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The Poly(ADP-ribose) polymerase inhibitors in pancreatic cancer

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Genome instability and mutations are the hallmarks of cancer. Mutations within *BRCA* genes increase the risk of pancreatic cancer (PC) development. Poly(ADP-ribose) polymerase inhibitors (PARPi) show the synthetic lethality phenomenon in tumoral cells with *BRCA* mutation and improve outcomes in patients with breast, prostate and ovarian cancer. Olaparib was the first PARPi registered for the patient with metastatic PC with a deleterious or suspected deleterious germline *BRCA*-mutation. The POLO phase III clinical trial shows that olaparib in PC increases progression-free survival, however it does not prolong the overall survival. Currently, many clinical trials are ongoing to determine the clinical utility of PARPi in monotherapy or polytherapy of PC. The role of PARPi in PC has not been well established and many questions remain unanswered. This review aims to summarise the rationales behind the use of PARPi and current clinical data.

Key words: PARP inhibitors, olaparib, pancreatic cancer, *BRCA* mutation

Introduction

It is estimated that 60,430 (31,950 men and 28,480 women) cases of pancreatic cancer (PC) will be diagnosed and 48,220 people (25,270 men and 22,950 women) will die in 2021 in the USA according to the American Cancer Society [1]. PC is the fourth leading cause of cancer death in men as well as women. The prognosis of PC is unfavorable and life expectancy is about 5% at 5 years [2]. The majority of patients at the time of diagnosis present unresectable tumours due to either local extension or distant metastases. The current treatment options for patients with metastatic PC include fibrinolysin, gemcitabine with nab-paclitaxel, or erlotinib regimens which significantly improved the clinical outcomes in comparison to gemcitabine monotherapy that was the standard therapy for many years [3, 4].

Advances in molecular biology and genetics allow designing poly(ADP-ribose) polymerase inhibitors (PARPi), which are a new class of drugs based on molecular profiling, including *BRCA* mutational status assessment. PARP belongs to a group of enzymes involved in DNA repair, which are activated by DNA damage [5, 6]. It includes olaparib, niraparib, talazoparib and rucaparib. PARPi improved treatment outcomes in patients with breast, prostate and ovarian cancer [7–12].

Currently, they are being tested in monotherapy or polytherapy in PC and may potentially improve the therapeutic armamentarium for that population of patients. In December

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2019, the Food and Drug Administration (FDA) approved olaparib as a maintenance treatment for patients with deleterious or suspected deleterious germline *BRCA*-mutated metastatic pancreatic adenocarcinoma [13]. Recently, in the phase III POLO trial, it was shown that olaparib increases the median of progression-free survival (mPFS), however without improving the median of overall survival (mOS) [14]. Nevertheless, PARPi are a promising new class of drugs that need further studies. This review aims to summarise the preclinical and clinical data on PARPi in PC.

The role of *BRCA* genes and BRCAness in PC

One of the hallmarks of cancer is genomic instability which leads to DNA alterations and predisposes to cancer development [15]. Two types of genetic alterations which lead to tumorigenesis can be distinguished – germline mutations and somatic – a somatic acquired mutation that arises spontaneously as a result of environmental factors like smoking [16]. The majority of PC, approximately 80%, do not have any associations with either positive family history, or inherited genetic causes. 5.2% are associated with an inherited component without positive family history and about 8% of patients with PC have a positive family history [17]. The most common mutation is in the *KRAS* (Kirsten rat sarcoma virus) gene whereas germline and somatic mutations in genes *BRCA* (breast cancer) *1/2, ATM* (ataxia–teleangiesctasia mutated) and *PALB2* (partner and localizer of *BRCA2*) occurs less common of cases [15]. The incidence of germline and somatic mutations in PC is presented in table I. BRCA1 and BRCA2 are proteins that are involved in DNA repair and transcriptional regulation in response to DNA damage. They also take part in replication fork protection and are important factors responsible for resistance to the activity of numerous nucleases, including MRE11, DNA2, EXO1 and MUS81 [20, 21]. Importantly, both proteins are involved in the homologous recombination repair (HRR) process, in which a homologous DNA sequence is used to guide repair that results in restoring the DNA sequence to its original form [22, 23]. Cells with dysfunction in *BRCA 1/2* genes have deficits in HRR and must use less accurate mechanisms to repair double-strand breaks, increasing the risk of cancer development [24]. In unselected populations, a pathogenic mutation in *BRCA1* is found in less than 1% and *BRCA2* mutation in up to 2% of PC cases [17]. Identifying the *BRCA* mutation status in patients is clinically relevant because the mutation provides the data on other possible cancer risks associated with the *BRCA* mutation, like breast, ovarian and prostate cancers. Additionally, identifying the *BRCA* mutation status allows for testing at-risk family members for the same mutation with limited cost [25].

The mOS of patients with PC and *BRCA1* and *BRCA2* mutations is approximately 15 and 13 months, respectively [24]. Among approximately 13 hereditary genes associated with PC development, *BRCA1* and *2* mutations are the most frequent genetic alteration responsible for FPC, which are diagnosed in 2.7% of patients with PC [17]. It has been reported that in about 3,9% of unselected patients, somatic *BRCA1/2* mutations drive the PC [28]. The mOS for patients who carry mutations in *HRR* genes (*ATM, BARD1* [*BRCA1-associated RING domain protein 1*], *BRCA1, BRCA2, BRIP1* [*BRCA1 interacting protein 1*], *PALB2, RAD51C, RAD51D*) associated with PC is 14.6 months, whereas mOS for patients without mutations was 11.7 months [26].

Apart from *BRCA1/2* mutations, the other mutations related to PC are alterations within other HRR genes like *ATM, CDKN2A* (cyclin-dependent kinase inhibitor 2a), *MLH1* (mutL homolog 1) [17]. As opposed to breast cancer and prostate cancer, mutations in *CHEK2* (checkpoint kinase 2) and *PALB2* have no si-

Table I. The incidence of germline and somatic mutations in PC

Gene – germline mutation	Incidence in PC	Incidence in patients with a positive family history of PC	Gene – somatic mutation	Incidence in PC	Reference
BRCA1 *BRCA2* *PALB2*	2.4% 26.2% 2.4%	– – –	*KRAS* *TP53* *SMAD4* *CDKN2A* *SMARCB1* *RB1*	88.1% 33.3% 16.7% 4.8% 2.4% 2.4%	[73]
ATM *BRCA1* *BRCA2* *PALB2* *RAD51*	2.1% 0.6% 2.2% 0.4% 0.2%	– – – – –	–	–	[26]
ATM *BRCA1* *BRCA2* *CDKN2A* *MSH2* *PALB2*	2.6% 0.7% 3.6% 1.3% 0.3% 0.3%	3.2% 1.1% 4.3% 2.2% 0.5% 0.5%	–	–	[33]

gnificant correlation to pancreatic cancer [17, 29]. The mOS for patients treated with FOLFIRINOX chemotherapy in metastatic PC, who have somatic or germline mutations in *BRCA1*, *BRCA2*, *PALB2*, *MSH2*, *FANC* (the Fanconi anemia) complementation group was 14 months in comparison to 5 months in patients without mutations [30].

BRCAness is a phenomenon referred to as the existence of a HRR defect despite the absence of a germline *BRCA1/2* mutation in tumour, which leads to oversensitivity to DNA damage as a result of increased genomic instability. The most common mutation in the HRR repair gene that contributes to the BRCAness phenotype is a somatic defect in *BRCA1* and *BRCA2*, however, BRCAness is also related to other genes involved in HRR, such as *ATM*, *PALB2*, *ATR* (ataxia teleangiectasia and Rad3 related), *CHEK1/2*, *RAD51*, *NBS1* (Nijmegen breakage syndrome) and *FANC* family of genes [19, 31]. The incidence of HRR mutations in PC is shown in table II.

The data describing the role of genes other than *BRCA* are limited. Among the HRR genes, one of the most relatively known mutations related to inherited and sporadic PC is the *ATM* mutation [32]. The incidence of *ATM* mutations in patients with a positive family history of PC is approximately 3.2% [30]. ATM serine/threonine kinase controls cells' survival, death, cell cycle arrest, apoptosis and DNA repair. Pathogenic germline *ATM* mutation increases the risk of PC [34–37]. However, *ATM* mutational status may be also important in predicting radiation and chemotherapy response [38, 39]. *ATM*-deficient PC cells are more sensitive to fractionated radiation than wild-type pancreatic cancer [38]. *ATM*-mutated PC cells treated with olaparib significantly enhance suppression of the PC proliferation *in vivo* and *in vitro* [40].

Furthermore, it has been demonstrated that tumours with BRCAness have similar therapeutic vulnerability as tumours with germline *BRCA* gene mutations. For that reason, it is considered as a potentially significant factor in PARPi therapy [41, 42].

Table II. Frequency of BRCAness mutations among patients with a positive family history of PC [17]

BRCAness	Prevalence in PC
BRCA1	0.6%
BRCA2	2.10%
ATM	3.29%
PALB2	0.6%
ATR	–
CHEK1	–
CHEK2	2.4%
RAD51	0%
NBS1	0.3%
FANC	0.3%

DNA damage response and PARP involvement in synthetic lethality

DNA damage occurs constantly in cells due to exogenous and endogenous stressors leading to genome instability. DNA damage response (DDR) is a central mechanism responsible for detecting DNA lesions and promoting their swift repair. In the process of DDR, a great amount of different intra- and extracellular signalling pathways and enzyme activities are activated. In suboptimal or lack of activity of DDR, an exaggerated level of genomic instability arises – a characteristic feature of cancers. In human cells, two major forms of DNA damage could occur, either a single-strand break (SSB) or double-strand breaks (DSB), whereby SSB occurs more often. Different forms of DNA damage bring responses by proper signalling pathways and repair mechanisms [43, 44]. There are four known repair pathways involved in SSB: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and trans-lesional synthesis. HRR and non-homologous end joining (NHEJ) are two pathways responsible for repair DSBs. The HRR process involves BRCA1/2, PALB2, ATM, RAD51, CHEK1/2, ATR, p53 proteins and MRN complex composed of Mre11, Rad50 and NBS1/NBN proteins [45–47]. When DSB occurs, it is detected by the MRN complex and the ATM and ATR – the cell cycle regulatory kinases are activated. Subsequently, ATM activates CHK2, which arrests cell cycle progression, contributes to regulating BRCA1 in DNA repair, and interacts with TP53, which is responsible for cell cycle and apoptosis control. The MRN complex also recruits BRCA1/2 and PALB2 to the DNA damage site. These proteins form a new complex, which finally activates RAD51 that is responsible for binding single-stranded DNA segments and invading the homologous sequences in the sister chromatid.

PARP enzymes are known as DNA damage sensors. This nuclear deoxyribonucleic acid-binding protein contains an N-terminal double zinc-finger DNA-binding domain, a nuclear localization signal, a central automodification and a C-terminal catalytic domain. Its basal enzymatic activity is low but the variety of allosteric activators, for example, damaged DNA, nucleosomes and a variety of protein-binding partners, strongly stimulates it. When SSBs occur, the PARP enzymes are activated and binds to the site of single-DNA damage using its zinc-finger DNA-binding domain. It cleaves NAD+ into nicotinamide and ADP-ribose. The latter cleavage product is covalently attached to glutamate or aspartate residues of nuclear acceptor proteins in the form of long branching ADP-ribose polymers. This results in a highly negatively charged polymer and subsequently leads to the unwinding and repair of the damaged DNA through the BER [48–52]. PARPi interfere with base excision repair by binding to the catalytic domain of PARP, which prevents PARylation, traps PARP to the SSB, and prevents repair. Consequently, an accumulation of SSB occurs, which degenerate into DNA DBS. As a result, cancer cells undergo cell cycle arrest and apoptosis when exposed to these agents.

Inhibition of PARP-1 in PC cells increases the caspase-3 activity, and by increasing the p53 protein expression suppresses BCL-2 (B-cell lymphoma 2), as a consequence leading to apoptosis and suppression of PC cell proliferation [53]. Except for SSB, in cells PARP enzymes also take part in HRR-mediated DSB repair [54]. Inhibition of these enzymes in cancer cells could cause cell death which is based on a phenomenon called synthetic lethality (fig. 1). It is defined as the situation when two or more separate genes are simultaneously mutated which lead to cell death. The product of one of these genes is crucial to the survival of the cell, whereas another gene is used as an alternative. In a situation when the gene is mutated, it is replaced by a second one that is involved in an alternative pathway of the same process. In cells with *BRCA* biallelic mutation, cells become incapable to properly perform HRR. In case of DNA damage, these disorders are repaired with PARP and BER repair. The use of olaparib in the presence of the mutation disrupts both repair mechanisms, leading to cell death, because inhibition of PARP activity leads to the accumulation of single-strand breaks, which can lead to double-strand breaks properly repaired by HRR [55–58]. The synthetic lethality in *BRCA*-mutated cancers caused by selective inactivation of PARP enzymes cells are unable to successfully repair DNA damaged, which consequently cause its death [59, 60].

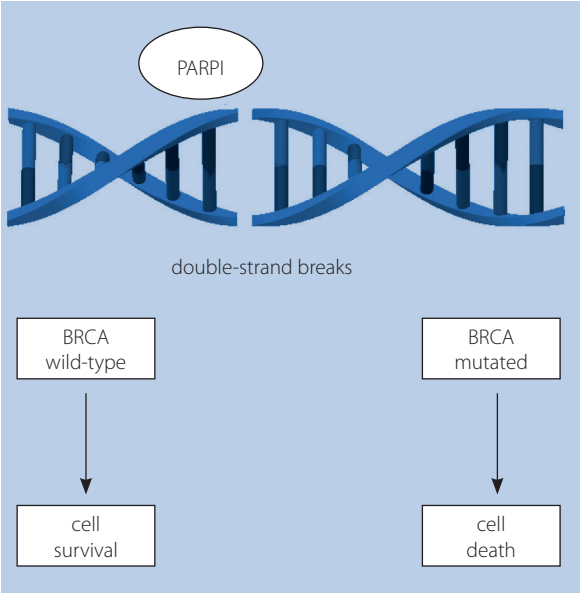

Figure 1. Synthetic lethality and PARPi

Pathobiology of PC

The expression and localization of PARP-1 in the pancreas and PC are different. In the human pancreas, only nuclear PARP-1 (nPARP-1) expression was shown, contrary to nPARP-1 and cytoplasmic PARP-1 (cPARP-1) expression in PC. In the pancreas, the expression of nPARP-1 is enough to maintain the cell's homeostasis by triggering apoptosis in response to DNA damage due to its proapoptotic activity; whereas in PC tissue, the lower expression of nPARP-1 prevents it. PARP-1 takes part in regulating TRAIL (TNF-related apoptosis-inducing ligand) induced apoptosis. Inhibition of PARP-1 may sensitize TRAIL resistant PC cells to TRA-8-induced apoptosis [57]. PARP expression was studied as a new potential prognostic factor in PC. Immunohistochemical analysis of cPARP and nPARP among 178 PC show that high nPARP was associated with a better prognosis (mOS14.5 *vs.* 9.6 months, p = 0.004), however, it did not show a statistically significant correlation with clinicopathological parameters [61]. FeiXu et al. in their studies focused on cPARP-1 and compared the frequency of cPARP-1 in well, moderately and poorly differentiated PC. Initially, they suggest potential relations between cPARP-1 expression on PC pathogenesis and progression, similar to recent breast cancer reports where the correlation between aggressiveness, higher risk of relapse and the death of patients were seen [57, 62]. In their studies, the expression of cPARP-1 was higher in moderately and poorly differentiated than well-differentiated pancreatic tumours. Furthermore, they linked PARP-1 in the cytoplasm to the extrinsic pathway of apoptosis [57].

Table III. Ongoing trials with PARPi in monotherapy in patients with PC

Name of the study	Phase	Indication/ tumour type	Study drug	Control arm	Mutational status	Primary outcome measure	Secondary outcome measure
NCT04005690	early I	stage I–IV PC	olaparib	cobimetinib	–	proportion of all feasibility – evaluable participants that have a measurable change in post-treatment tumour biology from baseline	• incidence of ≥ grade 3 toxicities for each assigned window treatment • proportion of feasibility – evaluable participants within each study arm that have a measurable change in post-treatment tumour biology from baseline
NCT01078662	II	ovarian, breast, prostate, pancreatic advanced tumours	olaparib	–	*BRCA1/2* mutation	tumour response rate	• ORR* • PFS • OS • duration of response

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Table III. cont. Ongoing trials with PARPi in monotherapy in patients with PC

Name of the study	Phase	Indication/ tumour type	Study drug	Control arm	Mutational status	Primary outcome measure	Secondary outcome measure
NCT02184195 (POLO)	III	PC	olaparib	placebo	germline *BRCA1/2* mutation	PFS	• OS • time from randomisation to second progression • time from randomisation to first and second subsequent therapy or death • ORR* • quality of life (QoL) • AEs
NCT02677038	II	metastatic PC	olaparib	–	• mutation in germline *BRCA1/2* negative • BRCAness pheno-type	ORR*	• OS • PFS • change in CA19-9 • AEs
NCT04858334 (APOLLO)	II	resectable PC	olaparib	–	*BRCA1/2, PALB2*	improvement in relapse-free survival	• RFS • OS • efficacy after chemotherapy • differences in survival
NCT03601923	II	advanced PC	niraparib	–	• *BRCA1* • *BRCA2* • *PALB2* • *CHEK2* or *ATM* mutation	PFS	• ORR** • OSR • AEs
NCT04171700 (LODESTAR)	II	solid tumours	rucaparib	–	• *BRCA1* • *BRCA2* • *PALB2* • *RAD51* • *RAD51* • *BARD1* • *BRIP1* • *FANC* • *NBN* • *RAD51* or *RAD51B* mutation	best ORR **	• ORR ** • PFS • AEs
NCT03140670	II	metastatic locally advanced PC	rucaparib	–	*BRCA1/2* or *PALB2* mutation	AEs	–
NCT04550494	II	malignant solid neoplasm including PC	talazoparib	–	germline or somatic aberrations in genes involved in DNA damage response	percent of patients who demonstrate simultaneous Rad51 activation	• ORR** • tumour genomic alterations potentially associated with sensitivity to talazoparib
NCT04182516	I	• locally advanced/ metastatic HER2 negative breast cancer • epithelial ovarian cancer • castration-resistant prostate cancer • PC	NMS –03305293	–	–	number of participants with first-cycle dose-limiting toxicity	AEs

AE – adverse events; ORR* – objective response rate; ORR** – overall response rate; OS – overall survival; OSR – overall survival rate; PC – pancreatic cancer; PFS – progression free survival; RFS – relapse-free survival

Table IV. Ongoing clinical trials with PARPi in polytherapy

Name of the study	Phase	Tumour type	Experimental arm	Control arm	Mutational status	Primary outcome measures	Main secondary outcome measures
NCT02498613	II	• PC • lung cancer • breast cancer	olaparib + cediranib	–	–	ORR*	• AEs • PFS
NCT03682289	II	• PC • renal cell carcinoma • urothelial carcinoma • other solid tumours	olaparib + AZD6738	AZD6738	–	• ORR* • composite prostate cancer • patient response • rate ORR for other solid tumours	• DOR • PFS • AEs
NCT04548752	II	metastatic PC	olaparib + pembrolizumab	olaparib	germline mutation in *BRCA 1/2*	PFS	• AEs • OS • ORR**
NCT04493060	II	metastatic PDAC pancreatic cancer	niraparib + dostarlimab	–	• *BRCA1/2* • *PALB2*	DCR – 12 weeks	• ORR* • time to next treatment • OS • PFS and AEs
NCT04673448	I	• PC • breast cancer • ovarian cancer • fallopian tube or primary peritoneal cancer	niraparib + dostarlimab	–	mutation in *BRCA1* or *BRCA2*	best objective response	• Aes • PFS • DOR • DCR • OS
NCT03404960 (Parpvax)	I/II	PC after platinum-based therapy	1 : niraparib + nivolumab	niraparib + ipilimumab	–	PFS	• the proportion of tumours with HRD, ORR*, DOR, OS, AEs • Immune activation prior/ during treatment
NCT03337087	I/II	metastatic PC	rucaparib + irinotecan liposome + leucovorin + fluorouracil	–	selected (*BRCA1* or *BRCA2* or *PALB2* mutation) and unselected	• number of participants with dose-limiting toxicities • objective response • best response rate	• DCR • OS • PFS • AE
NCT02890355	II	metastatic PC	veliparib + mFOLFIRI	FOLFIRI	–	OS	• AEs • PFS • ORR* • DCR
NCT01585805	II	• metastatic PC • recurrent PC • stage III PC	1: veliparib + gemcitabine + cisplatin 2: veliparib	gemcitabine + cisplatin	*BRCA1/2* or *PALB2* mutation	• the optimal dose of drugs • the response rate to gemcitabine hydrochloride and cisplatin with versus without veliparib • response rate of single-agent veliparib	• PFS • Aes • DCR • OS
NCT00576654	I	metastatic tumours or tumours that cannot be removed by surgery	veliparib + irinotecan	–		• optimal biologic dose • maximum administered dose of study drugs • maximally tolerated dose • recommended phase II dose	• AE • tumour response
NCT04228601	Ib/II	advanced PC	fluzoparib + mFOLFIRINOX	placebo + mFOLFIRI-NOX	mutation in germline *BRCA1/2* or *PALB2*	• number of participants with a dose limited toxicity • maximum tolerated dose • ORR*	• AEs • DCR • OS • PFS

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Table IV. cont. Ongoing clinical trials with PARPi in polytherapy

Name of the study	Phase	Tumour type	Experimental arm	Control arm	Mutational status	Primary outcome measures	Main secondary outcome measures
NCT04644068 (PETRA)	I	PC ovarian cancer breast cancer prostate cancer	AZD5305	AZD5305 + paclitaxel AZD5305 + carboplatin with or without paclitaxel	–	• the number of subjects with adverse events/ serious adverse events • the number of subjects with dose-limiting toxicity	• ORR* • PFS
NCT04503265	I/II	• PC • advanced malignant neoplasm • breast cancer • ovarian cancer • homologous recombination deficiency • prostate cancer	AMXI-5001	–	–	maximum-tolerated dose	recommended phase 2 dose

AE – adverse events; DCR – disease control rate; DOR – duration of response; HRD – homologous recombination deficits; ORR* – objective response rate; ORR** – overall response rate; OS – overall survival; PC – pancreatic cancer; PFS – progression free survival

The results of clinical trials in patients with PC

Currently, the PARPi (olaparib, niraparib, rucaparib and talazoparib) are being tested in monotherapy (tab. III) and polytherapy (tab. IV) on different stages of PC, however, the results of clinical trials are limited. Olaparib remains the most studied drug.

The NCT01078662, phase II trial assessed the efficacy of olaparib in 298 patients with many solid tumours, including PC. 23 patients with PC were enrolled. 74% of them had the *BRCA2* mutation. The primary outcome measure was the tumour response rate. The main secondary outcome measure was the objective response rate, progression-free survival (PFS) and overall survival (OS). Eligible patients had a deleterious or suspected deleterious germline *BRCA* mutation. The tumour response rate in the PC was 21.7% (5–23; 95% CI: 7.5–43.7). Stable disease (≥8 weeks) was observed in 35% (95% CI: 16.4–57.3) of PC patients. The median PFS was 4.6 months. The mOS was 9.8 months. The most common adverse event involved fatigue, nausea and vomiting [63]. Olaparib is also studied in phase II trials in U.S and Israel (NCT02677038, NCT02511223) among 32 patients with metastatic PC and the BRCAness phenotype but without the germline *BRCA1/2* mutation, who received at least one prior therapy. The antitumour activity was seen only in platinum-sensitive patients. The median PFS varies between 14 weeks (range: 5.7–40 weeks) in the Israel part of the study and 24.7 weeks (range: 3.9–41.1 weeks) in the U.S. group [64].

The POLO, a randomized, placebo-controlled phase III trial (NCT02184195), evaluated the role of olaparib as a maintained treatment among 154 enrolled patients with metastatic PC and deleterious/suspected deleterious germline *BRCA1/2* mutation that had not progressed within 16 weeks during the first-line platinum-based chemotherapy (mainly folfirinox). The patients were divided into two groups, the first was given olaparib 300 mg twice a day (n = 92), the second received a placebo (n = 62). The primary endpoint measure was PFS. The main secondary endpoint measure was the OS, time from randomization to the second progression, safety and tolerability. Initially, it was published that olaparib treatment significantly prolonged PFS in comparison to the placebo (7.4 *vs.* 3.8 months; HR = 0.53, p = 0.0038). Recently, on the ASCO Gastrointestinal Cancers Symposium 2021, the newest result data were shown. The OS analysis shows that the OS for the olaparib group was 19 *vs.* 19.2 months for placebo, which failed to be statistically significant (HR: 0.83; p = 0.3487), however, 33.9% of patients who received PARPi survived 3 years *vs.* 17.8% in the placebo group. The most common (≥15%) adverse events in the olaparib group across all grades were nausea, fatigue and diarrhoea. Anemia was the most common AE grade 3 in the study group [14, 65].

The NCT03140670 phase II study is evaluating Rucaparib among patients with metastatic or locally advanced PC and germline, somatic *BRCA1/2*, or *PALB2* mutation. The primary outcome measure is the number of adverse events. The initial results showed that the median PFS was 9.1 months and the ORR of 36.8% [66].

Veliparib was studied, in phase II trials in patients with germline *BRCA1/2* or the *PALB2* mutation and stage III and IV PC. The enrolled patients were treated with 1–2 previous chemotherapy regimen. The response rate was not confirmed. The mPFS was 1.7 ms (95% CI: 1.57–1.83) and mOS was 3.1 ms [67].

The results of clinical studies with drugs other than olaparib are limited. The currently ongoing clinical trials try to determine the biomarkers, the role of genes other than *BRCA* mutated genes and proper sequention of treatment. Among them, one of the most interesting studies is the APOLLO trial (NCT04858334) a phase II, randomized trial that determines the RFS benefit from the maintenance of olaparib therapy following chemotherapy in patients with resected PC and a pathogenic germline or somatic *BRCA1/2, PALB2* mutation.

The LODESTAR, a phase II study (NCT04171700) is evaluating the rucaparib in patients with solid tumours and with deleterious mutations in HRR genes. Patients enrolled to the study had solid tumors with the *BRCA1/2, PALB2, RAD51C, RAD51D, BARD1, BRIP1, FANC, NBN, RAD51*, or *RAD51B* mutation. The primary outcome measure is the best overall response rate. Niraparib is also being studied in a phase II trial (NCT03601923) among patients with the *BRCA1, BRCA2, PALB2, CHEK2*, or *ATM* mutation and advanced PC that is not curable with standard approaches. Talazoparib in monotherapy is studied in two clinical trials. The NCT04550494 trial is the II phase trial that evaluates the pharmacodynamic of PARPi in patients with advanced cancers and mutations in DDR genes. The NCT01286987 trials are a phase I study that evaluates the number of participants with objective response among patients with advanced or recurrent tumours.

PARPi are also being tested in polytherapy with other drugs. It has been hypothesized that combined therapy, especially with chemotherapy, may provide a synergistic therapeutic strategy for patients with PC. The rationale of this combination with a platinum is based on e.g. increased DNA damage by chemotherapy [68]. Initial results come from a phase I trial which assessed the combination of veliparib, gemcitabine and cisplatinin patients with *BRCA1/2* mutated and wild-type PC. The response rate within the *BRCA* mutated cohort was 77.8%. The mOS of patients with *BRCA1/2*-mutated PC and patients with wild-type PC was 23,3 months and 11 months respectively [69]. These promising results led to a phase II, randomized trial. Patients with *BRCA1/2* or *PALB2*-mutated PC were treated with gemcitabine and cisplatin chemotherapy with or without veliparib. The authors found non-significant benefit in the response rate between these two groups (74.1% in arm with veliparib *vs.* 65.2% in chemotherapy arm; $p = 0.55$) [70]. The trials did not show a survival benefit in mPFS (10.1 months for arm with veliparib (95% CI: 6.7–11.5 months) *vs*. 9.7 months for chemotherapy (95% CI: 4.2–13.6 months; $p = 0.73$). Median OS for veliparib and chemotherapy cohort was 15.5 months (95% CI: 12.2–24.3 months) *vs.* 16.4 months for chemotherapy (95% CI: 11.7–23.4 months; $p = 0.6$).

Currently, there are more clinical trials testing PARPi with chemotherapy mainly based on irinotecan-based chemotherapy regimens like (NCT03337087, NCT02890355, NCT00576654, NCT04228601) and cisplatin (NCT01585805). The PARPi are being tested with targeted therapy like cediranib (inhibitor of vascular endothelial growth factor receptor tyrosine kinases; NCT02498613), AZD6738 (ATR kinase inhibitor; NCT03682289), immunotherapy: pembrolizumab (anti-PD1 inhibitor; NCT04548752), dostarlimab (anti-PD1 inhibitor; NCT04493060, NCT04673448), nivolumab (anti-PD1 inhibitor; NCT03404960), ipilimumab (anti-CTLA4; NCT03404960). In addition, the new PARPi are being tested like AMXI-5001, an orally available dual PARP and microtubule polymerization inhibitor (NCT04503265), AZD5305 (NCT04644068) or NMS-03305293 (NCT04182516).

Conclusions

Pancreatic cancer remains one of the deadliest neoplasms with poor survival rates. There is a high need for new therapeutic regimens which improve the clinical outcomes of patients. In recent years, thanks to a deeper understanding of the molecular and genetic landscape of PC, PARPi has also emerged as a novel class of targeted therapy for patients with PC.

PARPi is a new class of drugs based on gene profiling that is currently being studied in PC. Many clinical trials are ongoing to determine the role of drugs in monotherapy and polytherapy. Despite that, the POLO trial did not show that olaparib increases the OS, yet many questions remain regarding the genetic status, role of other HRR genes in PC treatment and sequential treatment strategy. The new direction in PC treatment is signalling pathway inhibitors, immunotherapy agents, drugs targeting the metabolism of tumours and drugs targeting the tumour microenvironment, which could be studied as polytherapy with PARPi [71]. A better understanding of the action and responses at the molecular level of PC cells and the implementation of routine genetic testing in patients have the potential to reveal novel treatment opportunities and thus may broaden the treatment for patients with actionable aberrations [71]. NCCN recommends gene profiling for patients with locally advanced/metastatic PC. The testing should be performed to identify fusions (*ALK* [anaplastic lymphoma kinase], *NRG1* [neuregulin1], *NTRK* [neurotrophic receptor tyrosine kinase 1], *ROS1* [c-Ros Oncogene 1]), mutations (*BRAF, BRCA1/2, HER2* [human epidermal growth factor receptor 2], *KRAS, PALB2*), and MMR deficiency [72]. The recommended material for study is the tumour tissue or, if not available, the cell-free DNA. The preferred technique includes immunohistochemistry, polymerase chain reaction, or next-generation sequencing. Molecular tumour profiling is the future of personalized therapy in pancreatic cancer treatment, which may finally improve the survival rates of patients.

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