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PARP Inhibitors in Pancreatic Cancer

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Abstract

Despite representing only 5% of all annual cancer diagnoses in the United States, pancreatic cancer is projected to become the second-leading cause of cancer-related death within the next ten years. Progress in the treatment of advanced pancreatic cancer has been slow. Systemic therapies rely on combination cytotoxic agents, with limited options at progression. Recently, poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors have demonstrated clinical activity in patients with advanced pancreatic cancer and pathogenic variants in *BRCA1*, *BRCA2* and *PALB2*. In this review, we discuss the development of PARP inhibitors in pancreatic cancer, relevant clinical trials, and future directions.

Keywords

Pancreatic Cancer; PARP inhibitors; Homologous Recombination Repair; BRCA; DNA Damage Repair

Pancreatic cancer is an aggressive disease characterized by genomic instability and a high rate of activating mutations in oncogenes and tumor suppressor genes[1]. Although it accounts for approximately 5% of all cancer diagnoses in the United States, pancreatic cancer is a leading cause of cancer-related mortality and is projected to become the second leading cause of cancer death in the United States by 2030[2,3]. Due to a combination of late symptom onset and aggressive pathophysiology, the majority of pancreas cancer diagnoses are made in the advanced setting. Treatment in such cases is aimed at reducing symptom burden and extending life. Until very recently, the only available systemic options were cytotoxic chemotherapies delivered in a “one-size-fits-all” approach until disease progression, clinical decline or death[4,5].

A clearly defined, inherited genetic basis for the development of pancreatic cancer is identified in an estimated 5–15% of those with the disease, with variations in frequency depending on local population demographics[6]. National Comprehensive Cancer Network (NCCN) guidelines recommend that all patients with a diagnosis of pancreatic cancer undergo germline genetic panel testing, both to identify pathogenic variants that may influence treatment as well as to inform family members who may be offered cascade testing based on positive results[7]. The development of effective, targeted therapeutic strategies for those with particular genomic variants is an area of active scientific and clinical study.

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Indeed, it has been shown in retrospective and prospective studies that platinum chemotherapies such as cisplatin and oxaliplatin are particularly effective against pancreatic cancers that harbor pathogenic variants in *BRCA1, BRCA2* and *PALB2*, with sustained responses lasting months or even years[8–11]. However, although maintenance (de-escalation) chemotherapy strategies are being tested and are recommended by the NCCN, perpetual treatment with cytotoxic agents leads to cumulative toxicity in patients, resulting in progressive fatigue and organ dysfunction[4,5,7,12].

Over the past decade, poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors (PARPi) have shown efficacy in solid tumors driven by defects in homologous recombination (HR), particularly in the platinum-sensitive setting[13–23]. PARP inhibitors are oral agents with a manageable toxicity profile. The landmark phase 3 POLO study tested the PARPi olaparib against placebo as maintenance therapy for patients with metastatic, platinum-sensitive pancreatic cancer and a germline *BRCA* variant[24]. The study met its primary endpoint of progression-free survival (PFS), demonstrating a median PFS of 7.4 months versus 3.8 months in the experimental and control groups, respectively (hazard ratio 0.54)[24]. This resulted in the FDA approval of olaparib in the maintenance setting for this group of patients.

The FDA approval of olaparib as maintenance therapy for patients with metastatic pancreatic cancer and germline *BRCA* mutations represents a step forward in the development of targeted treatments for patients with pancreatic cancer. This preliminary success opens the door for further development of PARP inhibitors in a variety of clinical scenarios and in combinations with other therapies. By the same token, the high variability in efficacy, even in a narrow group of germline *BRCA* carriers, pushes the scientific community to better identify predictive biomarkers for response to PARP inhibition and to evaluate resistance mechanisms for next generation targeting. In this review, we will explore the development of PARPi in pancreatic cancer, prior key trials of PARPi in pancreatic cancer, and ongoing and future directions for PARPi in pancreatic cancer.

Biological Rationale and Preclinical Evidence for PARP Inhibition in Pancreatic Cancer

Up to 20% of pancreatic cancers possess defects in HR[25]. Most frequently, these are due to pathogenic variants in *BRCA2*[25]. Carcinogenesis results when cells containing a pathogenic *BRCA* mutation lose the remaining *BRCA* allele, resulting in DNA instability and an accumulation of mutations in other genes, a process termed “loss of heterozygosity”[26].The resulting tumors are particularly vulnerable to therapies that cause double stranded DNA breaks, as the tumor cells lack the ability to repair them via the high-fidelity HR pathway.

The PARP enzyme is involved in base-excision repair (BER), a pathway that is critical for fixing single-strand breaks in the DNA, and assists with DNA repair[27,28]. In HR proficient cells, PARP inhibition results in single strand breaks and collapse of the DNA replication fork that are subsequently repaired via HR[27,28]. In cells that are homologous recombination deficient (HRD), the double stranded breaks that result from the DNA replication fork collapse cannot be repaired, leading to cumulative DNA damage and,

ultimately, cell death[27,28]. PARP inhibitors (PARPi) have two primary mechanisms of action. First, is catalytic disruption of PARP's enzymatic activity whereby PARP is no longer able to participate in BER, resulting in an accumulation of single strand breaks (that otherwise would be repaired via HR), chromosomal instability, and apoptosis[28]. Second, and even more critical, is that PARPi's increase the affinity of PARP for the DNA strand, promoting DNA-protein crosslinks and thus "trapping" PARP on the DNA[29]. As a result, DNA replication during S-phase fails, as the replication fork cannot bypass the trapped PARP-DNA complex. The result is an accumulation of strand breaks that ultimately leads to cell death[30]. While the catalytic activity of most clinically used PARPi is similar, efficacy and toxicity seem linked to the ability of the drug to "trap"[29]. Veliparib, which does not trap, is the least effective of the class and the PARPi that can be most easily combined with other cytotoxic agents. Rucaparib, olaparib, and niraparib trap at similar levels, while talazoparib has the greatest ability to trap. As a result, talazoparib is the most potent and toxic of this drug class[29,31,32].

The observation that PARPi are effective against HRD cells was first demonstrated in Chinese hamster ovary cell lines that were HR deficient[27]. At low concentrations, the cells were exquisitely sensitive to PARP inhibition. However, when the HR deficiency was reversed, the cells were no longer sensitive to PARP inhibition[27]. Mice that were xenografted with *BRCA2*-deficient cancer cells and were treated with PARPi demonstrated less tumor formation compared to *BRCA2*-proficient counterparts[28]. Treatment of *BRCA*-mutated cancer cells with PARPi results in selective tumor toxicity with relative sparing of the normal, heterozygous cells that have intact HR[27,28]. The concept of selective toxicity of PARP inhibition for *BRCA*-mutated cells illustrates the concept of "synthetic lethality", the situation where two deficits have little individual effect on the cellular phenotype but their combination leads to cellular death[33,34]. This has been illustrated in pre-clinical models - knockout models of *Parp1* −/− mice are both viable and fertile, and mice without PARP do not develop early onset tumors compared to those with intact PARP[27]. However, absence of PARP activity results in increased reliance on HR[27]. *In vitro* deletion of *BRCA2* in human cell lines results in exquisite sensitivity to PARPi at even low concentrations[27]. A preclinical model of *BRCA*-deficient pancreatic cancer showed similar findings; treatment with PARPi reduced cellular viability *in vitro* and slowed the formation of tumors *in vivo*[35].

Phase 1 Trials of PARP inhibitors in Pancreatic Cancer

On the basis of this preclinical evidence, PARP inhibitors were subsequently trialed in humans. Table 1 lists PARPi's that have been trialed in patients with pancreatic cancer, including their specific pharmacologic properties and dosing. The initial phase 1 studies allowed enrollment of patients with advanced cancers, with mechanisms to enrich the population for *BRCA1* and *BRCA2* mutation carriers (Table 2) given the preclinical data that this drug class may be efficacious in the HRD setting.

Olaparib, rucaparib, niraparib, talazoparib, and fluzoparib have all completed monotherapy phase 1 clinical trials that included patients with pancreatic cancer. In these toxicity trials, it was strikingly obvious that patients with germline *BRCA* variants were more likely to benefit from PARPi treatment compared to patients with sporadic cancers[30,36–39]. For

example, in the phase 1 study of olaparib, 12 of 19 evaluable patients with germline *BRCA* mutations had either disease response or stabilization, while no patients with sporadic disease had such a result[36].

The observation that patients with HRDs had superior outcomes to those with sporadic cancers extended to patients with pancreatic cancer. In the phase 1/2 trial of rucaparib, one of two patients with *BRCA*-related pancreatic cancer experienced a prolonged partial response[30]. Similarly, of 13 pancreatic cancer patients enrolled in the phase 1 trial of talazoparib, two had partial responses to therapy: one with a *BRCA2* variant, the other with a *PALB2* variant[39]. These findings provided support to pursue PARPi therapy specifically in HRD pancreatic cancer.

Several notable phase 1 combination studies with PARPi have been completed. First, a phase 1 study of rucaparib in combination with temozolomide was performed following pre-clinical evidence of potentiation of alkylators by PARPi[40,41]. A total of 32 patients were treated, including one patient with pancreatic cancer. The combination was deemed to be safe and adequate PARP inhibition could be achieved, although myelosuppression was noted at lower-than-expected doses of temozolomide. The single patient with pancreatic cancer enrolled on the study experienced disease stability for more than six months[40]. This combination has not been pursued further so far and there are no active clinical trials of this combination on clinicaltrials.gov (as of August 9, 2021).

Second, a phase 1 study of veliparib in combination with cisplatin and gemcitabine was performed in patients with advanced pancreatic cancer and germline *BRCA* mutations or a family history of *BRCA*-related cancers[42]. Nine patients with *BRCA* mutations were enrolled and seven patients without *BRCA* mutations were enrolled. Seven patients on the study (all with *BRCA* mutations) had responses, six partial responses and one complete response. The patient with a complete response developed acute myeloid leukemia 2.5 years into therapy that was potentially related to the treatment. An additional eight patients with *BRCA* mutations had stable disease. No responses were seen in patients without *BRCA* mutations[42]. Given the promising signals of efficacy, this combination was then tested in a randomized phase 2 trial, which will be discussed later in this review[10].

Finally, a phase 1 study investigated the use of veliparib in combination with gemcitabine and radiotherapy for patients with locally advanced pancreatic cancer[43]. This single-institution trial enrolled patients with treatment-naïve locally advanced pancreatic cancer or borderline resectable pancreatic cancer. Thirty patients were enrolled, however none possessed *BRCA* mutations. Nine patients had tumors with mutations in other DNA damage repair genes (*ARID1A, ATM, CHEK2, PALB2, PTEN,* and loss of *MLH1*). The median OS seen in patients treated with this regimen was 14.6 months. A slightly longer median OS of 19 months was observed for patients with defects in DNA damage repair pathways, although this was not statistically significant[43].

Based on the findings that PARPi therapy was well tolerated and demonstrated efficacy in patients with DNA damage repair alterations, a number of phase 2 and 3 trials were

launched. Most prominent were trials in the canonical tumor types associated with *BRCA*, namely: breast, ovarian, prostate and pancreatic cancer.

Phase 2 Trials

Multiple phase 2 trials have investigated the efficacy of PARPi in pancreatic cancer (Table 3). The first of these was a multicenter phase 2 study that enrolled patients with pathogenic germline *BRCA1* or *BRCA2* mutations and recurrent solid tumors to receive olaparib monotherapy[44]. The primary endpoint was tumor response rate[44]. A total of 298 patients were enrolled, of whom 23 had advanced pancreatic cancer. The tumor response rate for patients with pancreatic cancer was 21.7% (95% CI 7.5–43.7%), although 65% had received prior platinum therapy. One patient had a complete response, and four patients had partial responses. The median duration of response for patients with pancreatic cancer was 4.4 months, the median PFS was 4.6 months, and the median OS was 9.8 months. Proportionally, more patients with pancreatic cancer who were not previously exposed to platinum chemotherapy had a response (two of eight patients without prior platinum use versus three of fifteen patients with prior platinum use)[44]. This study provided adequate rationale to continue the development of PARP inhibitors in *BRCA*-related pancreatic cancer.

RUCAPANC was a single arm phase 2 study testing monotherapy rucaparib in patients with locally advanced or metastatic pancreatic cancer and pathogenic germline or somatic *BRCA*1 or *BRCA2* mutations after progression on at least one prior line of chemotherapy[45]. The primary endpoint was objective response rate. A total of nineteen patients received at least one dose of rucaparib. The confirmed objective response rate was 15.8%, with two confirmed partial responses, one confirmed complete response, and one unconfirmed complete response[45]. Notably, responses were only observed in platinum-sensitive patients and two of the responses were seen in patients with somatic *BRCA2* variants[45].

Based on these observations, a single arm phase 2 maintenance trial of rucaparib in patients with somatic or germline variants in *BRCA* or *PALB2*, advanced pancreatic cancer and platinum sensitive disease was performed[46]. The primary endpoint was PFS. A majority of the 42 evaluable patients had received at least 16 weeks of platinum-based chemotherapy for locally advanced or metastatic disease without evidence of platinum resistance; eight patients received fewer than 16 weeks due to either intolerance or allergy to platinum. The median PFS was 13.1 months, with a six-month PFS of 59.5% and a 12-month PFS of 54.8%. The median OS was 23.5 months with eight patients alive more than two years after enrollment. Importantly, of the six patients with germline *PALB2* variants, three had responses, including one who had a CR. Of the two patients with somatic *BRCA2* variants, one had a prolonged partial response. A post-hoc analysis of patients who received at least 16 weeks of platinum-based chemotherapy compared to the eight patients who received fewer than 16 weeks of chemotherapy showed no difference in PFS or OS, raising the question whether a full four months of platinum-based chemotherapy prior to starting maintenance PARPi therapy is required. Although limited in sample size, patients with *BRCA1* pathogenic variants and those with higher disease burden at study start responded less favorably to maintenance PARPi[46]. Overall, this trial added credence to using PARPi for

patients with germline *PALB2* variants and somatic *BRCA* variants, expanding the group of patients for whom this therapy might be applied.

Veliparib was tested in a single-arm phase 2 trial of patients with previously treated stage III or IV pancreatic cancer with known germline *BRCA1*, *BRCA2* or *PALB2* mutations to determine the response rate, duration of response, PFS, and OS[47]. A total of 16 patients were enrolled, with 14 having had prior exposure to platinum-based therapy. The study was closed early due to insufficient activity. No confirmed responses were seen in this trial, although one patient who had not been previously exposed to platinum chemotherapy had an unconfirmed partial response. The best observed response was stable disease in five patients. The median PFS was 1.7 months and the median OS was 3.1 months[47]. Veliparib's inability to PARP trap and the high proportion of patients with platinum-resistant cancer likely contributed to these disappointing results.

Based on phase 1 data showing tolerance and efficacy of veliparib with platinum-based chemotherapy in patients with *BRCA*-related pancreatic cancer, O'Reilly et al performed a randomized, multicenter, phase 2 trial investigating the combination of gemcitabine and cisplatin with or without veliparib in patients with advanced, previously untreated pancreatic cancer and a germline *BRCA* or *PALB2* mutation[10]. Fifty patients were randomized 1:1 to receive cisplatin 25mg/m2 with gemcitabine 600 mg/m2 on days 3 and 10 with or without veliparib 80 mg twice daily on days 1–12 of each 21-day cycle. The primary endpoint was objective response rate (ORR). PFS, OS, safety, and disease control rate (DCR) were secondary endpoints. Twelve (24%) of the enrolled patients had *BRCA1* mutations, thirty-five (70%) had *BRCA2* mutations, and three (6%) had *PALB2* mutations. There was no significant difference in the ORR (74.1% vs 65.2%; p = 0.55), PFS (10.1mo vs 9.7mo) or OS (15.5 mo vs 16.4 mo) between groups. Myelosuppression requiring dose reductions was more common in the experimental group[10]. Importantly, although this trial was negative, it demonstrated an unprecedented ORR to first line palliative cisplatin plus gemcitabine in patients with *BRCA* and *PALB2* variants. This regimen is now considered a standard option for this patient population.

A major area of scientific interest is to expand upon the group of patients for whom PARPi therapy might be used. In an effort to explore this, two parallel phase 2 trials enrolled patients with advanced pancreatic cancer and either: (1) non-*BRCA* HRD variants, (2) a personal or family history of *BRCA*-related cancers or (3) ATM loss by IHC[48]. A total of 46 patients were enrolled and the primary endpoint was ORR by RECIST 1.1. Thirty-four patients were platinum-sensitive, two were platinum-naïve, and the remainder were platinum-refractory. Two patients in this combined study had a partial response and thirty-three had stable disease, with a median disease control rate of 2.9 months[48]. The median PFS was 3.7 months (consistent across both studies) and the median OS was 9.9 months. Patients with platinum-sensitive cancers experienced longer median PFS and OS (4.1 vs 2.2 months and 10.5 vs 5.4 months, respectively). Lastly, patients with mutations in DNA damage repair genes had longer PFS than those with a family history of *BRCA*-related tumors or those with ATM loss (5.7 mos [95% CI 3.6–8.8 mos] vs 2.6 mos [1.9–3.9 mos]), although this association was not formally tested[48]. The somewhat disappointing results of

this study highlight that our ability to identify patients for PARPi therapy remains crude and that functional assays for DNA damage repair deficiency are needed.

Phase 3 Trials

The POLO study is the sole completed phase 3 trial of a PARPi in pancreatic cancer. In this randomized, double-blind study, patients with metastatic disease and germline *BRCA1* or *BRCA2* mutations who had been treated with at least four months of platinum-based chemotherapy without progression were randomized 3:2 to receive maintenance olaparib or placebo. Patients who received olaparib experienced a longer median PFS compared to placebo (7.4 months vs 3.8 months; HR 0.54) while preserving quality of life[24,49]. Although this trial met the primary endpoint of improved PFS, there was no difference in median overall survival with olaparib compared to placebo (19.0 months vs 19.2 months, respectively)[50]. On the basis of these results, olaparib was approved by the United States Food and Drug Administration (FDA) for maintenance treatment of adult patients with *BRCA*-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed after at least 16 weeks of platinum-based chemotherapy[51]. The approval has made olaparib a therapeutic option in clinical practice for these patients.

An ongoing phase 3 trial of fluzoparib in patients with metastatic pancreatic cancer with germline *BRCA1/2* or *PALB2*.mutations that has not progressed on platinum-based chemotherapy hopes to further build on the success of POLO in moving PARPi into the maintenance space for patients with pancreatic cancer (NCT04300114).

Resistance to PARP Inhibition

Primary Resistance

Despite a strong biological rationale, not all patients with *BRCA* mutations or DNA damage repair gene alterations respond to treatment with PARPi. For example, roughly 20% of patients receiving olaparib on the POLO study progressed by the first planned assessment, despite entering the study with clinical platinum sensitivity[24]. In patients with pathogenic germline *BRCA* or *PALB2* mutations treated with rucaparib, approximately 16% progressed at first assessment[46]. This implies that even in the setting of platinum sensitivity, some HRD tumors are primarily resistant to PARPi treatment. In a series of cases of pancreatic cancer with pathogenic germline *BRCA* mutations, 12% of tested samples (6/49) retained the wild-type allele and were found to be homologous recombination proficient[52]. Consistent with clinical experience, this finding suggests that in some cases, a patient with a germline *BRCA* variant and pancreatic cancer would not be expected to respond favorably to targeted therapy, such as with PARPi.

Adaptive Resistance

Secondary resistance to PARP inhibitors develops almost inevitably in the palliative setting. Identifying mechanisms of the development of resistance to PARP inhibition is an area of focus, particularly as the development of successful second generation therapies will likely depend on understanding the key mechanisms of PARPi failure.

One described mechanism of adaptive resistance is the restoration of homologous repair by reversion mutations following treatment[53]. A recently published study collated all published literature on reversion mutations and characterized 300 reversion mutations in 91 patients that resulted in PARPi resistance[53]. Other purported mechanisms of resistance include mutations or downregulation in PARP1, increased drug efflux via p-glycoprotein, independent restoration of homologous repair (such as with loss of 53BP1, REV7, RIF1, and shielden), and restoration of replication fork stability (via loss of SLFN11, RADX or SMARCAL1 depletion) among others[54–62,62–67]. Strategies to overcome PARPi resistance with combination therapies are currently under development and are discussed later in this review.

Prospectively predicting which patients with HR mutations will benefit from PARP inhibition will be crucial to advancing the field and assays for HR are in development. Currently in clinical practice, HRD is assessed using genomic methods such as next generation sequencing specifically analyzing *BRCA1, BRCA2, PALB2, ATM, CHEK2,* and *FANC*[68,69]. In the context of clinical trials, HRD is usually determined by whole genome sequencing, whole exome sequencing, targeted next generation sequencing, or deep exome sequencing[68]. Other assays remain investigational but are promising due to their high sensitivity and specificity. Substitution base signature 3 (SBS3; indels>3 base pairs in length) is strongly associated with HRD, however requires whole genome sequencing to perform[70–72]. Myriad's MyChoice HRD assay performs whole exome sequencing to calculate a genomic instability score (GIS) that correlates with HRD[52,73–75]. Although this test is FDA approved in gynecological malignancies and requires formalin-fixed paraffin-embedded tissue to calculate the GIS; its use in pancreatic cancer may be challenging due to limited cellularity of tumor specimens[13,52,74,75]. In a series of pancreatic cancer patients with germline *BRCA* mutations described above, the authors used the HRDetect score, a combination score derived from mutational signatures[52]. HRDetect was found in this series to have 100% sensitivity and 98% specificity in identifying HRD pancreatic cancer, however it requires fresh frozen tissue for whole genome sequencing[52]. Measurement and detection of RAD51 foci by immunofluorescence or imunhistochemistry may serve as a marker for intact HR[69]. Early clinical evidence suggests this functional assay may correlate to sensitivity to PARPi or platinum[65]. A DNA fiber assay is also in development that seeks to measure stalled replication fork protein stability to correlate with resistance or sensitivity to PARPi or platinum[69,76]. Further refinement and technological availability is needed prior to these assays being employed clinically to fully realize the potential efficacy of PARP inhibition for a given patient.

Future directions

There are several ongoing trials to further define the role of PARPi in pancreatic cancer (Table 4). These include studies that move PARPi into the earlier disease setting and those combining PARPi with other agents based on synergy observed in preclinical models.

Curative Intent

The APOLLO study (ECOG-ACRIN 2192; NCT04858334) is a randomized phase 2 double blind study of adjuvant olaparib vs placebo for one year in patients with germline or somatic pathogenic mutations in *BRCA* or *PALB2* who have completed all curative intent treatment[77]. Patients who are within eight weeks of completing all standard therapy are randomized 2:1 to receive olaparib or a placebo pill. The primary endpoint is PFS. Information gleaned from this trial will further inform the use of adjuvant PARPi, a strategy that was recently shown to be effective in improving invasive disease-free survival in early stage, high-risk, *BRCA*-mutated breast cancer[78].

PARPi plus Immune Checkpoint Blockade

Combining PARPi with immunotherapy is a novel concept that is under investigation. The addition of PARPi to HRD cells results in cytosolic accumulation of DNA and leads to activation of the stimulator of interferon genes (STING) pathway. In turn, this triggers an inflammatory cascade that leads to enhanced tumor infiltration by lymphocytes and increased PDL1 expression. These observations provide an intriguing biological rationale for combining PARPi with immunotherapy and several studies are currently exploring this strategy[79–82]. The phase 1b/2 randomized PARPVAX study is enrolling patients with pancreatic cancer that have not progressed on platinum chemotherapy to receive niraparib with either ipilimumab or nivolumab (NCT03404960). The POLAR study, another non-randomized phase 2 trial, is testing the combination of pembrolizumab with olaparib in patients with metastatic pancreatic cancer and HRR deficiency in the maintenance setting (NCT04666740). The Southwest Oncology Group is running a similar trial, testing olaparib with or without pembrolizumab as maintenance therapy in patients with metastatic pancreatic cancer and germline *BRCA1/2* mutations (NCT04548752). If successful, these trials will open a potentially new combination of historically well-tolerated treatments to patients with metastatic pancreatic cancer and will further the development of maintenance combination therapies, both for patients with HRD and those without.

PARPi plus Other Agents

Several combinations with PARPi are in clinical development based on preclinical data showing synergy in the HRD and non-HRD settings. For example, preclinical data have shown that treatment of pancreatic cancer cells with bromodomain and extraterminal (BET) inhibitors results in cellular sensitivity to PARP inhibition by blunting DDR signaling and reducing transcription of *BRCA1* and *RAD51*[83,84]. Together, this produces a phenotype similar to the *BRCA*-mutated pancreatic cancers. A first in-human study testing this combination has been completed, however results have not yet been published (NCT03205176). Combining PARPi with vascular endothelial growth factor inhibitor bevacizumab is also of interest and has been approved for use in ovarian cancer following the results of the phase 3 PAOLA-1 trial demonstrating a 6 month median PFS improvement in patients with platinum-sensitive advanced ovarian cancer randomized to receive olaparin-bevacizumab compared to placebo-bevacizumab (22.1 vs 16.6 mos)[13]. It is suspected that the anti-tumor activity is derived from the relative tissue hypoxia produced by inhibiting angiogenesis. This results in decreased transcription of homologous recombination repair

genes and may increase the efficacy of concurrent PARP inhibition[85–87]. Clinical trials exploring this combination are underway in other cancer types[88]. A third combination that shows synergy in preclinical studies is PARPi plus inhibitors of ataxia telangiectasia and Rad3-related protein (ATR). This combination was first hypothesized to be effective following the observation that lung cancer cells lacking *ATM* were more sensitive to PARPi than expected[89]. Coinhibitory studies on biliary tract cancers support a synergistic antitumor effect from combination PARPi and ATR inhibition and early phase clinical trials are underway (NCT04298021)[90]. Another combination of interest is PARPi and AKT inhibition following preclinical evidence showing inhibition of the PI3K-AKT pathway results in suppression of BRCA1, promoting HR deficiency and PARPi sensitivity[91]. A recent phase 1 trial of PARP inhibition with olaparib with the AKT inhibitor capivasertib in advanced solid tumors recently showed preliminary signs of anti-tumor activity, particularly in *BRCA*-mutated cancers and even in patients with prior PARPi exposure[92].

Because primary and secondary resistance to PARPi remain a major hindrance for the clinical use of PARPi, rational mechanisms for overcoming resistance are needed. Co-inhibition of RAD52 and PARP may be a mechanism for suppressing alternative HR pathways. Pre-clinical data suggest a synergy between RAD52 inhibitors and PARPi in *BRCA*-deficient tumors, introducing the concept of “dual synthetic lethality”[60,93]. Altering cellular energy metabolism may also have a role in overcoming PARPi resistance. Preclinical inhibition of nicotinamide phosphoribosyltransferase (PAMPT) in combination with olaparib results in cellular depletion of NAD+ and slows the growth of tumors in a triple negative breast cancer model[60,94]. Suppression of microhomology-mediated end-joining via POL Ø inhibition may also prevent the emergence of PARPi resistance by preventing the hypermutating phenotype that results from reliance on microhomology-mediated end-joining[95]. In HR deficient cells, POL Ø deficiency is also synthetically lethal and co-inhibition with PARP inhibition results in effective cell killing[95–97].

Beyond BRCA

Finally, the study and treatment of patients with DDR alterations beyond those with *BRCA* and *PALB2* variants is of tremendous scientific interest, as this would expand the group of patients for whom PARPi might be used. Mounting data suggests that selecting therapies based solely on genotype is an insufficient strategy, as (1) not all patients with *BRCA* or *PALB2* mutations are truly DDR deficient, (2) patients without mutations may be DDR deficient when tested by functional assays and (3) there remains relatively little clarity around which variants outside the core DDR genes truly result in a PARPi responsive phenotype[52]. Highlighting this last point, when evaluated by the whole genome sequencing assay HRDetect, pancreatic tissue samples from patients with *ATM* or *CHEK2* variants do not appear to have an HRD, which would suggest that PARP inhibitors might not be an effective strategy for this group[52]. To date, multiple PARPi clinical trials have enrolled patients with one of a variety of mutations (Tables 2–4), but this “lumping” strategy is likely to dilute efficacy signals due to variability in HRD among variants. Therefore, there is substantial interest in developing clinically useful functional assays to more precisely identify the right patients for PARP inhibitor treatment.

Conclusions

Locally advanced and metastatic pancreatic cancer continues to have a poor prognosis. However, the recognition that a portion of patients with this disease possesses a uniquely targetable biology has changed the landscape of treatment and scientific research. PARP inhibitors are a molecularly targeted therapy that are well tolerated with sensitivity noted in patients with tumors possessing *BRCA1* and *BRCA2* mutations. The success of olaparib in the monotherapy setting for patients with metastatic disease has made this class of drugs an option for patients in clinical practice and has opened the doors for additional research that is focused on moving these agents into the curative intent setting, more precisely identifying and expanding the population for which they could be used, identifying and thwarting resistance mechanisms, and improving efficacy with combination therapies.

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Table 1.

PARPi that have been trialed in patients with pancreatic cancer. Dosing and common toxicities information obtain from FDA prescribing information. For drugs that are not FDA approved, dosing information was obtained from the most recent clinical trial report.

PARPi	Properties[60]	Dosing	Common Toxicities
Olaparib	Targets PARP1,2,3 and 4. Interacts with CYP	300 mg BID	Fatigue, anemia, thrombocytopenia, neutropenia
Rucaparib^	Targets PARP1,2,3 and 4. Interacts with CYP	600 mg BID	Thrombocytopenia, anemia, nausea, fatigue
Veliparib*	Weakest PARP trapping abillity	80 mg BID days 1–12 of 21 day cycles	Anemia, leukopenia, fatigue
Niraparib^	High CNS penetration, off-target interactions with doapnmine, serotoning, norepinephrine receptors	200–300 mg daily	Nausea, thrombocytopenia, anemia, fatigue
Talazoparib^	Most potent PARP-trapping ability, long half-life	1 mg daily	Anemia, neutropenia, thrombocytopenia
Fluzoparib*	No CNS penetration. Trapping ability not yet defined	150 mg BID	Anemia, neutropenia

*- denotes agent is still investigational and not approved by the US FDA for any cancers.

^ - denotes drug is not approved by the US FDA for the treatment of pancreatic cancers, but has been approved for the treatment of other cancer types

BID: twice daily

Table 2.

Sumary of completed phase 1 trials involving patients with pancreatic cancer

PARPi	Author	Design	N (N Pancreas)	Tumor types included	Mutations (n with mutations)	Key Findings	Ref
Olaparib	Fong	Phase 1 dose escalation with expansion phase of only patients with *BRCA* mutations	60 (2)	Advanced solid tumors refractory to established therapies (ovarian, breast, colorectal, melanoma, sarcoma, prostate, other)	Not required in the initial cohort, expansion cohort enrolled only patients with *BRCA1/2* mutations (n=22)	MTD 400 mg BID Sufficient inhibition of PARP achieved at olaparib 60 mg BID Fatigue and nausea were common side effects. 9 of 19 evaluable patients with *BRCA* mutations had a response	36
Rucaparib	Plummer	Phase 1 dose escalation in combination with temozolomide 100 mg/m2 escalating to 200 mg/m2 daily days 1–5 of 28 day cycles	32 (1)	Advanced solid tumors (sarcoma, melanoma, colorectal, other)	Not reported	RP2D: rucaparib 12 mg/m2 and temozolomide 200 mg/m2 days 1–5 of 28 day cycles. Grade 3 neutropenia occurred in high doses One patient with pancreatic cancer experienced prolonged disease stabilization	40
	Kristeleit	Phase 1 3+3 dose escalation	56 (2)	Ovarian cancer and other solid tumors	All patients had germline *BRCA1/2* mutations	RP2D: 600 mg BID Fatigue, myelosuppression. Gastrointestinal upset were common but manageable. One of the two patients with pancreatic cancer experienced a prolonged response	30
Niraparib	Sandhu	Phase 1 dose escalation	100 (1)	Advanced solid tumors	With (29) or without *BRCA* mutations	MTD and RP2D: 300 mg/day Anemia, thrombocytopenia, neutropenia, fatigue were common. Single patient with pancreatic cancer possessed *BRCA2* mutation and did not respond to treatment	37
Veliparib	O'Reilly	Single arm phase 1 dose escalation study with gemcitabine 600 mg/m2 day 3 and 10 and cisplatin 25 mg/m2 days 3 and 10	17 (17)	Advanced or metastatic pancreatic cancer and were naïve to platinum-based therapies	*BRCA* mutations (9) or family history of *BRCA*-related cancers	RP2D: 80 mg BID 11ay 1–12 of 21 day cycles in combination with cisplatin and gemcitabine Grade 4 neutropenia and thrombocytopenia were common Objective responses only seen in patients with *BRCA* mutations (7 of 9 patients) One patient developed acute myeloid leukemia 2.5 years into therapy	42
	Tuli	Single arm phase 1 combining veliparib with gemcitabine and radiation	30 (30)	Treatment-naïve locally advanced pancreatic cancer or borderline resectable pancreatic cancer	No patient had *BRCA1* or *BRCA2* mutations Nine patients with mutations in other DNA damage repair genes (*ARID1A, ATM, CHECK2, PALB2, PTEN,*	MTD: 40 mg BID Lymphopenia and Anemia were common Grade 3 Aes Slightly longer median OS in patients with mutations in DDR	43

PARPi	Author	Design	N (N Pancreas)	Tumor types included	Mutations (n with mutations)	Key Findings	Ref
					and loss of *MLH1*).		
Talazoparib	de Bono	Dose escalation followed by expansion cohort	113 (13)	Tumors predicted to be potentially sensitive to PARPi, including germline *BRCA1/2* mutations	With (59) or without germline *BRCA* mutations	4.0 mg/day RP2D Marrow toxicity common 2/13 pancreatic cancer patients had a PR (one with *BRCA2* mutation, one with *PALB2* mutation)	39
Fluzoparib	Li	Phase 1 3+3 dose escalation	79 (2)	Advanced solid tumors	With (59) or without *BRCA* mutations	MTD: 150 mg BID Antitumor responses seen in platinum resistant and platinum-refractory *BRCA* mutated cancers	38

RP2D: Recommended phase 2 dose, MTD: Maximum tolerated dose, BID: twice daily, AE: adverse event DDR: DNA Damage Repair, PR: partial response.

Table 3.

Summary of published phase 2 and 3 trials of PARPi in pancreatic cancer.

Phase 2 trials						
Author (Trial name)	**Design**	**Stage**	**Setting**	**Drug**	**Key Findings**	**Ref**
Kaufman	Non-randomized phase 2	Advanced or metastatic	• Progression after gemcitabine • Germline *BRCA1* or *BRCA2*	Olaparib	ORR: 21.7% DOR: 134 days OS: 18.4 mos PFS: 4.6 mos	44
Shroff (RUCAPANC)	Non-randomized phase 2	Locally advanced or metastatic	• Progression after 1–2 lines of chemotherapy • Germline or somatic *BRCA1* or *BRCA2*	Rucaparib	ORR: 15.8% DCR: 31.6%	45
Lowery	Non-randomized phase 2	Locally advanced or Metastatic	• Progression. • Germline *BRCA1, BRCA2,* or *PALB2*	Veliparib	ORR: 0% mPFS: 1.7 mo mOS: 3.1 mo	47
O'Reilly	Randomized phase 2	Locally advanced or metastatic	• First Line • Germline *BRCA1, BRCA2* or *PALB2*	Gem/Cis +/− Veliparib	(veliparib vs without) ORR: 74.1% vs 65.2% (p=0.55) DCR: 100% vs 78.3% (p=0.02) mOS: 15.5 mos vs 16.4 mos (p=0.6) mPFS: 10.1 mos vs 9.7 mos (p=0.73) G3–4 heme toxicities: 48% vs 30%	10
Javle	Two parallel non-randomized phase 2	Metastatic	• Second or Third Line DNA Damage Repair deficiencies other than *BRCA* mutations	Olaparib	ORR: mOS: 9.9 mos mPFS: 3.7 mos	48
Reiss	Non-randomized phase 2	Unresectable or metastatic	Maintenance • Germline or somatic *BRCA1* or *BRCA2*	Rucaparib	mPFS: 13.1 mos mOS: 23.5 mos DCR: 66.7% DOR: 17.3 mos ORR: 41.7%	46
Phase 3 trials						
Author (Trial Name)	**Design**	**Stage**	**Setting**	**Drug**	**Outcomes**	**Ref**
Golan (POLO)	Randomized phase 3	Metastatic	• Maintenance • Germline *BRCA1* or *BRCA2*	Olaparib vs placebo	mPFS 7.4 mo vs 3.8 mo (HR 0.43 95%CI 0.35–0.82, p=0.004) mOS 18.9mo vs 18.1 mo (HR 0.91 95% CI 0.56–1.46, p=0.68) HRQOL between group difference −2.47 (95%CI −7.27 to 2.33) on 100-point scale	24,49,50

mPFS = median progression-free survival, OS= median overall survival, HRQOL= health-related quality of life 95%CI = 95% Confidence Interval, ORR = objective response rate, DCR = disease control rate, G3–4 Heme toxicities = rates of grade 3 to grade 4 hematologic toxicity, gem= gemcitabine, cis= cisplatin. POLO HRQOL was assessed with the EORTC QLQ-C30 global health-related quality-of-life score. Javle study accepted DNA damage repair deficiencies: somatic *BRCA* variant, somatic or germline: *ATM, PALB2, CHEK1, FANCA, BARD1, RAD50*, and *ARID1A*.

Table 4.

Ongoing phase 2 or 3 studies of PARPi in pancreatic cancer. Status as of July 21, 2021. Trials may be open to other tumor types, visit clinicaltrials.gov for the latest information.

PARPi	ClinicalTrials.gov Identifier (Name)	Trial Phase	Setting	Drugs	Status
Olaparib	NCT04666740 (POLAR)	Non-randomized phase 2	Maintenance after first or second-line therapy for metastatic disease. Germline mutations in homologous recombination (*BRCA 1, BRCA2, PALB2, ATM, BAP1, BARD1, BLM, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, RAD50, RAD51, RAD51C, RTEL1*) Platinum sensitive or resistant.	Pembrolizumab + Olaparib	Recruiting
	NCT04548752	Randomized phase 2	Maintenance therapy in metastatic disease with germline *BRCA1* or *BRCA2* mutations after first line platinum-based chemotherapy	Pembrolizumab + Olaparib Olaparib monotherapy	Recruiting
	NCT02677038	Non-Randomized phase 2	Metastatic and with mutations in homologous recombination (e.g. somatic *BRCA* mutation, *FANC1*, *ATM* or *RAD51* mutations) or in patients with close family members with *BRCA*-driven cancers Negative for germline *BRCA1* and *BRCA2* mutations After at least one prior line of chemotherapy for metastatic disease and not have platinum-refractory cancer	Olaparib monotherapy	Active, not recruiting
	NCT04858334 (APOLLO)	Randomized phase 2	Adjuvant therapy following completion of surgery and chemotherapy Germline or somatic *BRCA1*, *BRCA2* or *PALB2* mutation	Olaparib monotherapy Placebo	Recruiting
	NCT02498613	Non-randomized phase 2	Maintenance therapy in advanced and metastatic pancreatic cancer	Cediranib + Olaparib	Recruiting
	NCT03682289	Non-randomized phase 2	Maintenance therapy in locally advanced or metastatic pancreatic cancer following at least one previous line of therapy	AZD6738 + Olaparib AZD6738	Recruiting
Rucaparib	NCT04171700 (LODESTAR)	Non-randomized phase 2	Maintenance therapy in unresectable, locally advanced, or metastatic solid tumors with deleterious mutations in BRCA1, BRCA2, PALB2, RAD51C or RAD51D. An expansion cohort is planned for patients with deleterious mutations in BARD1, BRIP1, FANCA, NBN, RAD51 or RAD51B. Following at least one but not more than three prior lines of systemic therapy	Rucaparib monotherapy	Recruiting
Niraparib	NCT03601923	Non-randomized phase 2	Maintenance therapy in metastatic or locally advanced pancreatic cancer with germline or somatic mutations in *BRCA1, BRCA2, PALB2, CHEK2* or *ATM.* No progression on prior oxaliplatin-containing regimens	Niraparib monotherapy	Recruiting
	NCT04409002	Non-randomized phase 2	Metastatic pancreatic cancer	Niraparib + Dostarlimab + Radiation	Recruiting
	NCT03553004 (NIRA-PANC)	Non-randomized phase 2	Metastatic pancreatic cancer with germline or somatic mutations in genes involved in DNA repair following progression after 1–2 lines of chemotherapy	Niraparib Monotherapy	Recruiting

PARPi	ClinicalTrials.gov Identifier (Name)	Trial Phase	Setting	Drugs	Status
	NCT04493060	Non-randomized phase 2	Metastatic pancreatic cancer with germline or somatic *BRCA1, BRCA2, or PALB2* mutations. Following progression on 1–2 prior lines of chemotherapy for metastatic disease, with prior exposure to a platinum agent.	Niraparib + Dostarlimab	Recruiting
	NCT03404960 (PARPVAX)	Randomized Phase 1b/2	Maintenance therapy for locally advanced or metastatic pancreatic cancer with stable disease after at least 16 weeks of platinum-based treatment	Niraparib + Nivolumab Niraparib + Ipilimumab	Recruiting
Talazoparib	No identified phase 2 or 3 trials				
Veliparib	NCT02890355	Randomized phase 2	Metastatic pancreatic cancer with recurrence following one prior systemic regimen *BRCA1, BRCA2,* or other defects in homologous recombination repair	Veliparib + mFOlFIRI FOLFIRI	Active, Not Recruiting
	NCT01585805	Randomized phase 2	Locally advanced or metastatic pancreatic cancer with *BRCA1, BRCA2,* or *PALB2* mutation. No prior treatment allowed for Arms A and B (GCV vs GC), up to two prior treatments allowed for Arm C (single agent veliparib)	Gemcitabine + Cisplatin and veliparib Gemcitabine + cisplatin Veliparib monotherapy	Active, not recruiting
Fluzoparib	NCT04300114	Randomized Double-Blind Phase 3	Maintenance therapy in patients with BRCA1/2 or PALB2-mutated pancreatic cancer that has not progressed on first-line platinum-based chemotherapy	Fluzoparib Placebo	Recruiting

GCV = Gemcitabine, cisplatin, veliparib. GC = Gemcitabine, Cisplatin, mFOLFIRI = modified fluorouracil, leucovorin, irinotecan.