Poly(ADP-ribose) polymerase inhibition in pancreatic cancer

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Funding information
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Abstract
Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with limited treatment options. Recently, the poly(ADP-ribose) polymerase inhibitor (PARPi) olaparib has been approved for maintenance therapy after successful platinum-based chemotherapy in patients with germline mutations in BRCA1 and BRCA2. Approval was based on the POLO study that has shown a significant improvement in progression-free survival for patients with metastatic PDAC after at least 4 months of platinum-based chemotherapy. Hopefully, this first biomarker-directed targeted therapy for a relevant subgroup of pancreatic cancer patients is only the beginning of an era of personalized therapy for pancreatic cancer. The potential role for PARPi in improving survival in patients with pancreatic cancer containing somatic tumor mutations has yet to be established. Multiple studies investigating whether PARPi therapy might benefit a larger group of pancreatic cancer patients with homologous recombination repair deficiency and whether combinations with chemotherapy, immunotherapy, or small molecules can improve efficacy are currently underway. We here review the molecular basis for PARPi therapy in PDAC patients and recent developments in clinical studies.

KEYWORDS
olaparib, pancreatic cancer, PARP inhibitor

1 INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease that has a 5 year survival of less than 10%, one of the worst outcomes of all major cancers.¹ According to the GLOBOCAN data, 458,918 new cases and 432,242 deaths worldwide have been estimated for 2018.² In contrast to most other cancer types, improvement of overall survival over the last decades has been very limited.³

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The main reason for the dismal survival is the fact that PDAC can only be cured by complete resection, but more than 80% of patients are diagnosed at a late disease stage when primary surgery is no longer possible. The ESPAC-4 and PRODIGE-24 studies have markedly improved adjuvant therapy and outcome after resection, but most patients still have recurrence after surgery. The mainstay of treatment for patients that cannot be resected or relapse after surgery is systemic chemotherapy. In contrast to other cancer types like breast cancer or colon cancer, PDAC is a relatively chemotherapy-resistant disease, and for most patients, only a small survival benefit can be achieved. Patients with metastatic disease treated with the currently most effective chemotherapy protocols, FOLFIRINOX and nab-paclitaxel/gemcitabine, have a median survival of only 11.1 months and 8.5 months, respectively. Immunotherapy, now an important treatment option in multiple cancers, has not yet been equally successful in PDAC. Targeted therapy is also rarely possible since more than 90% of PDAC patients have an activating mutation in the Kirsten rat sarcoma (KRAS) gene, which is the most important driver mutation in this cancer. There is no effective targeted therapy for KRAS mutated cancers, with the novel exception of the p. G12C mutation. Although this variant is quite commonly found in lung cancer it is very rare in PDAC. In the small subgroup of patients with KRAS wild type, addressable genomic alterations including structural variants are increasingly found and thus opportunities for targeted therapy arise, for example, in patients with NTRK-, NRG-1-, RET-, ROS1- and ALK-fusions or BRAF mutations. There are promising attempts to use transcriptional PDAC subtypes to guide systemic therapy, but this approach is not yet ready for clinical practice.

The poly(ADP-ribose) polymerase inhibitor (PARPi) olaparib has recently been licensed for PDAC patients with germline BRCA-mutations based on the randomized phase III POLO study. The option to treat a relevant fraction of PDAC patients with biomarker-guided targeted therapy is an exciting novelty for this notoriously difficult to treat cancer type and the focus of this review.

2 | HOMOLOGOUS RECOMBINATION REPAIR DEFICIENCY IN PANCREATIC CANCER

Genome instability caused by defects in the cellular DNA repair machinery has been recognized as a fundamental “enabling characteristic” of cancer. Homologous recombination repair (HRR) of DNA double-strand breaks is a crucial component of the DNA damage response. Germline mutations in genes involved in HRR including BRCA1/2 have long been known to increase tumor risk and lead to hereditary tumor syndromes. Loss-of-function mutations in BRCA1/2 can lead to homologous recombination repair deficiency (HRD) with accumulation of chromosomal rearrangements and copy-number alterations. Interestingly, tumors in patients with pathogenic germline BRCA mutations can also arise without signs of genomic instability, possibly since inactivation of the wild type allele might be a requirement for HRD. HRD can also be caused by somatic mutations in BRCA1/2 and other HRR genes in patients without pathogenic germline mutations. Finally, tumor cells can show characteristics of HRD without mutations in BRCA genes or other HRR genes. The term “BRCaness” was initially coined for tumors with HRD characteristics in the absence of germline BRCA mutations but is now also used in a broader sense for all tumors with HRD. While the detection of mutations in HRR genes in tumor tissue or, for germline mutations, in leukocytes, is commonly used in clinical routine, the validation of biomarkers and tests that directly detect HRD is still developing and an active area of research (reviewed in Reference 28).

Germline mutations in BRCA1/2 result in an increased lifetime risk for PDAC (2- to 4-fold for BRCA1 and 3- to 8-fold for BRCA2). In three large US studies, the prevalence of BRCA1 and BRCA2 germline mutations in PDAC patients was 0.3% to 2.4% and 1.4% to 5.7%, respectively. Other HRR genes with germline mutations were ATM (1.1%-2.88%) and PALB2 (0.2%-0.4%). Higher rates of germline BRCA mutations have been reported for Ashkenazi Jewish PDAC patients, ranging from 5.5% in one study with 137 resected patients to 21.6% in another single-site study with 37 patients.

HRD can also arise during PDAC carcinogenesis without predisposing germline mutations. It is difficult to estimate the prevalence of HRD mutations or “BRCaness” in PDAC patients since studies that report mutation frequencies have mostly been performed in selected populations, for example, resected stage I/II patients or patients from certain geographical regions. It is also conceivable that patients with a family history of pancreatic cancer have been preferentially referred to genetic profiling, introducing a selection bias that might overestimate the prevalence of germline mutations associated with familiar pancreatic cancer. Furthermore, many variants in genes related to HRD have not yet been clinically validated, and their relevance for therapeutic interventions remains unclear.

In the study by Wadell et al, whole-genome sequencing and copy number variation analysis was performed on 100 patients with primary operable, nonpretreated PDAC. Based on variations in chromosomal structure, four PDAC subtypes were described: stable, locally rearranged, scattered, and unstable. The genomic unstable subtype (14%) correlated with germline and somatic mutations in HRR genes and a mutational BRCA signature. Seven percent of patients in this study had germline mutations in BRCA2 (n = 4) and PALB2 (n = 3), and further 7% of patients had somatic mutations in BRCA1/2 and PALB2. Altogether, 24% of patients had a BRCA signature and/or unstable genome and therefore signs of HRD, some of them without an unequivocal causative mutation. In a large study with genomic profiling of 3594 PDAC samples, 14% of patients had mutations in HRR-related genes. Clinical information for this cohort is sparse, including the tumor stage and the trigger for molecular testing. There was no parallel germline sequencing, but it was estimated with a computational method that approximately half of the patients with mutations in HRR-related genes had germline alteration. In a detailed study on transcription phenotypes with microdissected tumor tissue from 206 resected patients and 111 patients with advanced disease from the COMPASS trial, 7% of patients had a unique mutational signature indicating HRD. Interestingly, HRD was not associated with any of the transcription subtypes. In a recent study with 62 patient-derived
PDAC cell lines, predictive biomarkers for HRD and response to platinum derivates and olaparib were described that also identify patients without mutations in the key HRR genes. These results indicate that the number of patients that might benefit from PARPi therapy is possibly not limited to patients with germline BRCA1/2 mutations. Further clinical studies are needed to evaluate the benefit for a larger group of patients, and to define the optimal testing strategy.

3 | THERAPEUTIC CONSEQUENCES OF HRD IN PanCREATIC CANCER

PARPi are drugs that exploit HRD to kill tumor cells based on a concept termed “synthetic lethality.” Different PARPi are now approved for the treatment of ovarian cancer, prostate cancer, breast cancer, and PDAC. The molecular basis for PARPi therapy is reviewed elsewhere in this volume. In short, inhibition of the poly(ADP-ribose)polymerase (PARP) interferes with the cellular ability to repair single-strand DNA breaks. In normal cells, PARP inhibition can be compensated since single-strand DNA breaks can also be repaired by HRR as an alternative pathway. However, in cells with HRD, inhibition of PARP is lethal due to accumulation of DNA damage and subsequent cell death. Unfortunately, patients treated with PARPi finally develop resistance and progress despite PARPi therapy. Different resistance mechanisms have been elucidated (reviewed in Reference 42), including the restoration of HRR capacity in tumor cells.

Secondary mutations emerging under PARPi treatment that probably reactivate BRCA2 function have already been reported in PDAC patients. In the clinic, PARPi are currently used as single agent therapy, but combination treatments may increase efficacy. Interestingly, sequential therapy involving PARPi and cell cycle checkpoint inhibitors can work not only in HRD tumors but also in tumors without HRD. Tumor cells with high-endogenous replication stress are more susceptible to therapy with cell cycle checkpoint inhibitors. In PDAC, the basal/squamous subtype has increased endogenous replication stress relative to the classical subtype, and basal/squamous tumors are therefore more likely to be susceptible to cell cycle checkpoint inhibitors irrespective of HR deficiency status. Thus, there might even be a role for PARPi combinations in HRR competent PDAC.

PARPi-induced DNA damage is known to trigger T-cell infiltration with potential anti-tumor effects, but also adverse inflammatory responses and increased immune checkpoint signaling. Furthermore, HRD in PDAC can be associated with a high-mutational burden. There is therefore a rationale for the combination of PARPi and immune checkpoint blockade. Whether such combination approaches will help to overcome the resistance of pancreatic cancer to immunotherapies has to be determined.

In addition to conferring sensitivity to PARPi, the inability to repair double-strand DNA breaks also increases the sensitivity of cancer cells to certain classes of chemotherapy, including platinum derivates. Interestingly, differences in the mode of action have been described between individual platinum-derived agents: cisplatin and carboplatin cause DNA cross-linking and induce a DNA damage response, while oxaliplatin tumor cells by inducing ribosome biogenesis stress. An increased sensitivity of patient-derived cell lines and PDX models with HRD to platinum derivates has been demonstrated. In the whole-genome sequencing study discussed above, hints for an association of unstable genome PDACs with successful platinum response were found, but this was based on only eight patients. In a retrospective analysis of resected patients after neoadjuvant chemotherapy with FOLFIRINOX the complete pathological response rate was higher in patients with germline BRCA mutations (44.4% vs 10%) which was also reflected in a better overall survival.

Further evidence for an increased susceptibility of HRD PDAC to platinum derivates has been reviewed in Reference 33. In a recent trial with cisplatin and gemcitabine for germline BRCA/PALB2-mutated stage III and IV PDAC patients, an exceptional response rate of 65.2% has been reported. The majority of patients in the study (56%) had one of the Ashkenazi Jewish “founder” mutations. It remains unclear if cisplatin/gemcitabine is superior to FOLFIRINOX in HRD PDAC patients since randomized trials are lacking and a response rate for FOLFIRINOX in PDAC patients with HRD has not yet been reported. The triple combination of cisplatin, gemcitabine, and nab-paclitaxel that had a response rate of 70% in unselected stage IV PDAC patients might also be a promising protocol in HRD PDAC patients. Notably, exceptional responses in HRD PDAC have also been reported for the alkylating agent mitomycin C and the topoisomerase inhibitor irinotecan.

4 | COMPLETED CLINICAL STUDIES

To date, 14 clinical trials of PARPi involving patients with pancreatic cancer have been reported (Table 1). Together, these trials have generated valuable data on the feasibility, safety, dosing, and preliminary efficacy of PARPi in pancreatic cancer. PARPi agents evaluated in completed studies include olaparib, niraparib, rucaparib, talazoparib, and veliparib. The overall safety profile of PARPi in pancreatic cancer seems favorable and is concordant with experiences in other solid tumors.

Early-phase trials focusing on the safety and pharmacokinetics of PARPi in pancreatic cancer often involved mixed cohorts of patients both with and without HRD-relevant mutations. However, most published studies in genetically unselected patients included exploratory analyses of HRD biomarkers. Together with data on the recruitment of phase 2 to 3 studies, these results provide some insights about the abundance of HRD-relevant mutations among the screening population in pancreatic cancer. To date, promising efficacy signals have been obtained with PARPi strategies in HRD-enriched pancreatic cancer cohorts. The efficient identification of pancreatic cancers with manifest HRD will be an important prerequisite for successful PARPi applications in clinical practice.

Results from selected phase 1 to 3 studies of PARPi in pancreatic cancer are summarized below. In addition to studies reviewed here, completed dose-escalation trials of both niraparib and talazoparib in
TABLE 1 Completed and published studies of PARPi in pancreatic cancer

| Phase | PARPi  | Combination | Condition | HRR status | \( n \) (total)* | Outcome | Registry No | PMID  | Reference |
|-------|--------|-------------|-----------|------------|----------------|---------|-------------|--------|-----------|
| 1     | Niraparib | –           | Solid tumors: Pretreated | gBRCA1/2 | 1 (100) | MTD: 300 mg per day; one patient with pancreatic cancer was included and was refractory (dose level 80 mg) | NCT00749502 | 23810788 | 79 |
| 1     | Olaparib | –           | Solid tumors: Pretreated | gBRCA1/2 | 2 (60) | MTD: 400 mg BID; no response assessment in pancreatic cancers | NCT00516373 | 19553641 | 59 |
| 1     | Olaparib | Gemcitabine | Pancreatic cancer: Untreated | Exploratory: 20%-80% positive for BRCA1/2 in dose expansion cohort | 68 | MTD: Olaparib capsule 100 mg BID or olaparib tablet 100 mg (days 1-14) plus gemcitabine 600 mg/m² (days 1, 8, 15) every 29 days; ORR: 27% | NCT00515866 | 25573533 | 61 |
| 2     | Olaparib | –           | Solid tumors: Pretreated (65% platinum) | gBRCA1/2 | 23 (209) | ORR: 26% (overall), 21.7% (pancreatic cancers) | NCT01078662 | 25366685 | 60 |
| 3     | Olaparib | –           | Pancreatic cancer: Maintenance after platinum | gBRCA1/2 | 154 | PFS: 7.4 months (olaparib) vs 3.8 months (placebo) (HR, 0.53; \(P = .004\)); ORR: 23% (olaparib) vs 12% (placebo) (n.s.) | NCT02184195 | 31157963 | 61 |
| 2     | Rucaparib | –           | Pancreatic cancer: Pretreated (79% platinum) | BRCA1/2 (germline or somatic) | 19 | ORR: 16% | NCT02042378 | 30051098 | 65 |
| 1     | Talazoparib | –          | Solid tumors: Pretreated | gBRCA1/2 or gPALB2 | 13 (110) | MTD: 1.0 mg per day; ORR: 20% (pancreatic cancers) | NCT01286987 | 28242752 | 80 |
| 1     | Veliparib | –           | Pancreatic cancer: Pretreated (88% platinum) | gBRCA1/2 or gPALB2 | 16 | ORR: No objective responses | N/A | 29223478 | 67 |
| 1     | Veliparib | mFOLFIRI   | Solid tumors: Pretreated (21% platinum) | Not assessed | 14 (92) | MTD: Not reached; RP2D: Veliparib 200 mg BID + mFOLFIRI (without 5-FU bolus) | NCT01123876 | 29527010 | 69 |
| 1     | Veliparib | Gemcitabine plus radiation therapy | Pancreatic cancer: Untreated | Exploratory: 34% positive for ARID1A, ATM, CHEK2, MLH1, PALB2, or PTEN (germline or somatic) | 34 | MTD: Veliparib 40 mg BID + gemcitabine 400 mg/m² + IMRT (36 Gy/15 fractions) | NCT01908478 | 30635165 | 82 |
| 1/2   | Veliparib | mFOLFOX-6  | Pancreatic cancer: Untreated and pretreated (56% platinum) cohorts | Exploratory: 30% positive for BRCA1/2, ATM, PALB2, or FANCG (germline or somatic) | 64 | ORR: 40% (untreated), 20% (pretreated) | NCT01489865 | 32669374 | 70 |
| 1     | Veliparib | Gemcitabine and Cisplatin | Pancreatic cancer: Untreated | gBRCA1/2 (53%) and wild-type cohorts | 17 | RP2D: Veliparib 80 mg BID on days 1-12 + gemcitabine (600 mg/m²) and cisplatin (25 mg/m²) on days 3 and 10, every 3 weeks | N/A | 29380808 | 68 |
| 2     | Veliparib | Gemcitabine and Cisplatin | Pancreatic cancer: Untreated | gBRCA1/2 or gPALB2 | 50 | RR: 74% (combination) vs 65.2% (chemotherapy) (n.s.); PFS: 10.1 months (combination) vs 9.7 months (chemotherapy) (n.s.) | NCT01585805 | 31976786 | 53 |

Note: Registered studies were retrieved from www.clinicaltrials.gov, and entries listed with status “completed” as of September 14, 2020 are shown. Registry No., ClinicalTrials.gov registry number.
Abbreviations: BID, twice daily; DCR, disease control rate; MTD, maximum tolerated dose; n.s., not statistically significant; ORR, objective response rate; PFS, progression-free survival; PMID, PubMed identifier; RP2D, recommended phase 2 dose; RR, response rate.
*Denotes the number of patients with pancreatic cancer, and numbers in brackets indicate the total number of patients enrolled in trials involving multiple cancer types.
advanced solid tumors also included patients with pancreatic cancer (Table 1).

### 4.1 | Olaparib

Olaparib was the first PARPi to enter clinical trials as a single agent cancer therapy. Along the clinical pipeline in pancreatic cancer, olaparib is also the most advanced candidate. The landmark phase 1 study of olaparib in BRCA1/2 mutation carriers included two patients with pancreatic cancer in the safety cohort, however, no data on antitumor activity were published for these patients.

Two subsequent phase 1 to 2 studies of olaparib included patients with pancreatic cancer, and the majority in both trials were germline BRCA1/2-positive (Table 1). In a phase 2 trial of single agent olaparib in advanced solid tumors, an objective response rate (ORR) of 21.7% was reported for the subset of pancreatic cancers (n = 23), compared to an ORR of 26% across all tumor types. Seventy-eight percent of pancreatic cancer patients were BRCA1/2 positive, and 65% had received prior platinum-based therapies. The other study was a phase 1 trial of olaparib plus gemcitabine in pretreated unresectable pancreatic cancer (n = 68), including a dose expansion cohort of 22 patients. The combination of either olaparib 100 mg twice daily (capsules) or 100 mg once daily (tablets) on days 1 to 14 plus gemcitabine 600 mg/m² (days 1, 8, 15 of every 29 day cycle) was well tolerated. In the dose expansion part, combination treatment (n = 15) resulted in an ORR of 27% vs 14% with gemcitabine alone (not statistically significant).

The only phase 3 trial of PARPi in pancreatic cancer with published results to date (POLO, Pancreas Cancer Olaparib Ongoing; NCT02184195) evaluated maintenance olaparib in patients with germline BRCA1/2 mutations who had at least stable disease after first-line platinum-based chemotherapy. One hundred fifty-four patients were randomized 3:2 to receive either olaparib 300 mg twice daily (n = 92) or placebo (n = 62). Maintenance treatment was initiated within 8 weeks after completion of at least 16 weeks of platinum-based chemotherapy for metastatic disease. The primary endpoint was PFS, with overall survival, second PFS, ORR, and change in global health-related quality of life as secondary endpoints. One-hundred-eight patients had deleterious germline BRCA2 mutations, 45 had BRCA1 mutations, and one patient had both. Prior to maintenance treatment, most patients had received polychemotherapy with FOLFIRINOX variants (84%), followed by FOLFOX (6%), GEMOX (4%), and gemcitabine/cisplatin (3%). All randomized patients were included in the efficacy analysis at a data maturity of 68% regarding the primary endpoint. Maintenance olaparib significantly prolonged median PFS compared to placebo (7.4 months vs 3.8 months; HR, 0.53; 95% confidence interval [CI], 0.35-0.82; P = .004). Kaplan-Meier analysis revealed a separation of time-to-event curves after approximately 5 months on maintenance treatment. The overall response rate was 20% with olaparib and 10% with placebo. The median duration of response in the olaparib arm was 24.9 months, indicating that there is a subgroup of patients that might derive a huge benefit from olaparib therapy. No subgroup-specific differences in efficacy were reported. At a data maturity of 46% regarding overall survival, no significant effect of maintenance olaparib was detectable. Adverse events ≥ grade 3 occurred in 40% and 23% of patients treated with olaparib and placebo, respectively. Finally, no significant difference between treatment groups was found in the global health-related quality of life.

Based on the positive results of the POLO trial, olaparib was approved in the United States in 2019 and in Europe in 2020 for maintenance treatment of patients with germline BRCA1/2 mutations and pancreatic cancer that is nonprogressing after 16 weeks of first-line platinum-based chemotherapy. To date, olaparib is the only PARPi with regulatory approval in pancreatic cancer.

### 4.2 | Rucaparib

Rucaparib has been evaluated in completed trials both as a monotherapy in pretreated patients and as a maintenance strategy for platinum-sensitive pancreatic cancer.

A phase 2 trial (RUCAPANC) tested single agent rucaparib (600 mg twice daily) in patients with pretreated locally advanced or metastatic pancreatic cancer and either germline (n = 16) or somatic (n = 3) BRCA1/2 mutations. The ORR was 16%, including at least one CR, and the observed DCR (disease control rate) was 32%. Recruitment was stopped based on an unmet efficacy threshold among the first 15 cases. Patients had received a maximum of two prior lines of therapy, predominantly including platinum-based regimens (78.9%). Of note, all patients experiencing a response to rucaparib had platinum-sensitive disease.

### 4.3 | Veliparib

Veliparib has been extensively studied in pancreatic cancer, either as single agent or in combination with existing regimens (Table 1). Veliparib has relatively low PARP trapping activity compared to other PARPi but may be especially suited for combination with chemotherapies.

Single agent activity of veliparib 400 mg twice daily in locally advanced or metastatic pancreatic cancer was assessed in a phase 2 trial in patients with germline BRCA1/2 or PALB2 mutations (n = 16). Patients had received a maximum of two prior lines of treatment, and the majority (88%) had been pretreated with platinum-based chemotherapy. The outcomes did not support clinical activity of veliparib monotherapy in this population, as no objective responses were observed. However, 25% of patients had stable disease on veliparib for at least 4 months.

In a subsequent series of phase 1 to 2 trials, veliparib was evaluated in combinations with several polychemotherapies, including gemcitabine and cisplatin, modified FOLFIRI, and modified FOLFOX (Table 1).

A phase 1 trial of veliparib (80 mg twice daily on days 1-12) plus gemcitabine (600 mg/m²) and cisplatin (25 mg/m²) on days 3 and
of every 21 day cycle in 17 patients with previously untreated advanced pancreatic cancer established this regimen as the recommended phase 2 dose (RP2D). The DLT was myelotoxicity with 40% grade 4 toxicities. In addition, two grade 5 events occurred, including one patient who developed acute myeloid leukemia after several years. The study included both germline BRCA1/2-positive (n = 9) and -negative (n = 7) patients in separate cohorts. Seven of the nine BRCA1/2-positive patients achieved a response (ORR, 77.8%), resulting in a median OS in this cohort of 23.3 months (95% CI, 3.8-30.2 months).

The established regimen of gemcitabine and cisplatin plus concurrent veliparib was compared to chemotherapy alone in a recently completed, randomized phase 2 trial. Patients had to have germline BRCA1/2 or PALB2 mutations and untreated locally advanced or metastatic pancreatic cancer. Only platinum-naïve patients were eligible, including prior adjuvant therapy. Primary endpoint was ORR. The prespecified activity threshold of 20% was exceeded in both treatment arms, and recruitment was stopped after 50 patients had been enrolled. However, addition of veliparib to gemcitabine and cisplatin did not result in a superior ORR compared to chemotherapy alone (ORR, 74.1% vs 65.2%, P = .55). Likewise, PFS did not differ significantly between the study arms (10.1 months vs 9.7 months, P = .73). After completion of combination treatment, seven patients with clinical benefit transitioned to optional maintenance veliparib (400 mg twice daily), and one remained on maintenance at 3 years after diagnosis. Among the entire study population, 2 year OS was 30.6%.

In a phase 1 dose-escalation study in patients with advanced solid tumors, veliparib was combined with three different modifications of the FOLFIRI regimen. Assessment of DDR status was not part of the protocol. Ninety-two patients were enrolled, including 14 patients with pancreatic cancer. Among all patients, 21% had received prior oxaliplatin-based therapies. The RP2D was established at veliparib 200 mg twice daily plus modified bimonthly FOLFIRI (irinotecan 150 mg/m² or 180 mg/m² and 5-FU 2400 mg/m² continuous infusion over 46 hours). Bolus 5-FU was omitted from the combination to improve tolerability. Among all patients treated at the determined RP2D, the most frequent grade 3 to 4 adverse events (AEs) included neutropenia (54.8%), anemia (16%), and diarrhea (16%). Two of 14 pancreatic cancer patients achieved a response (ORR, 14.3%).

A recently published phase 1 to 2 study of veliparib plus modified FOLFOX-6 in patients with pancreatic cancer (n = 64) established the RP2D at veliparib 200 mg twice daily plus oxaliplatin 85 mg/m² and 5-FU 2400 mg/m²/continuous infusion over 46 hours. Again, the 5-FU bolus was omitted due to prolonged myelotoxicity among the first treated patients, and additional dose reductions of at least one component were necessary in all patients. The most common grade 3 to 4 AE was neutropenia (16%). Patients were included regardless of HRD status, and exploratory analysis revealed germline or somatic mutations in HRD-related genes in 30%. In the second part of the trial, two additional cohorts of untreated (n = 15) and pretreated (n = 18) patients were recruited for efficacy analysis. Responses differed by pretreatment and HRD status (Table 1), with an overall ORR of 26% among all evaluable patients from phase 1 to 2 (n = 58), and an ORR of 57% in a subgroup of HRD-positive patients who had not progressed on prior platinum therapy.

## 5 | CURRENT CLINICAL STUDIES

Current clinical studies of PARPi in pancreatic cancer build on data from completed trials, and several studies are testing established agents in novel combination approaches. Many ongoing trials aim to expand existing PARPi strategies to a patient population beyond germline mutation carriers. Early studies of new PARPi candidates are also underway. Selected clinical trials in progress involving PARPi in pancreatic cancer are summarized in Table 2 and in the following section.

### 5.1 | Single agent therapy

Single agent niraparib (200 or 300 mg daily) is being evaluated in two phase 2 trials in advanced pancreatic cancer. One study evaluates niraparib in pretreated patients with germline or somatic mutations in BRCA1, BRCA2, PALB2, CHEK2, or ATM, excluding oxaliplatin-refractory disease (NCT03601923). The second trial (NCT03553004) evaluates niraparib in pancreatic cancer patients with germline or somatic mutations in a broader panel of DDR-related genes and regardless of pretreatment status.

Single agent olaparib is being studied in two parallel phase 2 trials in the United States and Israel in advanced pancreatic cancer patients without germline BRCA1/2 mutations (NCT02677038). In addition to patients with DDR deficiency, patients without evidence for genetic alterations but with a positive family history of BRCA-related cancers are eligible (“BRCaness phenotype”). As patients without germline BRCA1/2 mutations were excluded from previous trials of olaparib in pancreatic cancer, the study will provide first efficacy data in this more heterogeneous population. So far, 32 patients have been recruited, and a preliminary PFS of 14 weeks (Israel trial) and 24.7 weeks (US trial) has been reported upon interim analysis.

Single agent rucaparib is currently under study in patients with advanced solid tumors (including pancreatic cancer) and germline or somatic HRD-relevant mutations (LODESTAR, NCT04171700). Patients with mutations in BRCA1/2, PALB2, RAD51C, or RAD51D are eligible for the main cohort. The trial also includes a smaller, exploratory cohort with mutations in BARD1, BRIP1, FANCA, NBN, RAD51, or RAD51B.

With respect to maintenance therapy, a phase 2 trial of rucaparib (600 mg twice daily) following platinum-based chemotherapy for advanced pancreatic cancer is ongoing (NCT03140670). Recruitment has been completed, and interim results have been published in abstract form. Patients with germline or somatic BRCA1/2 or PALB2 mutations and at least stable disease after 4 months of platinum were eligible. This study also includes patients who have had previous lines of therapy prior to starting platinum. For the first 19 patients on rucaparib maintenance therapy, an ORR of 36.8% and PFS of 9.1 months were reported.
| Phase | PARPi | Combination       | Condition                          | HRR status                                                                                      | n*  | Endpoint        | Registry No  | Reference |
|-------|-------|-------------------|------------------------------------|-------------------------------------------------------------------------------------------------|-----|----------------|--------------|-----------|
| 1/2   | Fluzoparib | mFOLFIRINOX | Pancreatic cancer: Untreated | gBRCA1/2 or gPALB2                                                                 | 66  | MTD, ORR       | NCT04228601  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 3     | Fluzoparib | -                 | Pancreatic cancer: Maintenance after platinum | gBRCA1/2 or gPALB2                                                                 | 136 | PFS            | NCT04300114  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Niraparib | -                 | Pancreatic cancer: Pretreated     | BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51/B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCA/ C/D/G, RPA1, ARID1A (germline or somatic) | 18  | ORR            | NCT03553004  | 71        |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Niraparib | -                 | Pancreatic cancer: Pretreated     | BRCA1/2, PALB2, CHEK2, or ATM (germline or somatic)                                            | 32  | PFS            | NCT03601923  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 1/2   | Niraparib | Ipilimumab or Nivolumab | Pancreatic cancer: Maintenance | Not required for enrollment                                                               | 84  | PFS            | NCT03404960  | 83        |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Niraparib | Dostarlimab       | Pancreatic cancer: Untreated or pretreated | BRCA1/2, PALB2, BRAD1, RAD51c, or RAD51d (germline or somatic)                                        | 20  | DCR            | NCT04493060  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Niraparib | Dostarlimab plus radiation therapy | Pancreatic cancer: Pretreated | Not required for enrollment                                                               | 25  | DCR            | NCT04409002  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 1     | NMS-03305293 | -                 | Solid tumors: Untreated or pretreated | Not required for enrollment                                                               | 100 | DLT            | NCT04182516  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 1     | Olaparib | -                 | Pancreatic cancer: Untreated or pretreated | Only non-gBRCA 1/2 patients are included. Exploratory: 53% positive for ATM, PALB2, BRCA1/2 (germline or somatic), FANCB, PTEN, or CCNE1 (interim analysis) | 14  | Biomarker evaluation prior to and after window therapy with olaparib or cobimetinib | NCT04005690  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Olaparib | -                 | Pancreatic cancer: Pretreated     | Only non-gBRCA 1/2 patients are included. Exploratory: 53% positive for ATM, PALB2, BRCA1/2 (germline or somatic), FANCB, PTEN, or CCNE1 (interim analysis) | 34  | ORR            | NCT02677038  | 72        |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 1     | Olaparib | Copanlisib plus Durvalumab | Solid tumors: Pretreated | Mutation in a panel of DDR genes (germline or somatic)                                         | 102 | MTD            | NCT03842228  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Olaparib | Cediranib         | Solid tumors: Pretreated          | Not required for enrollment                                                               | 126 | ORR            | NCT02498613  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Olaparib | AZD6738 (ATR kinase inhibitor) | Solid tumors: Pretreated | Stratification by ARID1A status and ATM loss                                                                 | 68  | ORR            | NCT03687289  | N/A       |
|       |        |                   |                                    |                                                                                                 |     |                |              |           |
| 2     | Olaparib | Trabectedin       | Solid tumors, Pretreated          | Positive genetic HRD score                                                                 | 90  | DCR, ORR       | NCT03127215  | N/A       |

(Continues)
Fluzoparib is a relatively new third-generation PARPi currently in clinical trials in several malignancies. A randomized placebo-controlled phase 3 trial of maintenance fluzoparib (150 mg twice daily) in patients with pancreatic cancer and germline BRCA1/2 or PALB2 mutations is recruiting (NCT04300114). Similar to the published POLO study of maintenance olaparib, only patients without progression after at least 4 months of first-line platinum-based therapy are eligible. The primary endpoint is PFS, and final data collection is awaited in 2022.

5.2 Combination therapy

Anti-tumor effects of PARPi not only depend on HRD, but also on the rate at which DNA damage is accumulated. A number of existing cancer therapies increase genotoxic stress at the cellular level. It is hoped that the co-administration of PARPi with some of these agents will further improve clinical response rates and efficacy. Beyond immediate cytotoxicity to tumor cells, synergistic effects of PARPi and immunotherapy are being studied. Along these lines, several combination therapies involving PARPi are under investigation in pancreatic cancer (Table 2). Clinical trials of PARPi in combination with different cancer therapies are discussed in the following sections.

| Phase | PARPi | Combination | Condition | HRR status | n* | Endpoint | Registry No | Reference |
|-------|-------|-------------|-----------|------------|----|----------|-------------|-----------|
| 2     | Rucaparib | - | Pancreatic cancer: Maintenance after platinum | BRCA1/2 or PALB2 (germline or somatic) | 50 | PFS: 9.1 months; ORR: 37% (interim analysis) | NCT03140670 | 73 |
| 2     | Rucaparib | - | Solid tumors: Pretreated | BRCA1/2, PALB2, RAD51, BARD1, BRIP1, FANCA, or NBN (germline or somatic) | 220 | ORR | NCT04171700 | N/A |
| 1/2   | Rucaparib | Nal-IRI and 5-FU/LV | Solid tumors: Untreated or pretreated | Phases 1b and 2: BRCA1/2, PALB2, or positive HRD signature | 110 | MTD, ORR | NCT03337087 | N/A |
| 2     | Veliparib | mFOLFIRI | Pancreatic cancer: Pretreated (second line) | Exploratory interim analysis: 9% positive for BRCA2, PALB2, ATM, or CDK12 (germline or somatic); 20% positive for other DDR-related genes (germline) | 123 | OS | NCT02890355 | 76 |

Note: Registered studies were retrieved from www.clinicaltrials.gov, and entries listed with status “recruiting” or “active, not recruiting” as of September 14, 2020 are shown. Registry No., ClinicalTrials.gov registry number. Abbreviations: DCR, disease control rate; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. *Denotes the estimated (planned) total enrollment.
fluozoparib is added to first-line modified FOLFIRINOX in chemotherapy-naive patients, followed by single agent fluozoparib maintenance (NCT04228601). This randomized, placebo-controlled trial aims to establish the RP2D and first efficacy data for the combination. Patients with advanced pancreatic cancer and germline BRCAl/2 or PALB2 mutations are eligible.

The NCT-PMO-1603 study of the German Cancer Consortium (DKTK) investigates the combination of olaparib with trabectedin. Patients with solid tumors beyond standard treatment and a positive genetic HRD score are randomized to the combination of olaparib with trabectedin or physician's choice treatment. Primary endpoints are DCR and ORR.

5.4 | Combination with immunotherapies

In an ongoing phase 1/2 trial of a combined maintenance treatment, patients are randomized to niraparib (200 mg daily) plus either ipilimumab or nivolumab (NCT03404960). Patients with at least stable disease on a platinum-based regimen are eligible, independent of HRD status. Twenty-five of 84 patients were enrolled according to an interim report in 2019, but no results have been published yet. The primary endpoint is PFS, and both genomic and immunologic analyses of biopsy materials are part of the trial.

Niraparib is also combined with immunotherapy in two phase 2 trials in metastatic pancreatic cancer that involve the programmed cell death 1 (PD-1) antibody dostarlimab. A study of the triple combination of niraparib plus dostarlimab plus radiotherapy for patients with metastatic disease is currently recruiting (NCT04409002). Positive HRD status is not required for enrollment in this trial. The schedule includes daily niraparib plus intravenous dostarlimab once every 3 weeks. Radiotherapy is applied on every second day during cycle two only.

Another study of niraparib and dostarlimab in pancreatic cancer patients with germline or somatic mutations in HRD-related genes (BRCA1/2, PALB2, BRAD1, RAD51c, or RAD51d) is being initiated (NCT04493060). Patients will receive daily niraparib plus intravenous dostarlimab (once every 3 weeks for 4 cycles, then every 6 weeks). The primary endpoint for both trials will be the DCR.

5.5 | Combination with other targeted therapies

Several early-phase clinical trials of PARPi in combination with other targeted therapies in pancreatic cancer are underway. Biomarker-driven studies are shifting patient selection criteria from a previous focus on germline mutations toward more general surrogates for HRD. Through rational combinations, some targeted approaches also aim to induce HRD phenotypes rather than just exploit them. Molecular rationales that could complement PARPi in pancreatic cancer include targeted interferences with proliferation signaling, chromatin remodeling, cell cycle control, or the microenvironment. On the long term, these strategies might further improve the efficacy of PARPi and provide answers to emerging resistance mechanisms.

In a recruiting phase 1 study, olaparib is under evaluation in a triple combination with copanlisib, an inhibitor of phosphoinositide 3-kinase (PI3K), and the programmed cell death-1 ligand 1 (PD-L1) antibody durvalumab (NCT03842228). Patients with advanced solid tumors and with germline or somatic mutations in a broad panel of DDR genes are eligible. Treatment consists of olaparib twice daily plus intravenous copanlisib (on days 1, 8, and 15) and durvalumab (once per 28 day cycle). The primary endpoint is the MTD of olaparib and copanlisib. Olaparib has also been combined with promising results with the AKT inhibitor capivasertib.77

Potential biomarkers for a combination of olaparib and cebimetinib (an inhibitor of mitogen-activated protein kinase 1, MEK1) in pancreatic cancer are being studied in a phase 1 trial (NCT04005690). After acquisition of tumor biopsies, olaparib is given for a period of 10 consecutive days, followed by either repeat biopsy or tumor surgery. Patients in a second treatment arm receive single agent cebimetinib instead of olaparib. Specimens obtained before and after window therapy with either cebimetinib or olaparib will then be used to identify predictive biomarkers that could guide patient selection for this combination therapy.

Olaparib is combined with the ATR kinase inhibitor AZD6738 in an ongoing phase 2 trial in advanced solid tumors, including pancreatic cancer (NCT03682289). Participants are stratified into two arms according to their molecular ATM and ARID1a status. Patients with preserved expression of both ATM (mutation profiling or immunohistochemistry) and ARID1a (by immunohistochemistry) are treated with a combination of daily olaparib plus AZD6738 on the first 7 days of every 28 day cycle. Patients with either ATM loss or who are ARID1a negative receive AZD6738 monotherapy. Primary endpoint is the ORR.

In a phase 2 trial in patients with unresectable solid tumors, the combination of olaparib plus cediranib, an inhibitor of vascular endothelial growth factor receptors (VEGFR) is being assessed (NCT02498613). Besides inhibition of angiogenesis, cediranib has been shown to interfere with HR in tumor cells.78 Patients with pretreated pancreatic cancer are eligible, and HRD status is not required for enrollment. Final data collection for the primary endpoint ORR is awaited end of 2020.

6 | OUTLOOK

The recent approval of olaparib for maintenance therapy in PDAC patients with germline BRCA mutations following successful platinum-based therapy is an important new step in pancreatic cancer therapy. However, several unanswered questions remain. One crucial focus of research is the identification of patients suitable for PARPi therapy. On the one hand, carriers of germline BRCA mutations might not benefit from PARPi therapy in case their tumor lacks an HRD phenotype. On the other hand, there are possibly additional PDAC subgroups that might be successfully treated with PARPi therapy, including patients with somatic BRCA mutations and with mutations in other HRR-related genes or with BRCA1ess-signatures or unstable genomes. Equally important is the improvement of tailored therapy by
defining the optimal chemotherapy regimens for PDAC with HRD. Hopefully, combining PARPi therapy with other modalities like chemotherapy, immunotherapy, and small molecules will lead to further advances in therapeutic results. There is little doubt that progress in these research areas will be made in the near future—a promising new perspective for patients with this devastating disease.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by ProjektDEAL.

DATA AVAILABILITY STATEMENT

n.a.

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**How to cite this article:** Singh HM, Bailey P, Hübschmann D, et al. Poly(ADP-ribose) polymerase inhibition in pancreatic cancer. *Genes Chromosomes Cancer*. 2021;60:373-384. https://doi.org/10.1002/gcc.22932