were defined as any of the following treatment-related adverse events (TRAEs): grade 2 cardiac insufficiency, renal impairment, or neurotoxicity; grade ≥ 3 non-hematological toxicity (with the exception of alopecia, controllable nausea or vomiting, pyrexia of known causes such as tumor or infection, and laboratory abnormalities not requiring hospitalization); grade 4 decreased neutrophil count that persisted for ≥ 5 days despite symptomatic treatment; grade 3 febrile neutropenia; grade 3 decreased platelet count with bleeding; grade 4 decreased platelet count; grade 4 anemia.

AEs were recorded from the time of informed consent to 30 days after the last dose or until the start of a new antitumor therapy, whichever occurred earlier. TRAEs were evaluated until 30 days after the last dose. All AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Tumor responses were assessed using CT and MRI by investigators at baseline and every 8 weeks after treatment, according to RECIST, version 1.1. Complete and partial responses were required to be confirmed at least 4 weeks after the first documented response. Survival was assessed every 2 months during follow-up.

The plasma concentrations of fuzuloparib were determined by using a validated high- performance liquid chromatography coupled with tandem mass spectrometry. The mutation status for HRR genes (including *ATM, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*) was tested using a custom-designed next-generation sequencing panel containing 1021 cancer-associated genes on a DNBSEQ-T7RS sequencer. The serum CA19-9 levels were monitored at baseline, every 4 weeks during treatment, and 30 days after the last dose of study treatment. CA19-9 response was defined as a ≥ 50% decrease in CA19-9 occurring at any time point versus the baseline value.

Statistical analysis

DLTs were assessed in all patients who enrolled in the dose-escalation phase, received at least one dose of study treatment, and completed the 28-day evaluation period or experienced any DLT during the period. Patients had to receive ≥ 75% of the dose of assigned therapy during the DLT observation period to be evaluable for DLT assessment. Safety, efficacy, and pharmacokinetics were analyzed in patients who received at least one dose of study treatment and had at least one corresponding post-baseline evaluation. CA19-9 response was assessed in patients with a CA19-9 level exceeded twice the upper limit of the normal range at baseline who received at least one dose of study treatment and had at least one post-baseline evaluation.

AEs were summarized descriptively. The point estimates of ORR, DCR, and CA19-9 response rate as well as their two-sided 95% CIs were calculated using the Clopper-Pearson method. Time-to-event outcomes including DoR, PFS and OS were estimated using the Kaplan-Meier

method, and their two-sided 95% CIs were calculated on the basis of the Brookmeyer-Crowley method. For patients without progression or death, PFS was censored on the date of the last imaging examination. For patients who had disease progression or died after missing two or more consecutive tumor response assessments, PFS was censored on the date of the last imaging examination before the missing visits. Pharmacokinetic parameters of fuzuloparib following single administration were determined by non-compartmental analysis methods using Phoenix WinNonlin, version 8.0 or above. Other analyses were done using SAS, version 9.4.

Results

Patients and treatment

Between May 7, 2020 and Dec 20, 2021, a total of 39 eligible patients were recruited from 6 study sites in China, and all were administrated with at least one dose of trial therapy (Fig. 1). The demographic and clinical characteristics of patients at baseline are shown in Table 1. Most patients had an ECOG performance status of 1 (34, 87.2%). 24 (61.5%) patients were male. 35 (89.7%) patients had metastases, with the most common sites being liver (28, 71.8%), regional lymph nodes (16, 41.0%), peritoneum (5, 12.8%), and lung (4, 10.3%). HRR gene mutations were detected in 5 (12.8%) patients, including 2 (5.1%) with germline mutation in *ATM*, 1 (2.6%) with somatic mutation in *ATM*, 1 (2.6%) with somatic mutation in *BRCA1* and *CHEK2*, and 1 (2.6%) with germline mutation in *FANCA*.

As of data cutoff on Jan 15, 2023, the median follow-up duration was 11.4 months (range, 0.3–32.0). Of the enrolled 39 patients, 38 discontinued all study treatment components, mainly due to radiographical progression (Fig. 1).

Tolerability

In the dose-escalation phase, 12 patients were enrolled (4 in the 30 mg cohort, 6 in the 60 mg cohort, and 2 in the 100 mg cohort). DLTs were observed in one of the 6 patients in the 60 mg cohort (grade 4 decreased platelet count and grade 4 decreased neutrophil count lasting for ≥ 5 d) and 1 of the 2 patients in the 100 mg cohort (grade 4 decreased neutrophil count lasting for ≥ 5 d; Additional file 1: Table S1). Another patient in the 100 mg cohort experienced grade 4 decreased neutrophil count and grade 3 decreased platelet count during the first treatment cycle, and study treatment was interrupted due to AEs in this patient. Thus, enrollment for the 100 mg cohort was halted, dose escalation was terminated (no

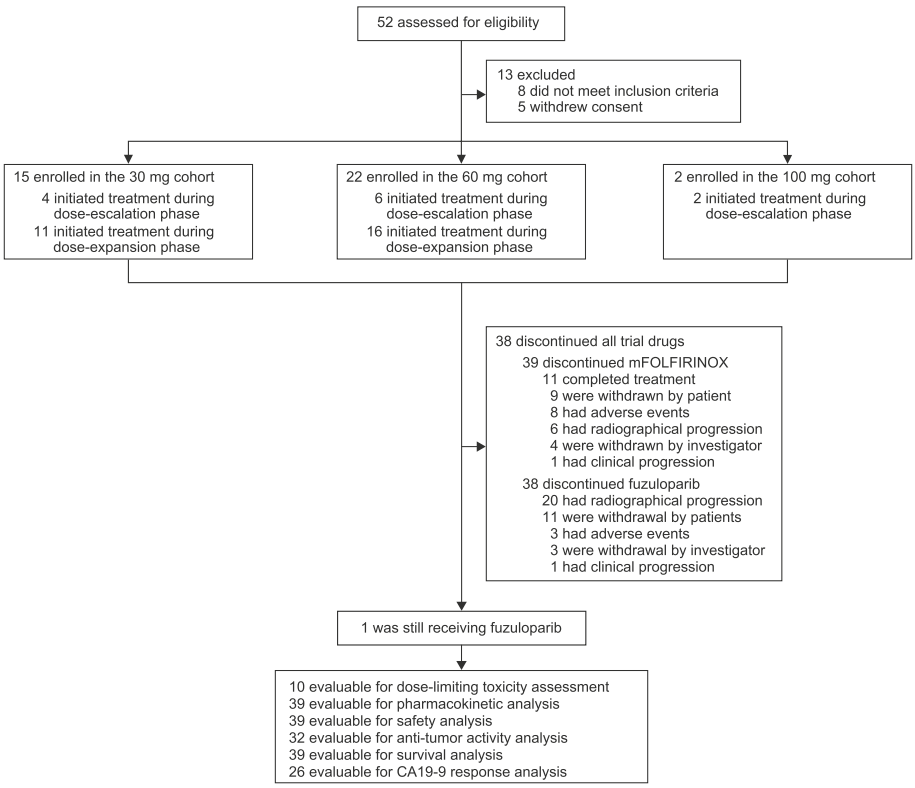

Fig. 1 Trial profile. CA19-9, carbohydrate antigen 19-9

Table 1 Patient demographics and clinical characteristics at baseline

	30 mg BID (*n* = 15)	60 mg BID (*n* = 22)	100 mg BID (*n* = 2)	Overall (*N* = 39)
Age, years	57.0 (31.0–71.0)	57.5 (32.0–74.0)	45.0 (37.0–53.0)	57.0 (31.0–74.0)
Sex				
Male	9 (60.0)	13 (59.1)	2 (100.0)	24 (61.5)
Female	6 (40.0)	9 (40.9)	0	15 (38.5)
ECOG performance status				
0	2 (13.3)	3 (13.6)	0	5 (12.8)
1	13 (86.7)	19 (86.4)	2 (100.0)	34 (87.2)
Pancreatic tumor location				
Head	5 (33.3)	7 (31.8)	0	12 (30.8)
Body	4 (26.7)	6 (27.3)	1 (50.0)	11 (28.2)
Tail	6 (40.0)	8 (36.4)	1 (50.0)	15 (38.5)
Multicentric	0	1 (4.5)	0	1 (2.6)
Disease characteristics				
Metastatic	13 (86.7)	20 (90.9)	2 (100.0)	35 (89.7)
Locally advanced	4 (26.7)	2 (9.1)	0	6 (15.4)
Number of organs with metastases[a]				
0	4 (26.7)	2 (9.1)	0	6 (15.4)
1	6 (40.0)	12 (54.5)	2 (100.0)	20 (51.3)
2	1 (6.7)	5 (22.7)	0	6 (15.4)
3	4 (26.7)	3 (13.6)	0	7 (17.9)
Common metastatic sites (≥ 10%)				
Liver	10 (66.7)	16 (72.7)	2 (100.0)	28 (71.8)
Regional lymph nodes	7 (46.7)	8 (36.4)	1 (50.0)	16 (41.0)
Peritoneum	3 (20.0)	2 (9.1)	0	5 (12.8)
Lung	1 (6.7)	3 (13.6)	0	4 (10.3)
CA19-9 level				
Normal	4 (26.7)	5 (22.7)	0	9 (23.1)
Elevated, < 59xULN	5 (33.3)	11 (50.0)	1 (50.0)	17 (43.6)
Elevated, ≥ 59xULN	1 (6.7)	3 (13.6)	0	4 (10.2)
Unknown	5 (33.3)	3 (13.6)	1 (50.0)	9 (23.1)
HRR gene mutations	2 (13.3)[c]	3 (13.6)[d]	0	5 (12.8)
Previous surgery	0	1 (4.5)	0	1 (2.6)[b]

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

ECOG Eastern Cooperative Oncology Group, *CA19-9* Carbohydrate antigen 19-9, *HRR* Homologous recombination repair

[a] did not include regional lymph nodes metastases. [b]palliative surgery. [c]1 with germline mutation in *ATM* and 1 with germline mutation in *FANCA*; [d]1 with germline mutation in *ATM*, 1 with somatic mutation in *ATM*, and 1 with somatic mutation in *BRCA1* and *CHEK2*

patient was enrolled in the 150 mg cohort), and 60 mg BID was established as the MTD. Subsequently, 60 and 30 mg cohorts were expanded to 22 and 15 patients, respectively.

Pharmacokinetics

Pharmacokinetic characteristics of fuzuloparib, when combined with mFOLFIRINOX, were available in all 39 patients enrolled in the dose-escalation and dose-expansion phases. Plasma fuzuloparib level showed an increasing trend with ascending dose (Additional file 1: Fig. S1). In the 30, 60, and 100 mg cohorts, the geometric mean maximum plasma concentrations of fuzuloparib were 992 ng/mL (percentage geometric coefficient of variation [GeoCV%], 47.5%), 1940 ng/mL (GeoCV%, 47.7%), and 3320 ng/mL (GeoCV%, 11.3%); the geometric mean area under the curve from the first dose to 10 h thereafter were 6140 h*ng/mL (GeoCV%, 42.9%), 11,900 h*ng/mL (GeoCV%, 46.6%), and 19,800 h*ng/mL (GeoCV%, 4.5%); and the median of time to peak fuzuloparib concentration after single administration were 3.00 h (range, 0.98–10.00), 2.99 h (range, 0.98–6.07), and 4.51 h (range, 2.97–6.05), respectively. The geometric mean steady-state trough concentrations of fuzuloparib were

699 ng/mL (GeoCV%, 80.6%) with 30 mg BID, 1310 ng/mL (GeoCV%, 74.6%) with 60 mg BID, and 883 ng/mL (GeoCV%, 6549.7%) with 100 mg BID.

Treatment exposure

The median cycle of combination treatment was 7 (range, 1–12). Exposure of the individual components during combination of fuzuloparib and mFOLFIRINOX are shown in Additional file 1: Table S2. The median relative dose intensity of fuzuloparib during combination in all patients was 84.6%, with the highest value observed in the 60 mg cohort (90.3%). The median relative dose intensities of chemotherapeutic agents ranged from 91.4% to 95.2%, with no obvious differences among the 3 cohorts.

After completing the combination treatment without disease progression, 21 patients received maintenance fuzuloparib (including 7 in the 30 mg cohort, 13 in the 60 mg cohort, and 1 in the 100 mg cohort), with a median treatment duration of 11.9 weeks (range, 1.3–107.9; Additional file 1: Table S3). The median relative dose intensity of fuzuloparib during maintenance was 96.0%, with similar values among the 3 cohorts.

Safety

All 39 patients were included for safety assessment. Grade ≥ 3 TRAEs were reported in 34 (87.2%) patients. The most common TRAEs of grade 3 or 4 were hematologic toxicities, including decreased neutrophil count, decreased platelet count, decreased white blood cell count, and anemia (Table 2).

TRAEs led to interruption of any study treatment component in 33 (84.6%) patients. Dose reduction of any study treatment component due to TRAEs occurred in 22 (56.4%) patients, with 10 (25.6%) patients due to AEs related to fuzuloparib and 19 (48.7%) due to AEs related to mFOLFIRINOX (Additional file 1: Table S4).

Five (12.8%) patients discontinued treatment because of TRAEs, including decreased platelet count in 3 (7.7%)

Table 2 Common TRAEs

	30 mg BID (*n* = 15)		60 mg BID (*n* = 22)		Overall (*N* = 39)	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Anemia	14 (93.3)	3 (20.0)	20 (90.9)	10 (45.5)	36 (92.3)	13 (33.3)
Neutrophil count decreased	13 (86.7)	11 (73.3)	20 (90.9)	13 (59.1)	35 (89.7)	26 (66.7)
White blood cell count decreased	13 (86.7)	6 (40.0)	18 (81.8)	10 (45.5)	33 (84.6)	17 (43.6)
Platelet count decreased	10 (66.7)	6 (40.0)	16 (72.7)	11 (50.0)	28 (71.8)	18 (46.2)
Weight decreased	9 (60.0)	0	16 (72.7)	1 (4.5)	26 (66.7)	1 (2.6)
Vomiting	10 (66.7)	1 (6.7)	12 (54.5)	0	24 (61.5)	1 (2.6)
Aspartate aminotransferase increased	11 (73.3)	0	10 (45.5)	0	23 (59.0)	0
Nausea	11 (73.3)	0	11 (50.0)	0	23 (59.0)	0
Asthenia	12 (80.0)	1 (6.7)	10 (45.5)	1 (4.5)	22 (56.4)	2 (5.1)
Decreased appetite	9 (60.0)	0	11 (50.0)	1 (4.5)	21 (53.8)	1 (2.6)
Alanine aminotransferase increased	8 (53.3)	1 (6.7)	10 (45.5)	0	20 (51.3)	1 (2.6)
Hyponatremia	9 (60.0)	2 (13.3)	10 (45.5)	2 (9.1)	19 (48.7)	4 (10.3)
Alopecia	8 (53.3)	0	7 (31.8)	0	16 (41.0)	0
Diarrhea	6 (40.0)	0	6 (27.3)	0	14 (35.9)	2 (5.1)
Hypokalemia	5 (33.3)	3 (20.0)	9 (40.9)	3 (13.6)	14 (35.9)	6 (15.4)
Hypoalbuminemia	4 (26.7)	0	9 (40.9)	0	13 (33.3)	0
Peripheral sensory neuropathy	5 (33.3)	0	6 (27.3)	0	12 (30.8)	0
Proteinuria	4 (26.7)	0	7 (31.8)	0	11 (28.2)	0
Blood bilirubin increased	4 (26.7)	0	5 (22.7)	0	9 (23.1)	0
Constipation	4 (26.7)	0	5 (22.7)	0	9 (23.1)	0
Mouth ulceration	7 (46.7)	0	1 (4.5)	0	9 (23.1)	0
Lymphocyte count decreased	4 (26.7)	1 (6.7)	4 (18.2)	3 (13.6)	8 (20.5)	4 (10.3)
Stomatitis	2 (13.3)	0	6 (27.3)	0	8 (20.5)	0
Hypocalcemia	2 (13.3)	0	6 (27.3)	0	8 (20.5)	0
Pyrexia	4 (26.7)	0	4 (18.2)	0	8 (20.5)	0

Data are *n* (%). Table lists TRAEs of any grade that occurred in at least 20% of the safety population of 39 patients and corresponding TRAEs of grade 3 or 4. Grade 5 TRAE occurred in 1 (2.6%) patient, which was septic shock. TRAE, treatment-related adverse event

patients, septic shock in 1 (2.6%), and neurotoxicity in 1 (2.6%). All of these AEs were related to mFOLFIRINOX, and only septic shock was also related to fuzuloparib.

Twenty-four (61.5%) patients experienced serious TRAEs (Additional file 1: Table S5), mainly including decreased neutrophil count in 12 (30.8%) patients, decreased platelet count in 8 (20.5%), febrile neutropenia in 6 (15.4%), decreased white blood cell count in 5 (12.8%), and anemia in 4 (10.3%). One (2.6%) patient had treatment-related death, caused by septic shock.

Efficacy

Of enrolled 39 patients, 7 patients were unevaluable for tumor response due to the absence of post-baseline assessments. Among the 32 patients who had post-baseline assessments for tumor response, shrinkage in target lesions was observed in 26 (81.3%) patients (Fig. 2A). The ORR in overall population was 34.4% (11/32; 95% CI, 18.6–53.2), and DCR was 87.5% (28/32; 95% CI, 71.0–96.5; Table 3). Substantial reductions in tumor burden were durable (Fig. 2B and C). Median DoR was 7.5 months (95% CI, 3.5–not reached).

A total of 24 of 39 (61.5%) patients had disease progression or died, and median PFS was 7.3 months (95% CI, 5.3–10.1; Fig. 3A). Twenty-six (66.7%) patients had died, and median OS was 11.5 months (95% CI, 7.8–14.2; Fig. 3B). CA19-9 responses were evaluable in 26 patients, and 57.7% (95% CI, 36.9–76.7) of patients had a CA19-9 response (Additional file 1: Table S6).

Generally, efficacy in 60 mg cohort seemed to be most favorable, with an ORR of 50.0% (9/18; 95% CI, 26.0–74.0), DCR of 94.4% (17/18; 95% CI, 72.7–99.9), median PFS of 7.2 months (95% CI, 5.1–13.9), median OS of 12.5 months (95% CI, 7.8–not reached), and CA19-9 response rate of 71.4% (95% CI, 41.9–91.6) (Table 3, Additional file 1: Fig. S2, and Additional file 1: Table S6).

Combined with the safety, tolerability, pharmacokinetics, and clinical activity findings, 60 mg BID was established as the RP2D of fuzuloparib when combined with mFOLFIRINOX.

Discussion

To the best of our knowledge, this study is the first to report the addition of a PARP inhibitor to standard first-line therapy and its continued use as maintenance therapy in patients with advanced or metastatic pancreatic cancer. Fuzuloparib at 30 or 60 mg BID combined with mFOLFIRINOX for 8 to 12 cycles followed by maintenance with fuzuloparib at 150 mg BID was generally safe. The most common TRAEs were hematological toxicities. When combined with mFOLFIRINOX, 60 mg BID fuzuloparib exhibited the most favorable activity, with an ORR of 50.0% and DCR of 94.4%, and was established as the RP2D.

An important consideration for the design of this study was the choice of chemotherapy regimen to be used in combination. Anti-cancer platinum drugs, such as cisplatin and oxaliplatin, exert their cytotoxic action by covalently binding to the DNA strand, which leads to DNA damage in tumor cells. PARP is involved in DNA repair. Inhibitors targeting PARP can further impair the ability of cancer cells to repair DNA damage, thereby enhancing the cytotoxic effects of platinum-based chemotherapeutic regimens. Therefore, we selected the mFOLFIRINOX in order to maximize the efficacy and safety. Fuzuloparib at 60 mg BID combined with mFOLFIRINOX achieved an ORR of 50.0% (first response in all responders occurred during the combination), which was numerically superior to historical data of standard chemotherapeutic regimens (23% [99/431] with GA, 31.6% [54/171] with FOLFIRINOX, and 35.1% [13/37] with mFOLFIRINOX) [7–9].

There were several early-phase clinical trials assessing PARP inhibitors combined with chemotherapeutic agents as front-line treatment for pancreatic cancer. In an expansion cohort of a phase 1 study in patients with genetically unselected, advanced or metastatic disease, olaparib plus gemcitabine had an ORR of 27% (4/15), compared with 14% (1/7) with gemcitabine alone [27]. Veliparib in combination with 5-fluorouracil and oxaliplatin demonstrated an ORR of 40% (6/15) in patients with known pathogenic HRR mutations or a family history suggestive of a breast or ovarian cancer syndrome in a phase 1/2 study [28]. Similarly, a phase 1 study of veliparib in combination with gemcitabine and cisplatin reported an ORR of 41.2% (7/17) [22]. However, this triple-combination therapy did not show any improvement in ORR, PFS, or OS compared to gemcitabine and cisplatin [29]. Our study was the first to explore the anti-tumor activity of combining a PARP inhibitor with mFOLFIRINOX, and the results indicated that FOLFOX-based chemotherapy might be a better choice.

Additionally, transitioning patients to maintenance therapy with a single-agent PARP inhibitor after achieving a tumor response or stable disease with combination therapy perhaps represents a favorable treatment strategy. Such a strategy was proven to be effective in the VELIA/GOG-3005 phase 3 study of ovarian cancer, where veliparib plus chemotherapy followed by veliparib maintenance therapy led to significantly longer PFS than chemotherapy alone in the *BRCA*-mutation cohort, HRR gene mutation cohort, and the overall population [30]. We also used this scheme in this study. First-line fuzuloparib at 60 mg BID combined with mFOLFIRINOX followed by maintenance with fuzuloparib at 150 mg BID

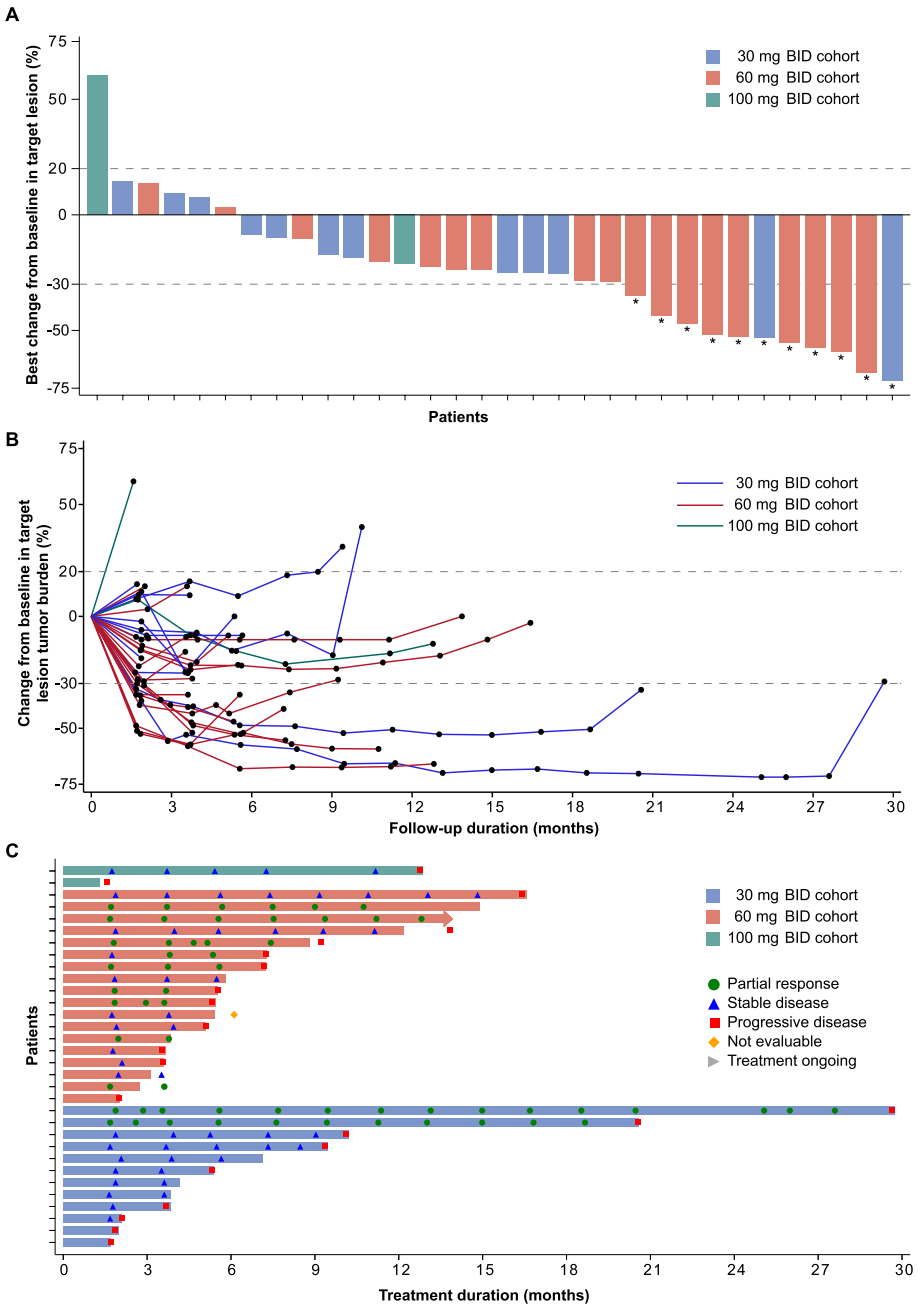

Fig. 2 Tumor responses. **A** Best percentage change from baseline in the sum of perpendicular diameters of target lesions. **B** Percentage change from baseline in target lesion tumor burden over time. **C** Tumor responses per RECIST v1.1 over time. *confirmed responses. BID, twice daily; HRR, homologous recombination repair

showed a median PFS of 7.2 months and a median OS of 12.5 months, only slightly longer than FOLFIRINOX and mFOLFIRINOX [7, 8]. However, this was an early-phase study with exploratory nature. Whether patients can truly benefit from fuzuloparib plus mFOLFIRINOX followed by fuzuloparib maintenance, and the contributions of fuzuloparib during combination and maintenance treatment period, still need to be investigated in large-scale randomized trials with appropriated controls.

The safety profile was similar with that of fuzuloparib monotherapy and mFOLFIRINOX [8, 18, 21]. No unexpected TRAEs were observed. A total of 12.8% of patients permanently discontinued the study treatment due to TRAEs; among them, only septic shock was deemed to

Table 3 Tumor response

	30 mg BID (*n* = 12)	60 mg BID (*n* = 18)	100 mg BID (*n* = 2)	Overall (*N* = 32)
Best overall response, *n* (%)				
Partial response	2 (16.7)	9 (50.0)	0	11 (34.4)
Stable disease	8 (66.7)	8 (44.4)	1 (50.0)	17 (53.1)
Progressive disease	2 (16.7)	1 (5.6)	1 (50.0)	4 (12.5)
Confirmed ORR, % (95% CI)	16.7 (2.1–48.4)	50.0 (26.0–74.0)	0 (0–84.2)	34.4 (18.6–53.2)
Confirmed DCR, % (95% CI)	83.3 (51.6–97.9)	94.4 (72.7–99.9)	50.0 (1.3–98.7)	87.5 (71.0–96.5)
DoR, median (95% CI), months	23.4 (18.9–NR)	5.5 (3.5–NR)	NA	7.5 (3.5–NR)

Tumor response was assessed in the evaluable set. Seven patients had no post-baseline assessments for tumor response, including 4 patients who withdrew from the study by their own decision, 2 due to adverse events, and 1 due to investigator decision

BID Twice daily, *ORR* Objective response rate, *DCR* Disease control rate, *DoR* Duration of response, *NA* Not applicable, *NR* Not reached

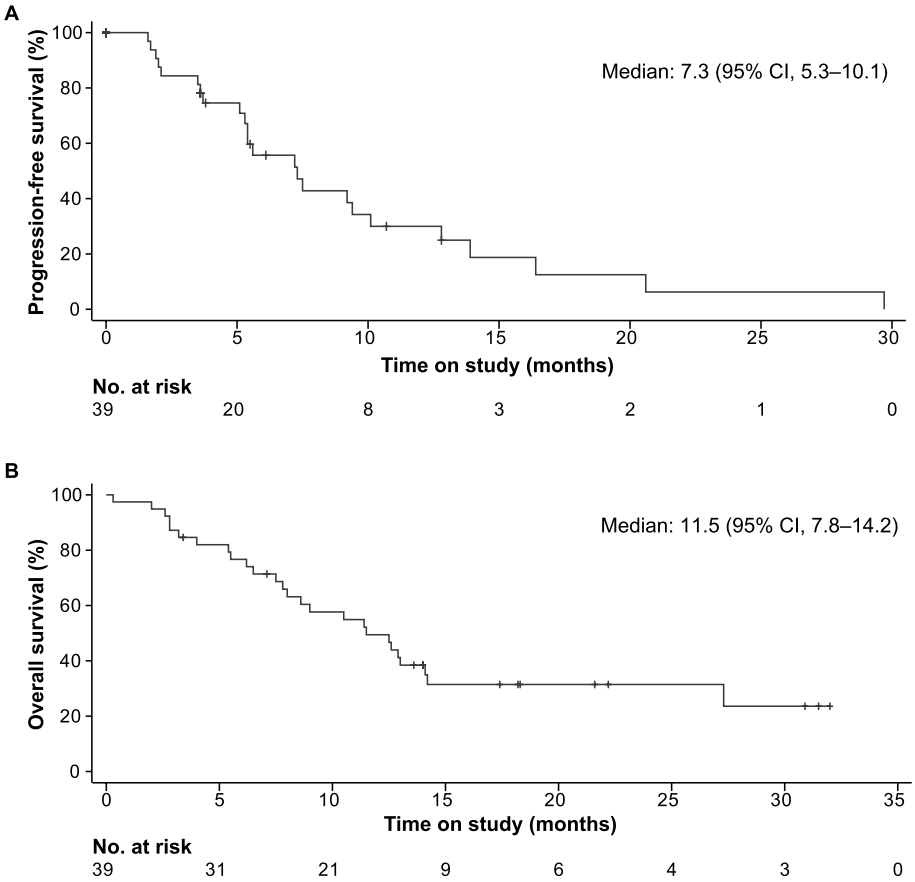

Fig. 3 Kaplan-Meier estimates of progression-free survival (**A**) and overall survival (**B**) in overall population

be related to both fuzuloparib and mFOLFIRINOX by the investigator, while others were considered related to mFOLFIRINOX. Addition of fuzuloparib to mFOLFIRINOX resulted in a high incidence of hematological toxicities, including decreased neutrophil count, decreased platelet count, decreased white blood cell count, and anemia, which required strict monitoring and consideration of pharmacological prophylaxis in subsequent trials.

Conclusions

In summary, first-line fuzuloparib plus mFOLFIRINOX followed by fuzuloparib maintenance was generally safe, with no unexpected toxicities, and showed encouraging

efficacy in advanced or metastatic pancreatic adenocarcinoma. Particularly, the administration of fuzuloparib at 60 mg BID demonstrated enhanced anti-tumor activity when combined with mFOLFIRINOX, indicating that this combination might be effective as neoadjuvant therapy and thereby potentially beneficial for surgical resection. A phase 1 study of fuzuloparib in combination with mFOLFIRINOX in patients with resectable pancreatic cancer is ongoing (ClinicalTrials.gov Identifier: NCT04425876).

Abbreviations

AG	Nab-paclitaxel plus gemcitabine
BID	Twice daily
CA19-9	Carbohydrate antigen 19-9
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
FOLFIRINOX	Oxaliplatin, irinotecan, leucovorin, and fluorouracil
HRR	Homologous recombination repair
MTD	Maximum tolerated dose
ORR	Objective response rate
OS	Overall survival
PARP	Poly (adenosine diphosphate-ribose) polymerase
PFS	Progression-free survival
RP2D	Recommended phase 2 dose
TRAEs	Treatment-related adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03581-y.

Additional file 1: Fig. S1. Pharmacokinetic profiles of fuzuloparib, when combined with mFOLFIRINOX. Fig. S2. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in 30 and 60 mg BID cohorts. Table S1. Dose-limiting toxicities. Table S2. Exposure of the individual components during combination of fuzuloparib and modified FOLFIRINOX. Table S3. Exposure of fuzuloparib during maintenance**.** Table S4. Safety summary. Table S5. Treatment-related serious adverse events. Table S6. CA19-9 response rate.

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Authors' contributions
MW: Data curation, Investigation, Methodology, Validation, Writing – original draft. RL: Data curation, Investigation, Methodology, Validation, Writing – review & editing. YX: Data curation, Investigation, Methodology, Validation, Writing – review & editing. XC: Data curation, Investigation, Methodology, Validation, Writing – review & editing. CL: Data curation, Investigation, Methodology, Validation, Writing – review & editing. XB: Data curation, Investigation, Methodology, Validation, Writing – review & editing. XZ: Data curation, Investigation, Methodology, Validation, Writing – review & editing. SG: Data curation, Investigation, Methodology, Validation, Writing – review & editing. JL1: Data curation, Investigation, Methodology, Validation, Writing – review & editing. ZS: Formal Analysis, Methodology, Software, Validation, Visualization, Writing – review & editing. JL2: Methodology, Project administration, Resources, Validation, Writing – review & editing. WW: Methodology, Project administration, Resources, Validation, Writing – review & editing. JZ: Data curation, Investigation, Methodology, Validation, Writing – review & editing. SS: Data curation, Investigation, Methodology, Validation, Writing – review & editing. JX: Data curation, Investigation, Methodology, Validation, Writing – review & editing. XY: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. All authors read and approved the final manuscript.

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Availability of data and materials
The individual patient data generated during this study will be considered for sharing after the product and indication have been approved by major health authorities. Data may be request 24 months after study completion. Qualified researchers should submit a proposal to the corresponding author outlining the reasons for requiring the data. The sponsor will provide the data if the proposal is approved, provided that the requestor signs a data-access agreement. Use of data must comply with the requirements of Human Genetics Resources Administration of China and other country or region-specific regulations.

Declarations

Ethics approval and consent to participate
The protocol and all amendments were approved by the Ethics Committee of Fudan University Shanghai Cancer Center (1911210-13-2108C), Zhejiang Provincial People's Hospital (2020YW011-A3), Henan Cancer Hospital (2020011002), Sun Yat-sen Memorial Hospital (2020-YW-025-004), and the First Affiliated Hospital, Zhejiang University School of Medicine (2021-573). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Consent for publication
Not applicable.

Competing interests
Zhen Sheng, Jianpo Lian, and Wenliang Wang report being employed by Jiangsu Hengrui Pharmaceuticals. All other authors declare no competing interests.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209–49.
2. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388:73–85.
3. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet. 2020;395:2008–20.

4. Tonini V, Zanni M. Pancreatic cancer in 2021: what you need to know to win. World J Gastroenterol. 2021;27:5851–89.
5. De Dosso S, Siebenhuner AR, Winder T, Meisel A, Fritsch R, Astaras C, et al. Treatment landscape of metastatic pancreatic cancer. Cancer Treat Rev. 2021;96:102180.
6. Park W, Chawla A, O'Reilly EM. Pancreatic Cancer: A Review. JAMA. 2021;326:851–62.
7. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
8. Stein SM, James ES, Deng Y, Cong X, Kortmansky JS, Li J, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer. 2016;114:737–43.
9. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–703.
10. Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015;33:3124–9.
11. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science. 2009;324:217.
12. Lal G, Liu G, Schmocker B, Kaurah P, Ozcelik H, Narod SA, et al. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res. 2000;60:409–16.
13. Roberts NJ, Jiao Y, Yu J, Kopelovich L, Petersen GM, Bondy ML, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012;2:41–6.
14. de Bono J, Ramanathan RK, Mina L, Chugh R, Glaspy J, Rafii S, et al. Phase I, Dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. Cancer Discov. 2017;7:620–9.
15. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33:244–50.
16. Shroff RT, Hendifar A, McWilliams RR, Geva R, Epelbaum R, Rolfe L, et al. Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation. JCO Precis Oncol. 2018;2:1–15.
17. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531:47–52.
18. Li N, Zhang Y, Wang J, Zhu J, Wang L, Wu X, et al. Fuzuloparib maintenance therapy in patients with Platinum-Sensitive, Recurrent Ovarian Carcinoma (FZOCUS-2): a multicenter, randomized, double-blind, placebo-controlled. Phase III Trial J Clin Oncol. 2022;40:2436–46.
19. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med. 2015;373:1697–708.
20. Wang L, Yang C, Xie C, Jiang J, Gao M, Fu L, et al. Pharmacologic characterization of fluzoparib, a novel poly(ADP-ribose) polymerase inhibitor undergoing clinical trials. Cancer Sci. 2019;110:1064–75.
21. Li N, Bu H, Liu J, Zhu J, Zhou Q, Wang L, et al. An open-label, multicenter, single-arm, phase II study of fluzoparib in patients with germline BRCA1/2 mutation and platinum-sensitive recurrent ovarian cancer. Clin Cancer Res. 2021;27:2452–8.
22. O'Reilly EM, Lee JW, Lowery MA, Capanu M, Stadler ZK, Moore MJ, et al. Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma. Cancer. 2018;124:1374–82.
23. Rajan A, Carter CA, Kelly RJ, Gutierrez M, Kummar S, Szabo E, et al. A phase I combination study of olaparib with cisplatin and gemcitabine in adults with solid tumors. Clin Cancer Res. 2012;18:2344–51.
24. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:1949–61.
25. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381:317–27.
26. Li H, Liu R, Shao B, Ran R, Song G, Wang K, et al. Phase I dose-escalation and expansion study of PARP inhibitor, fluzoparib (SHR3162), in patients with advanced solid tumors. Chin J Cancer Res. 2020;32:370–82.
27. Bendell J, O'Reilly EM, Middleton MR, Chau I, Hochster H, Fielding A, et al. Phase I study of olaparib plus gemcitabine in patients with advanced solid tumours and comparison with gemcitabine alone in patients with locally advanced/metastatic pancreatic cancer. Ann Oncol. 2015;26:804–11.
28. Pishvaian MJ, Wang H, He AR, Hwang JJ, Smaglo BG, Kim SS, et al. A Phase I/II Study of Veliparib (ABT-888) in combination with 5-Fluorouracil and Oxaliplatin in Patients with Metastatic Pancreatic Cancer. Clin Cancer Res. 2020;26:5092–101.
29. O'Reilly EM, Lee JW, Zalupski M, Capanu M, Park J, Golan T, et al. Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline BRCA/PALB2 Mutation. J Clin Oncol. 2020;38:1378–88.
30. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381:2403–15.

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