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Therapeutic resistance in pancreatic ductal adenocarcinoma: Current challenges and future opportunities

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REVIEW

Therapeutic resistance in pancreatic ductal adenocarcinoma: Current challenges and future opportunities

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related deaths in the United States. Although chemotherapeutic regimens such as gemcitabine+ nab-paclitaxel and FOLFIRINOX (FOLinic acid, 5-Fluroruracil, IRINotecan, and Oxaliplatin) significantly improve patient survival, the prevalence of therapy resistance remains a major roadblock in the success of these agents. This review discusses the molecular mechanisms that play a crucial role in PDAC therapy resistance and how a better understanding of these mechanisms has shaped clinical trials for pancreatic cancer chemotherapy. Specifically, we have discussed the metabolic alterations and DNA repair mechanisms observed in PDAC and current approaches in targeting these mechanisms. Our discussion also includes the lessons learned following the failure of immunotherapy in PDAC and current approaches underway to improve tumor's immunological response.

Key Words: Pancreatic cancer; Metabolism; DNA repair; Therapy-resistance; Immunotherapy

Core Tip: With a five-year survival rate of 10%, pancreatic adenocarcinomas are one of the most aggressive forms of cancer. Despite extensive efforts, only a few drug combinations have been found to be effective in improving patient outcomes. The drug-resistant mechanisms active in pancreatic ductal adenocarcinoma contribute to the

quality classification
Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
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ineffectiveness of therapies. Through this review, we discuss key mechanisms that contribute to the development of resistant phenotype in pancreatic tumors and how these mechanisms are being sought as a target to treat this cancer.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive tumor, with a 5-year overall survival of 10%. As the cause of approximately 47000 deaths annually, it is the third leading cause of cancer-related mortality in the United States and is expected to be the second primary cause of cancer-related deaths by 2030[1,2]. Surgical resection of the tumor remains the only curative option for patients with PDAC. However, due to late diagnosis, only a limited number of patients qualify for it. Relapse is common and often observed as early as two months post-surgery. Therefore, adjuvant chemotherapy is often prescribed to improve patient outcomes. For over a decade, gemcitabine was the mainstay for chemotherapy for resectable PDACs. The drug advanced the patient survival to 5.65 mo compared with 4.41 mo with 5-fluorouracil[3]. Recently, a combination therapy FOLFIRINOX (FOLinic acid, 5-Fluroruracil, IRINotecan, and Oxaliplatin) displayed better patient outcomes than gemcitabine[4]. The four-drug cocktail, although toxic, significantly improved survival in PDAC patients and is currently approved for both resectable and metastatic PDAC[5-9] (Table 1).

The complex pancreatic cancer biology is often attributed as the underlying cause of the poor chemotherapeutic response. This review will highlight the current knowledge of the therapeutic resistance mechanisms prevalent in PDAC and the opportunities PDAC tumor biology provides for its efficient targeting.

CURRENT THERAPIES IN PDAC

Gemcitabine

Gemcitabine has been a mainstay for PDAC treatment since 1997, when it was found to improve median and overall survival compared to 5-fluorouracil[3]. Gemcitabine (2′, 2′- difluorodeoxycytidine) is a difluoro analog of deoxycytidine which inhibits DNA synthesis through (1) inhibition of ribonucleotide reductase (RR), (2) inhibition of DNA polymerase (*via* diphosphate analog), or (3) mis-incorporation into the DNA, thus preventing chain elongation (*via* triphosphate analog)[10,11]. The inhibition of RR by the diphosphate analog depletes the deoxy-ribonucleotide pool essential for DNA synthesis.

Numerous mechanisms for gemcitabine inactivity have been demonstrated. Although resistance can be divided into innate and acquired forms, we will present evidence referring to both as "resistance" for this review.

The first interaction of gemcitabine with the cells occurs at the nucleotide transporter level. These transporters-concentrative nucleoside transporters (hCNTs) and equilibrative nucleoside transporters (hENTs) allow the transport of gemcitabine into the cells[12]. Evidence of the importance of nucleotide transporters for gemcitabine activity includes the observation that, in the absence of hENT1, PDAC patients treated with gemcitabine have reduced survival[13]. The enzyme deoxycytidine kinase (dCK) is the rate-limiting enzyme that converts gemcitabine into di-fluoro deoxycytidine mono-phosphate and is essential for gemcitabine-induced cytotoxicity[14]. Acquired resistant models demonstrate reduced expression of dCK in cells that do not respond to gemcitabine[14,15]. However, a recent analysis of the patient-derived xenograft PDAC model found no change in dCK levels in the gemcitabine-resistant tumors[16], indicating that mechanisms independent of dCK contribute to poor response to gemcitabine.

Table 1 Landmark trials for approved pancreatic ductal adenocarcinoma therapies

Treatment	Tumor characteristic	Primary endpoint	Ref.
Gemcitabine	Advanced PDAC	Median survival, 5.65 mo	Burris *et al*[3]
Gemcitabine + Erlotinib *vs* Gemcitabine	Locally Advanced or metastatic PDAC	Overall survival (OS), 6.24 mo *vs* 5.91 mo	Hoffmann *et al*[59]
FOLFIRINOX *vs* Gemcitabine	Metastatic PDAC	OS, 11.1 mo *vs* 6.8 mo	Conroy *et al*[4]
Gemcitabine + nab-paclitaxel *vs* Gemcitabine	Metastatic PDAC	OS, 8.5 mo *vs* 6.7 mo	Couvelard *et al*[60]
Gemcitabine + Capacitabine *vs* Gemcitabine	Resectable PDAC	OS, 28 mo *vs* 25.5 mo	Neoptolemos *et al*[8]

PDAC: Pancreatic ductal adenocarcinoma.

As mentioned earlier, when gemcitabine inhibits RR, the deoxy-ribonucleotide pool of the cells becomes depleted, leading to cell death. Overexpression of M1 and M2 isoforms, namely RRM1 and RRM2, is associated with reduced cellular response to gemcitabine[16-18]. Micro RNAs such as miR20a-5 and miR211 have been shown to downregulate RR, enhancing pancreatic cancer's sensitivity to gemcitabine and inhibiting cellular invasion[19,20]. Similarly, natural product, small molecule, and miRNA-based inhibition of RR sensitizes PDAC cells to gemcitabine[19-21-24]. Although strong *in vitro* data indicate RRM1/RRM2 play a key role in gemcitabine sensitivity, conflicting clinical outcomes have limited the utility of these enzymes for PDAC prognosis[25-28].

Other cellular processes such as epithelial-mesenchymal transition (EMT), mitogenic signaling, and tumor-stroma interaction also contribute to gemcitabine resistance [29]. Analysis of PDAC lines revealed that the EMT gene expression profile differs considerably between drug-sensitive and -resistant cells[30]. The drug-resistant cells showed reduced response to gemcitabine, 5-fluorouracil, and cisplatin, and expressed elevated levels of EMT marker Zeb1[30]. In addition, suppression of EMT enhanced the sensitivity of PDAC to gemcitabine by regulating the expression of nucleoside transporters[31].

5-Fluorouracil

Similar to gemcitabine, 5-fluorouracil belongs to the antimetabolite class of anti-cancer agents. 5-Fluorouracil inhibits the enzyme thymidylate synthetase (TS), which is responsible for methylation of deoxyuridine mono-phosphate to deoxythymidine mono-phosphate, a precursor for DNA synthesis. 5-Fluorouracil was the first drug to be approved as PDAC adjuvant therapy[32,33]. Although no longer used as monotherapy, 5-fluorouracil forms a part of the PDAC chemotherapeutic regimen FOLFIRINOX. Compared to gemcitabine therapy, combination therapy with FOLFIRINOX improved the overall survival and median progression-free survival of patients with metastatic PDAC[4]. Although any improvement in PDAC patient outcomes should be observed as a positive sign, the high toxicity of the drug regimen, limited patient eligibility for FOLFIRINOX, and prevalence of 5-fluorouracil resistant mechanisms may further limit the use this combination therapy in PDAC[34-38]. Multiple mechanisms have demonstrated to contribute to 5-fluorouracil resistance, such as alteration in (1) 5-fluorouracil metabolizing enzymes, (2) membrane transporters, and (3) pro-survival/ pro-apoptotic pathways. High TS expression is associated with poor survival in PDAC patients, however, the difference in survival is more significant in patients that received 5-fluorouracil based therapy[39,40]. The enzyme dihydropyrimidine dehydrogenase (DPD) catabolizes the 5-fluorouracil in the liver. In colorectal cancer patients receiving 5-fluorouracil based therapy, high DPD levels was associated with significantly shorter disease-free survival and overall survival[41]. In vitro analysis of PDAC cells lines and 5-fluorouracil-resistant sub-lines revealed that high expression of TS and DPDY is associated with poor 5-fluorouracil response[42].

Targeted therapies in PDAC

Comprehensive genetic analysis has revealed that pancreatic cancers are a host of numerous genetic mutations[43]. Mutation of *K-ras* is the most frequent genetic alteration observed in more than 90% of pancreatic cancer cases[44]. K-ras protein is a downstream signaling molecule activated by various transmembrane receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR), insulin-like growth factor receptor, and c-met. EGFR, overexpressed in more than 40% of pancreatic

cancers, is associated with poor disease prognosis, invasion, and aggressive clinical behavior[45,46]. Given its importance, therapies targeting EGFR have been tested to determine their ability to improve the outcomes of PDAC patients. In one phase III trial, the addition of erlotinib (EGFR tyrosine kinase inhibitor) to gemcitabine-based therapy significantly improved the overall survival of PDAC patients[47]. A recent clinical trial compared the efficacy of gemcitabine + erlotinib in rash-positive pancreatic cancer patients and found similar one-year survival and better quality of life compared to patients on FOLFIRINOX[48]. Some trials however, have failed to show the clinical benefit of adding EGFR targeting drugs to PDAC chemotherapy[49-52]. Therapies targeting other molecular mechanisms active in pancreatic cancer have not shown beneficial effects, and EGFR targeting may have a place in PDAC therapy as precision medicine[53-57].

FUTURE OPPORTUNITIES TO TARGET PDAC

Pancreatic tumor metabolism

Pancreatic cancer is characterized by a dense stroma surrounding the tumor. This dense stromal region limits vascularization, creating an environment limiting oxygen and nutrient supply[58,59]. Limited oxygen gives rise to hypoxia that is associated with poor patient prognosis[59-61]. In an abundance of oxygen, the non-malignant cells produce most of their energy from mitochondrial oxidative phosphorylation (OXPHOS) while cancer cells exhibit an altered metabolism, first observed in the 1920s by Warburg[62], in which they produce most of their energy from glycolysis. Further, Warburg[62] observed that the majority of the glucose taken up by the cancer cells is converted to lactate rather than CO_2, an observation that has since been witnessed and verified by various researchers in various tumors, including PDAC[63-70]. Pancreatic cancer shows upregulation in glycolysis, pentose phosphate pathway (PPP), fatty acid synthesis, and purine/pyrimidine synthesis, and downregulation of enzymes involved in Kreb's cycle and the OXPHOS.

Analysis of the pancreatic cancer progression model revealed that the metabolic alterations precede tumor formation[71]. Metabolic rewiring in the early stages involves upregulated glycolytic and PPP. The altered metabolic profile allows quick ATP production and provides nucleotides and other metabolic intermediates required for proliferating cancer cells[72]. However, the suppression of OXPHOS can lead to excessive acid build-up within the cancer cells in the form of lactate. To circumvent this, pancreatic cancers express monocarboxylate transporters (MCT1 and MCT4) to efflux out lactate[73,74]. These metabolic adaptations, aided by the upregulation of glucose transporters GLUT1, allow the cancer cells to utilize glucose for their energy and biosynthetic needs. In addition, the molecular biology of pancreatic cancers, such as mutation of KRAS and P53, contribute to the so-called "glycolytic switch" in the PDACs by regulating genes like hexokinase-2, glucose transporters GLUT-1, and PKM2, and by promoting anabolic processes[75-78].

Altered tumor metabolism is also associated with poor therapy response in pancreatic tumors. Acquired gemcitabine-resistant models of pancreatic cancer show a marked increase in aerobic glycolysis that maintains the EMT phenotype and reduced responsiveness to the therapeutic agent[79]. The resistant cells exhibit elevated glycolytic enzymes HK2, LDHA and PKM2, and glucose transporter GLUT1. Below we discuss the central carbon metabolic pathways — namely, glycolysis, tricarboxylic acid (TCA) cycle, and the PPP — as therapeutic targets in pancreatic cancer.

Glycolysis as therapeutic target: Analysis of pancreatic tumors reveals that HK2 expression is upregulated in localized tumors as well as metastatic tumors compared to non-malignant tissues[80]. Since HK2 plays a crucial role in pancreatic tumors, efforts have been made to evaluate HK2 as a therapeutic target for pancreatic cancers. We were among the first to show that inhibition of glycolytic enzymes HK2 inhibits the growth and pro-survival signaling in pancreatic cancers[81]. In addition, inhibition of HK2 in pancreatic cancer cells suppresses their anchorage-independent growth and invasion[80]. The role of HK2 has also been implicated in gemcitabine resistance, as HK2 dimerization is enhanced in cells that do not respond to gemcitabine[82]. *In vitro* and *in vivo* analysis revealed that inhibition of HK2 enhanced the sensitivity of PDAC to gemcitabine. Similarly, in another study, inhibition of HK2 using chemical inhibitor 2-deoxyglucose enhanced resistant cells' sensitivity to gemcitabine[79].

PKM2: Pyruvate kinase (PK) is a glycolytic enzyme that catalyzes the conversion of phosphoenol pyruvate and ADP into pyruvate and ATP. Four isoforms of the enzyme

exist in vertebrates: PKR in erythrocytes; PKL in liver and kidney; PKM1 in adult muscle, brain, and heart; and PKM2 in most adult tissues and fetal tissues[83]. Phosphorylation of PKM2 at tyrosine residue 105 (Y105) is associated with reduced PKM2 activity and enhanced tumor growth[84,85]. Analyses of PKM isoform show abundance of isoform M2 in tumor cells compared to high levels of M1 in normal tissues[52,53]. In cancer cell lines, high PKM2 Levels are associated with proliferation, metastasis, and angiogenesis[54-56]. The role of PKM2 in pancreatic tumors is, however, controversial. Using the mice model of PDAC, a recent report demonstrated that although PKM2 expression is elevated in PDAC, the loss of PKM2 does not significantly affect the size of tumors or the survival of mice bearing PDAC[86]. Surgical specimens from 115 PDAC patients show that PKM2 expression is associated with better overall survival[87]. However, others have shown that high PKM2 expression correlates with poor patient outcomes[88,89]. Considering several observations demonstrating a vital role of PKM2 in pancreatic cancer survival, invasion, angiogenesis, metastasis, and drug resistance, we believe the PKM2 serves as an attractive target for the treatment of PDAC, even though its role in pancreatic cancer tumorigenesis is still unproven[90-95].

Lactate dehydrogenase (LDH): LDH is an enzyme that exists as a tetramer and catalyzes the conversion of pyruvate to lactate and *vice versa*. LDHA (LDH gene product) regulates pyruvate's conversion to lactate, thus preventing the entry of pyruvate into the TCA cycle. Deregulated expression of LDHA is observed in various tumors, including pancreatic, gastric, bladder, cholangiocarcinoma, lung, and endometrial cancers[96-102]. Numerous oncogenic signaling molecules, namely, HIF1 alpha, myc, FOXM1, and tyrosine kinase receptors, can regulate the level or the activity of LDH[96,103-106]. Elevated levels of LDH are associated with unfavorable prognoses for PDAC patient survival, chemotherapy response, and recurrence[107-112]. Preclinical studies have revealed that inhibition of LDH reduces the survival of PDAC cells[113,114].

PPP as therapeutic target: The PPP branches from glycolysis and contributes to the cancer phenotype through (1) synthesis of NADPH (oxidative PPP), which is important for redox regulation and fatty acid synthesis, and (2) supplying the proliferating cells with pentose sugar (non-oxidative PPP) for nucleic acid biosynthesis [115]. Accumulating evidence indicates that PPP plays a vital role in pancreatic tumor survival, metastasis, and therapy resistance. Our lab and others have shown that MYC regulates the activity of both oxidative and non-oxidative PPP through the regulation of G6PD and the RPIA (non-oxidative PPP) gene[78,116,117]. The regulation of RPIA *via* MYC appears to be under the directive of KRAS. The MAPK-MYC-RPIA-nucleotide biosynthesis pathway is shown to be important for KRAS-mediated maintenance of PDAC[78,116]. Considering that most PDAC patients (90%) express mutant KRAS, inhibition of PPP is an attractive strategy for developing more efficient pancreatic cancer therapies that would target KRAS-induced metabolic abnormalities. Our recent results found that pancreatic cancer cells resistant to erlotinib express elevated levels of G6PD. The upregulated G6PD prevents the induction of ROS in response to erlotinib, thus protecting the cells from drug-induced cytotoxicity[117]. The non-oxidative PPP has also been implicated in PDAC therapy resistance. Shukla *et al*[118] found that gemcitabine-resistant cells express enhanced carbon flux into the non-oxidative PPP, aided by elevated non-oxidative PPP enzyme levels. This alteration in metabolic flux allows elevated pyrimidine synthesis that contributes to gemcitabine resistance[118].

TCA cycle and OXPHOS as therapeutic target: Although cancer cells exhibit an elevated flux of glycolytic intermediate into branched pathways, the TCA cycle is still functional. The TCA cycle continues to provide proliferating cancer cells with energy, macromolecules and maintain the cellular redox balance. Recent reports have demonstrated the importance of the TCA cycle and OXPHOS in pancreatic cancer survival[119-123]. Due to their critical roles, the TCA cycle and OXPHOS have been tested as a therapeutic target for PDAC therapy. Three major approaches have been sought to this end: (1) Targeting TCA cycle enzyme/intermediates; (2) Targeting glutamine-dependent anaplerosis; and (3) Targeting the OXPHOS.

Glutamine, a non-essential amino acid, is considered an important energy source for PDAC along with glucose[124,125]. Accumulating evidence demonstrates that glutamine plays a vital role in PDAC proliferation, invasion, maintenance of redox balance, chemotherapy, and radiotherapy resistance, underlining glutamine metabolism as a potential therapeutic target[126-132]. However, conflicting results show that the presence of glutamine suppresses PDAC growth and invasion, dampening

enthusiasm for targeting glutamine metabolism[133-135]. A current clinical trial (NCT04634539) is analyzing whether adding glutamine improves efficacy and reduces the toxicity of PDAC chemotherapy. The results from this trial will shed light on the effect of glutamine on PDAC chemotherapy.

Two additional approaches, targeting the OXPHOS and the TCA cycle, have shown promise in preclinical evaluations, and agents targeting them are currently in clinical trials (Table 2). IACS-010759 inhibits mitochondrial complex one and has recently completed a phase I study in different tumor types, including advanced pancreatic cancers (Table 2). Although the preclinical data regarding the effect of IACS-010759 on pancreatic tumors is lacking, inhibition of OXPHOS complex one appears to be a promising strategy for overcoming drug resistance[136-139]. The anti-diabetic drug metformin has been tested and continues to be tested for its efficacy in PDAC (NCT01210911, NCT02336087, and NCT01666730). Although the experience with metformin in clinical settings has not resulted in improved patient outcomes, a recent meta-analysis indicated survival benefits in patients with PDAC and concurrent diabetes mellitus, highlighting a need for a personalized therapeutic approach for the success of this therapy[140-142].

CPI-613 or Demivistat (Table 2) is a TCA cycle targeting agent that inhibits the activity of pyruvate dehydrogenase and α- ketoglutarate dehydrogenase. In a phase 1 trial, 61% of patients achieved an objective response, and 3 (17%) patients achieved a complete response after receiving CPI-613[143].

Targeting PDAC DNA repair

Activating KRAS mutations are major drivers of malignant growth in PDAC and have remained undruggable until recent promising developments. Oncogenic KRAS-induced DNA replication stress drives genomic instability and tumorigenesis in PDAC. Genomic analysis have also revealed that modifications in "DNA damage control" is a prominent genetic alteration observed in PDAC[43]. Recently, genetic alterations in PDAC have been classified into four sub-types by Waddell *et al*[144]: (1) Stable; (2) Locally rearranged; (3) Scattered; and (4) Unstable. The "unstable" phenotype harbors mutations in the DNA damage repair (DDR), such as BRCA1, BRCA2, PALB2, and ATM. Mutations in ATM account for the most frequently occurring somatic mutations in approximately 4% of PDAC cases, followed by BRCA2, STK11, and BRCA1[144-147]. Given the important role these DDR genes play in a significant proportion of human PDACs, patients are likely to benefit from tailored, targeted therapies, including platinums, directed against specific DDR (Table 3). The following paragraphs will discuss these therapies.

Platinums: Platinum agents (cisplatin, oxaliplatin) cause DNA damage by forming platinum adducts on the DNA and causing DNA interstrand crosslinks[148]. Oxaliplatin is a component of the standard of care FOLFIRINOX, and platinum compounds alone are well suited in cancers that have a deficiency in the homologous repair (HR) pathway. Many studies have highlighted the advantageous use of platinum compounds for HR-deficient PDAC. Golan *et al*[149] showed a survival benefit (22 mo *vs* 9 mo) in platinum-treated *vs* platinum-naïve BRCA1/2 mutated advanced PDAC. Similarly, platinum improved overall survival in patients with HR-deficient PDACs and in patients with germline BRCA1, BRCA2, and PALB2 mutations[150,151]. Hence careful patient selection depending on the genetic make-up of the tumor would be essential for platinums to succeed.

Poly (ADP-ribose) glycohydrolase: Poly (ADP-ribose) glycohydrolase (PARG) is a macrodomain protein with exo- and endo-glycohydrolase activity[152,153]. It critically regulates DNA damage responses by removing poly (ADP-ribose) molecules (PARylation) on modified proteins during the DNA repair process. It is the primary PAR degrading enzyme and reverses poly (ADP ribose) polymerase (PARP) functions by hydrolyzing the ribose-ribose bonds present in PAR molecules. By preventing cytoplasmic PAR accumulation, PARG prevents PAR-mediated apoptosis, termed as parthanatos[154]. Inhibiting PARG causes DNA replication fork collapse, which leads to irreparable DNA damage and cell death. Recent studies have highlighted the benefits of selectively targeting PARG as an anti-cancer therapeutic strategy alone or in combination with other genotoxic therapies[155-157]. Targeting PARG was shown to enhance chemotherapeutic effects of DNA damaging agents, like oxaliplatin and 5-fluorouracil in PDAC, and was also synergistic with mitotic kinase, Wee-1 inhibition. In a siRNA screen with DNA replication factors, PARG inhibition was shown to be synergistic with TIMELESS, HUS1, MCM2, CHK1, and RFC2 proteins in an ovarian cancer model, indicating that combinations of PARGi and DNA replication stress

Table 2 Pancreatic ductal adenocarcinoma trials involving agents that target tumor metabolism

Drug	Target	Trial description	NCI trial number
IACS-010759	OXPHOS inhibitor	Phase I, in advanced cancers	NCT03291938
CPI-613	PDH/alpha KDH inhibitor	Phase I, combination with Gem + nab-paclitaxel	NCT03435289
CPI-613	PDH/alpha KDH inhibitor	Phase II, combination with FOLFIRINOX	NCT03699319
CPI-613	PDH/alpha KDH inhibitor	Phase III, combination with modified FOLFIRINOX	NCT03504423
Metformin and atorvastatin	Metabolic inhibitors	Metformin + Atorvastatin + Doxycycline + Mebendazole in cancers	NCT02201381
L-glutamine	Glutamine analog	Phase I, combination with Gem + nab-paclitaxel	NCT04634539

OXPHOS: Oxidative phosphorylation; PDH: Pyruvate dehydrogenase; KDH: Ketoglutarate dehydrogenase.

Table 3 Pancreatic ductal adenocarcinoma trials involving agents that target DNA repair

Drug	Target	Trial description	NCI trial number
M6620 (VX-970)	ATR	Phase I, M6620 and irinotecan hydrochloride in treating patients with solid tumors that are metastatic or cannot be removed by surgery	NCT02595931
AZD6738/olaparib	ATR/PARP	Phase II, Phase II trial of AZD6738 alone and in combination with olaparib	NCT03682289
BAY1895344	ATR	Phase I, testing the addition of an anti-cancer drug, BAY 1895344 ATR inhibitor, to the chemotherapy treatment (Gemcitabine) for advanced solid tumors, pancreatic cancer, and ovarian cancer	NCT04616534
Olaparib	PARP	Phase II, a study of pembrolizumab and olaparib for people with metastatic pancreatic ductal adenocarcinoma and homologous recombination deficiency or exceptional treatment response to platinum-based therapy	NCT04666740
Olaparib	PARP	Phase I, targeted PARP or MEK/ERK inhibition in patients with pancreatic cancer	NCT04005690
Olaparib	PARP	Phase II, a phase 2 study of cediranib in combination with olaparib in advanced solid tumors	NCT02498613
Olaparib	PARP	Phase II, olaparib in treating patients with stage IV pancreatic cancer	NCT02677038
Talazoparib	PARP	Phase II, measuring the effects of talazoparib in patients with advanced cancer and DNA repair variations	NCT04550494
Talazoparib	PARP	Phase I/II, a study of avelumab, binimetinib and talazoparib in patients with locally advanced or metastatic RAS-mutant solid tumors	NCT03637491
Niraparib	PARP	Phase II, niraparib in metastatic pancreatic cancer after previous chemotherapy (NIRA-PANC): A phase 2 trial	NCT03553004
Niraparib	PARP	Phase II, niraparib in patients with pancreatic cancer	NCT03601923
Rucaparib	PARP	Phase II, maintenance rucaparib in BRCA1, BRCA2 or PALB2 mutated pancreatic cancer that has not progressed on platinum-based therapy	NCT03140670
MK1775	WEE1	Phase I/II, a phase i and randomized phase II study of nab-paclitaxel/gemcitabine with or without AZD1775 for treatment of metastatic adenocarcinoma of the pancreas	NCT02194829

PARP: Poly (ADP ribose) polymerase.

inducers should be evaluated as potential therapeutic strategies for PDAC treatment [158]. A synthetic lethal relationship with PARG inhibition and DDR proteins like BRCA1, BRCA2, ABRAXAS, BARD1, and PALB2 was reported in an MCF7 breast cancer model[159]. Since genomic screens in PDAC have revealed alterations/mutations in similar DDR proteins, it is valuable to target PARG in such DDR-deficient PDAC tumors.

Wee-1: WEE1 kinase is an important cell cycle regulator of the G2-M checkpoint and is overexpressed in various cancers, including glioblastoma, breast cancer, osteosarcoma, and hepatocellular carcinoma[160-163]. It phosphorylates and inactivates CDK1 to allow for the repair of damaged DNA before entering mitosis. Wee-1 has regulatory roles in DNA replication stress and HR mechanisms[164-166]. In PDAC, Wee-1 expression is upregulated by a post-transcriptional mechanism regulated by RNA

binding protein, HuR[167], and its inhibition has been found to be effective in DNA repair-deficient PDAC cells[168]. In one study, Wee-1 inhibition was found to sensitize PDAC cells to gemcitabine chemo-radiation therapy[165]. Another study showed Wee-1 inhibition was synergistic with gemcitabine in p53-deficient PDAC xenografts[169]. Co-targeting WEE1 and ATM was shown to synergistically reduce cell proliferation and migration *via* downregulation of PDL-1 expression in pancreatic cancers[170]. Recently, it was also published that a combination of Wee-1 with another DNA repair target, PARG, enhances DNA damage and decreases cell survival in PDAC cells[171].

PARP: PARP is a DNA repair enzyme that plays a role in inflammation, regulation of cell death, transcription, and modulation of post-transcriptional gene expression. In response to DNA damage, PARP-1 could either promote cell survival and DNA repair or cause cell death when the damage is high[172]. PARP covalently adds Poly (ADP ribose) (PAR) chains onto its target proteins by consuming beta nicotinamide adenine dinucleotide (β NAD+). PAR further recruits other DNA repair proteins in the process of damage repair. Chemical competitive inhibitors of PARP enzymatic activity have gained interest as treatment options for many cancers, like ovarian, breast, uterine, and prostate[173], specifically for patients with tumors harboring somatic or germline defects/mutations in HR genes like *BRCA1/2*. Recent whole-genome sequencing studies done in patients with familial pancreatic cancer show that mutations in *BRCA2* gene accounts for 5%-10% of familial pancreatic cancers. In the Ashkenazi Jewish population with PDAC, this percentage increases to 13.7% and represents a major subgroup of PDAC cases that could benefit from PARP inhibitor (PARPi) therapy. In the context of synthetic lethality, impairment of two DNA repair pathways induces cell death and thus targeting HR deficient cells (*BRCA1/2* mutants or others) with PARP inhibitors was found to be lethal[174,175]. Following the success of POLO trial (Pancreas Cancer Olaparib Ongoing), in 2019 FDA approved olaparib (PARPi) as a maintenance therapy in patients with a germline BRCA mutated metastatic PDAC that had not progressed on first-line platinum therapy[174]. An increasing amount of ongoing preclinical and clinical studies suggest that PARPi in combination with either conventional chemotherapeutics (gemcitabine/nab-paclitaxel) or radiation therapy could benefit patients in the long run[176]. However, recent research suggests that although these respond greatly to PARP inhibitors, there is still 40%-70% of BRCA1/2-mutated cancers that fail to respond to PARPi therapy and in those settings PARPi cannot be used. Novel efforts to create a 'BRCAness-tumors harboring mutations in HR beyond BRCA1/2' phenotype in the cells by use of other small molecule inhibitors and their combination with PARPi is now being exploited. Bagnolini *et al*[174] discovered a small molecule disruptor of RAD51-BRCA2 interaction synergizes with olaparib in pancreatic cancer cells. Another study showed synthetic lethaility with PARPi therapy and FGFR1 blockade in pancreatic cancer[177]. Failure of PARPi therapy can also be attributed to acquired resistance mechanisms[178]. A study in pancreatic cancer showed a secondary mutation in BRCA2 emerged after the patient's exceptional response to platinum and PARPi therapy, which likely restored BRCA2 function in PARP inhibitor-resistant tumor cells[179]. Thus, careful evaluation and design of PARPi therapy should be pursued, and novel targets for PARPi beyond BRCA1/2 should be explored.

Other inhibitors of DDR pathway: Ataxia telangiectasia mutated (ATM) and RAD-3 related (ATR) are serine/threonine protein kinases that are involved in double/single-strand break repair and modulate DNA replication stress and DDR signaling[180-182]. ATM is one of the most commonly mutated DDR genes, and many whole genomic sequencing studies in PDAC have reported both somatic or germline ATM loss-of-function mutations. ATM loss drives pancreatic cancer progression, angiogenesis, epithelial-to-mesenchymal transition, and stemness[183]. Radiosensitization of cells with ATM loss/inhibition has been well documented in many tumor types, including pancreatic cancers[184-186]. ATM loss can also synergize with platinums and PARP inhibitor therapies, emphasizing its role in DNA repair. Specific to PDAC, two studies have shown that patients with ATM/ATR mutated tumors respond well to oxaliplatin-based chemotherapy, experiencing either improved progression-free survival or a stable disease[187,188]. Based on these data, multiple ongoing clinical trials (Phase I/II) involving ATM-deficient solid tumors have been initiated with DNA damage agents like PARP inhibitor therapies (olaparib, talazoparib, and niraparib), some of which accept pancreatic cancer patients. Chemical inhibition of ATM *via* small molecule inhibitors (AZD0156, AZD1390) is also being tested in combination with other agents in early stage clinical trials in patients with advanced solid tumors and brain tumors (NCT02588105, NCT03423628). Lack of ATM function may lead to

increased dependence on ATR for DDR, and thus ATR inhibition may be particularly potent in PDACs with somatic mutations in ATM. A recent study employing a multi-DDR interference strategy that included an ATR inhibitor and PARP and DNA-PKC inhibitor was shown to inhibit FOLFIRINOX-induced invasive clones in ATM-deficient PDAC tumors[189]. In 2012, a study tested VX-970, an ATR inhibitor, and found it sensitizes PDAC cells to radiation therapy *in vivo* and *in vitro*[190]. Another study found that a combination treatment of AZD6738 (ATR inhibitor) and gemcitabine induces PDAC regression by preventing checkpoint activation by gemcitabine[191]. The ATR inhibitors (VX-970, AZD6738, BAY18953[43]) are currently in the early stages of clinical development, like ATM inhibitors in patients with advanced solid tumors and lymphomas (NCT03188965, NCT03682289, NCT02595931, and NCT03718091), with or without other chemotherapeutic agents. Although these appear to be promising therapies, their clinical activity in PDAC patients is yet to be shown[183].

Immunotherapy

Immunotherapy has achieved promising outcomes in certain cancers, however is yet to be realized in PDAC[192-194]. Tumors with high tumor mutation burden (TMB, approximate mutations per megabase), such as melanomas and NSCLC, have shown to respond better to immunotherapy[195-197]. These TMBs are generally associated with mismatch repair (MMR) deficiency. PDACs intrinsically have low MMR deficiencies, which may explain the lower response to immunotherapy approaches such as immune checkpoint inhibitors (ICI)[198]. The immunosuppressive nature and "*T cell exhaustion*" further contributes to the poor response of PDAC to immunotherapy.

The PDAC is characterized by the presence of dense stroma in the tumor microenvironment. The stromal components include T cells (cytotoxic and regulatory) and myeloid cells such as tumor-associated macrophages (TAM). Infiltration with macrophages is observed in early PDAC tumor development stages and is associated with poor prognosis in PDAC patients[199-201]. These macrophages secrete immunosuppressive factors such as arginase and TGFβ, and thereby regulate T-cell mediated cytotoxicity and surveillance[200]. The myeloid-derived suppressor cells are immature myeloid cells that suppress T cell proliferation and promote ROS-induced T cell apoptosis[202,203]. The term "T cell exhaustion" is used for T cells' differentiation state in chronic antigen exposure. The exhaustion stage is driven by persistent T cell receptor signaling leading to ineffective T cell functioning[204-206]. Recent evidence has shown that the T cells present in the PDAC tumor microenvironment are defective in the production of interferon and tumor necrosis factors following peptide recognition[207,208]. However, the T cells with identical peptide specificity in the spleen retain functionality in tumor-bearing animals[209].

Some approaches that are currently under investigation for improving the immunological response of PDAC include as follow.

Cancer vaccines and immune checkpoint blockade: Monotherapies targeting programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) have not shown promising responses in PDAC. However, the therapy showed tumor regression and disease stabilization in other advanced cancers such as NSCLC, melanoma, and renal cancers[193]. Similarly, inhibition of PD-1 or PD-L1 failed to demonstrate a positive response in PDAC animal models[207,210-212]. Similar to ICI inhibitors, vaccine trials using vaccine-GVAX pancreas (granulocyte-macrophage colony-stimulating factor-secreting allogeneic pancreatic tumor cells) failed to improve overall survival in PDAC patients compared to single-agent chemotherapy[213]. Since the vaccines were able to recruit T cells, one approach to improve their efficacy would be to promote the activation of T cells, which may be achieved through the combination of vaccines with ICI[214]. Currently, clinical trials are underway for establishing the safety and efficacy of these GVAX with ICIs (NCT03153410, NCT02451982, and NCT02648282).

Targeting tumor associated macrophages: Another way to improve the efficacy of immunotherapies is to inhibit the immunosuppressive signaling that originates from the tumor microenvironment. For this, one strategy being tested is to inhibit myeloid cells. Researchers found that CD11b agonist reduces the total number of myeloid cells and improves survival in PDAC mice. In addition, when CD11b was combined with anti-PD-1, anti-CLTA-4, and gemcitabine, enhanced infiltration of tumor with CD8 T cells was observed[212]. Similarly, other studies have confirmed that targeting TAMs improves therapeutic and T-cell checkpoint immunotherapy response in PDAC models[215-217]. Blockade of Csf1/Csf1R (macrophage colony-stimulating factor

1/receptor) reduces collagen deposits and enhances CD8 T cell infiltration in the PDAC mice model[218]. Currently, a phase II trial is underway to determine the efficacy of cabralizumab (CSF1R inhibitor) in combination with nivolumab and chemotherapy in PDAC (NCT03336216).

Adoptive T cell therapy

Adoptive T cell therapy involves isolating T cells from tumors and then engineering, expanding, and infusing them back into the patients[219]. The chimeric antigen receptor (CAR) T cell therapy is an example of adoptive T cell therapy wherein the T cells are manipulated to express CAR to assist tumor recognition[220]. Antigen targets that are being tested for PDAC include mesothelin, prostate stem cell antigen, CEA, MUC1, and HER2[221]. However, the immunosuppressive microenvironment remains a hindrance in CAR-T cell therapy's success in PDAC[222,223]. Other barrier to the success of adoptive T cell therapy in PDAC include antigen selection and toxicities [224-226]. Still, a few promising outcomes have sustained hope for the use of this approach in PDAC. A phase 1 trial found that treatment of PDAC patients with mesothelin-targeting-CART-T cells stabilized disease in 2 out of 6 patients[227]. Similarly, analysis of efficacy and safety of MUC1-targeting CART-T cells found the therapy to be safe and successfully elevated the levels of CD4+ and CD8+ T cells at the tumor[228]. Currently, clinical trials are underway to determine MUC-1-targeted CAR-T cell therapy's efficacy and safety in patients with solid tumors, including PDAC (NCT02587689 and NCT02617134).

CONCLUSION

The PDAC remains an intractable disease that is slated to be the second leading cause of cancer-related deaths by 2030. Although surgical resection remains the only curative treatment option, late diagnosis, in addition to the patient's performance status, limits the scope of surgical intervention. Chemotherapeutic regimens such as gemcitabine+nab-paclitaxel and FOLFIRINOX has shown promise in improving patient survival; however, drug resistance remains a continuing challenge that has limited their efficacy. Two approaches that may improve PDAC patient outcomes include inhibiting the mechanism(s) that promote therapy resistance and targeting the key pathways essential for PDAC survival. The altered metabolism provides the PDAC cells with energy (ATP) and macromolecules essential for tumor growth. Additionally, studies have shown that metabolism plays a key role in PDAC therapy resistance. Similarly, PARP targeting therapies' success has once again brought the importance of DNA repair mechanisms in PDAC into the center. The limited success of immunotherapy has dampened the enthusiasm for targeting PDAC using this approach. However, the uncovering of mechanisms contributing to poor PDAC's response to immunotherapy has provided opportunities to test newer approaches. Even though the strategies mentioned above have shown promising pre-clinical results individually, a regimen targeting multiple aspects of PDAC will likely deliver a better clinical outcome in this deadly disease.

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