Review Article

Targeted therapy for pancreatic cancer: lessons learned and future opportunities

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is associated with a very poor prognosis because of its aggressive character, late-stage diagnosis, and resistance against systemic treatments. The current standard of care treatment for advanced PDAC is a combination of nab-paclitaxel and gemcitabine. However, other therapeutic approaches are necessary to combat cases where PDAC develops significant resistance against conventional chemotherapy. So far, targeted therapies have not been highlighted significantly with regards to facilitating successful treatment in PDAC patients. This review focuses on different targeted therapies tested in PDAC preclinically and clinically, such as antiangiogenic therapy, DNA repair inhibitors, KRAS pathway inhibitors, and anti-stromal therapy, summarizing data obtained regarding their implementation in treating PDAC, both by themselves and in combination with other drugs. This review also highlights recent advances in PDAC targeted therapies that may provide avenues for improved survival and facilitate further investigation into other potential therapeutic approaches in the future, including direct KRAS inhibitors, novel anti-stromal therapies, multikinase inhibitors, nanoparticle targeted therapy, and immunotherapy. Given the multifactorial nature of PDAC and how this disease has immense complexity in its treatment response with the development of resistance mechanisms, greater consideration and evaluation of novel targeted therapies are necessary towards improving PDAC treatment efficacy and patient outcomes.

Keywords: Pancreatic cancer; chemotherapy; targeted therapy; angiogenesis; KRAS

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the third-leading cause of cancer mortality in the United States (1) and is projected to become the second-leading cause in the next decade (2). PDAC has an extremely poor prognosis, with 1- and 5-year survival rates of only 18% and 7%, respectively (3), primarily due to late-stage diagnosis, its aggressive nature regarding early local invasion and metastasis, and high levels of resistance to conventional chemotherapies and radiotherapies. The increasing incidence and poor prognosis for PDAC patients demonstrate the unmet need for both earlier diagnosis and effective treatment strategies.

The current clinical standard of care for PDAC patients revolves around surgical resection and/or cytotoxic chemotherapy regimens (4). Surgical resection represents the only curative treatment, especially in cases where PDAC has

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Table 1 Timeline of FDA approved treatments for advanced pancreatic cancer

Cytotoxic chemotherapy	Year approved	Median survival	Notes	References
Gemcitabine	1997	6.1 months	A nucleoside analog	Burris *et al.* (6)
Gemcitabine plus erlotinib	2005	6.1 months plus 10 days	Erlotinib: an EGFR inhibitor	Moore *et al.* (7)
FOLFIRINOX	2011	11.1 months	Fluorouracil/leucovorin, irinotecan, oxaliplatin	Conroy *et al.* (8)
Nab-paclitaxel plus gemcitabine	2013	8.5 months	Nab-paclitaxel: albumin-bound paclitaxel	Von Hoff *et al.* (9)

no arterial and/or limited venous contact with the vasculature, with only 10–15% of patients meeting these criteria (5). In patients with advanced disease with metastases or in cases where PDAC is recurring, cytotoxic chemotherapy regimens are the standard treatment, with overall survival (OS) in the range of weeks to a few months (4). Single-agent gemcitabine was approved in 1997, and it remained the standard of care for PDAC for more than two decades, despite having a dismal clinical response with a median survival of approximately 6 months (6). Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, in combination with gemcitabine, improved OS of PDAC patients by 10 days compared with gemcitabine alone and received FDA approval in 2005 (7). In 2011, a more intense chemotherapeutic regimen, FOLFIRINOX (oxaliplatin, irinotecan, and fluorouracil/leucovorin), was approved for PDAC treatment, with improved survival of approximately 11 months (8). However, as expected, this regimen has higher toxicity, so only patients with high-performance status are eligible to receive this treatment. In 2013, nab-paclitaxel (an albumin-bound formulation of paclitaxel) in combination with gemcitabine (NPT + Gem) demonstrated median survival of 8.5 months, which led to FDA approval of this combination as a first-line treatment for PDAC patients (9) (*Table 1*).

A challenging aspect in improving the treatment of PDAC is the lack of accurate predictive biomarkers that can be used to evaluate response to chemotherapies and targeted therapies. In addition, most of the time, promising results on preclinical animal models do not translate to clinical trials (4). Patient-derived xenograft, organoid, and genetically engineered preclinical models that enable a better understanding of the disease progression at molecular levels may enable the improved translation of therapies (4,10). Genomic testing to determine specific genetic PDAC mutations might also help in tailoring targeted treatment regimens for improved efficacy and OS (4).

Targeted therapies that directly block specific oncogenic pathways in PDAC progression have thus far played a limited role in the treatment of this disease. The consensus statement from the National Cancer Institute (NCI) indicated the need for targeted agents, predictive biomarkers, and improved preclinical models for PDAC (11). Additional molecular pathways and genetic mutations of PDAC can be utilized for targeted or precision therapies (12,13). Targeting oncogenes (such as *KRAS*), reactivating inactivated tumor suppressors (such as *p53*, *CDKN4*, *p16*, *BRCA1/2* and *SMAD4*), and exploiting DNA repair pathways and the immune system might be potential treatment options for PDAC (5,14). Aberrant genes and signaling pathways for microRNAs (miRNAs) as biomarkers or therapeutic targets also have potential in PDAC (15). In this review, we will discuss potential oncogenic molecular pathways involved in PDAC progression and targeted therapies to block these pathways for improved clinical PDAC therapy.

Oncogenic pathways involved in PDAC progression

The growth and progression of PDAC involve many different, interconnected signaling pathways (*Figure 1*). The KRAS signaling pathway is predominant in PDAC, as oncogenic mutations of the *KRAS* gene facilitate many downstream pathways promoting cancer development and metastasis and impact metabolism (16). Once mutated, KRAS remains bound to GTP, leading to greater PDAC growth (16). Two well-known pathways activated by oncogenic KRAS include the RAF-MEK-ERK (MAPK) pathway and the PI3K-AKT-mTOR pathway, both promoting tumor cell proliferation, division, and survival as well as angiogenesis and invasion/migration (*Figure 1*). KRAS can be understood as a central mediating point regarding the network of oncogenic signaling in PDAC, as KRAS is implicated with many other downstream proteins involved in PDAC initiation, maintenance and progression,

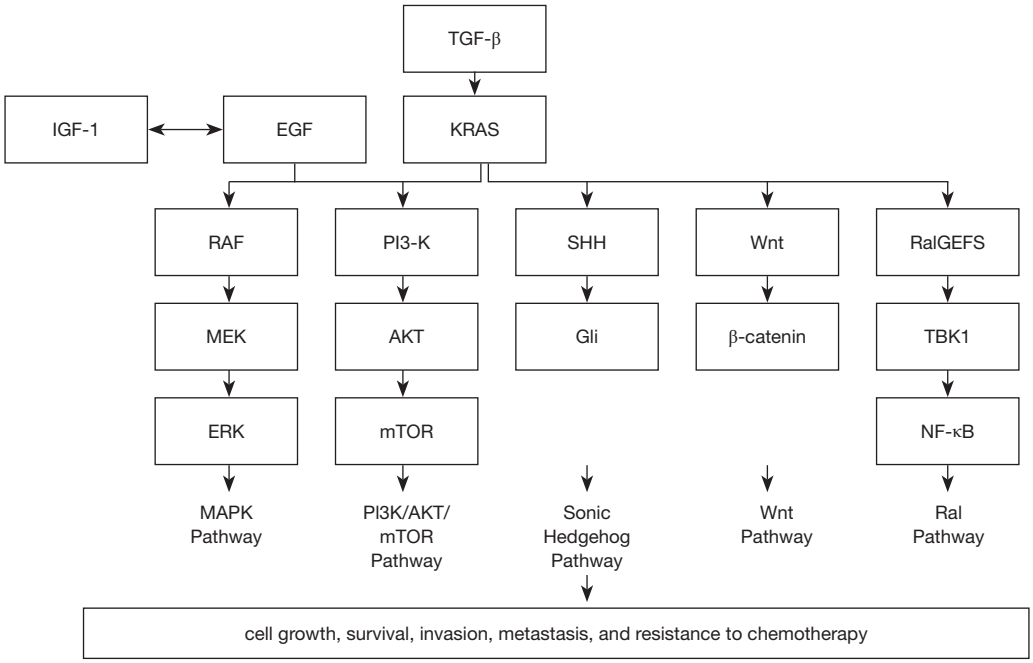

Figure 1 Oncogenic signaling pathways involved in pancreatic cancer progression.

and growth of the characteristic PDAC stroma (17). Activation of hedgehog signaling pathways, initiated by oncogenic KRAS activity, causes greater cancer cell proliferation and invasive activity and promotes cancer cell survival through increased resistance to apoptotic mechanisms (18). Oncogenic KRAS signaling also regulates Wnt protein signaling, as inhibition of Wnt/Ca^{2+} activity is conducive towards supporting PDAC tumor growth and development (19). Another pathway affected by oncogenic KRAS signaling involves Ral guanine nucleotide exchange factors (RalGEFs) (20) (*Figure 1*).

Other related pathways that intersect with oncogenic KRAS signaling are as follows: EGFR signaling pathways are pertinent in PDAC progression, as EGFR proteins are overexpressed in most PDAC cases (21). Additionally, EGFR-mediated signaling can also activate the MAPK and the PI3K-AKT signaling pathways (21). Higher activity of insulin-like growth factor-1 (IGF-1) and its receptor (IGF-1R) has also been shown to play a role in PDAC progression (22) (*Figure 1*). EGFR pathways also intersect with IGF receptors, as such intersectionality between these signaling pathways is conducive to greater growth and development of PDAC. Accordingly, mechanisms of resistance to pathway inhibitors emerge across these signaling pathways (22). Also, vascular endothelial growth factor (VEGF) and its receptor 2 (VEGFR2) signaling are involved in activating angiogenesis and promoting vascular growth, which in turn facilitates PDAC progression (23). The TGF-β signaling in PDAC can also promote disease progression by activating Ras and consequently ERK protein signaling facilitating angiogenesis, metastasis, and suppression of immune cells as part of the pancreatic tumor microenvironment (13) (*Figure 1*). However, other TGF-β signaling pathways, specifically SMAD protein-dependent pathways, have tumor-suppressive functions (13). Regardless, such signaling is prevented in many cases of PDAC, as there are mutations that inactivate SMAD-dependent TGF-β signaling, which in turn also promotes further progression of this disease (13). Some oncogenic pathways are more directly implicated in the PDAC microenvironment. Met (hepatocyte growth factor receptor) signaling regulates the relationship between pancreatic stellate cells (PSCs) of the tumor stroma and PDAC epithelial cells, promoting PDAC growth and metastasis (24). Moreover, integrins and their related signaling pathways also function within the PDAC microenvironment, as they facilitate PSCs transitioning into different kinds of cancer-associated fibroblasts (CAFs) through differentiation as well as regulate paracrine signaling effects mediated within the tumor microenvironment promoting greater PDAC growth

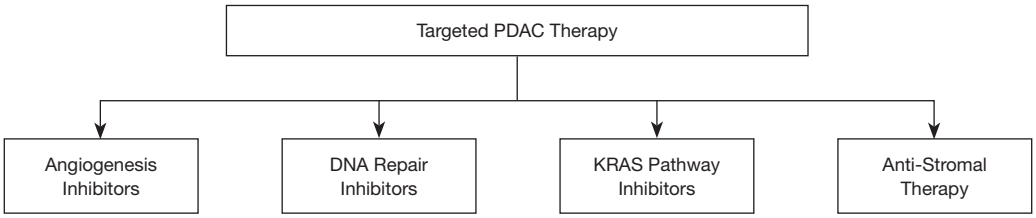

Figure 2 Broad classification of targeted therapies investigated in pancreatic cancer.

and progression (25).

Targeted therapies investigated for PDAC

Antiangiogenic therapies

Angiogenesis plays an integral role in promoting tumor growth and metastasis in many solid tumors (26). Although many types of cancers present with hypervascularity, corresponding to angiogenic processes, PDAC, in contrast, is characterized by its hypovascular nature, having fewer blood vessels associated with its tumors (27). Nonetheless, pro-angiogenic processes and factors are still important in the growth and development of PDAC, as these tumors often have multiple areas consisting of high levels of vascular, microvessel networks (27). Therefore, targeted therapies to block angiogenesis are important to consider for potential PDAC treatment modalities (*Figure 2*).

Antiangiogenic therapies for PDAC have focused on targeting VEGF signaling, as it facilitates tumor angiogenesis, creating greater tumor blood vessel density (28). Two types of antiangiogenic agents studied in PDAC are (I) monoclonal antibodies, such as bevacizumab (anti-VEGF antibody) and ramucirumab (anti-VEGFR2 antibody), and (II) small-molecule tyrosine kinase inhibitors (TKIs), including sunitinib, sorafenib, imatinib, and axitinib as early-generation TKIs, as well as newer therapeutic agents, such as nintedanib, which have shown greater promise with better safety profile.

Preclinical studies involving VEGF-targeted inhibition presented promising results regarding antitumor activity (27). However, such trends did not translate in clinical studies involving gemcitabine in combination with bevacizumab or axitinib, as there was no significant OS difference observed (29,30). Therefore, it is imperative to extend the scope of antiangiogenic drugs considered beyond targeting only VEGF to inhibit angiogenesis more effectively (28).

Sunitinib, a multikinase inhibitor targeting VEGFR, platelet-derived growth factor receptors (PDGFR), colony-stimulating factor receptor (CSFR) and the stem cell factor receptor (c-KIT), demonstrated effectiveness in blocking angiogenesis in the treatment of pancreatic neuroendocrine tumors, showing improvements in OS (31). However, sunitinib's efficacy has shown to be only temporary, as mechanisms of resistance have developed against this treatment with tumor hypoxia (32). In PDAC murine xenografts, sunitinib demonstrated antitumor activity as monotherapy and in combination with gemcitabine (33). Sorafenib, another multitarget TKI that blocks B-Raf, VEGFR, PDGFR, c-KIT and RET, demonstrated promising results in combination with gemcitabine in preclinical studies (34), but this combination was inactive in a clinical study (35). Nintedanib, a triple angiokinase inhibitor that targets VEGFR, PDGFR and FGFR, has shown significant antitumor response in preclinical models of several solid tumors (36). Treatment of PDAC tumors in xenograft models with nintedanib monotherapy or in combination with gemcitabine demonstrated significant anti-tumor activity (37). Nintedanib is currently under clinical investigation in combination with nab-paclitaxel plus gemcitabine for advanced PDAC (38).

More broadly, although antiangiogenic therapies presented some potential in preclinical contexts, there is limited evidence of their effectiveness in clinical studies of PDAC. The factors of drug resistance such as tumor hypoxia as well as alternative mechanisms of angiogenesis further complicate utilizing antiangiogenic therapies for this disease. Vascular mimicry presents an alternative mechanism of angiogenesis, as this allows for the building of compensatory vascular networks that evade antiangiogenic therapies (27,32). Antiangiogenic therapies can reduce the effectiveness of other treatment modalities, as they have been shown to compromise blood vessel structures, diminishing the efficacy of drug delivery to tumors (27,28). An important consideration for improving antiangiogenic therapies in personal treatment contexts is a better understanding of biomarkers, as these can provide

information regarding which patients could have better treatment outcomes with these therapies (27,32).

DNA repair targeted therapy

Although cancer cells have inherently damaged DNA, they can block and repair DNA damage induced by therapeutic agents. Accordingly, DNA repair targeted therapy in cancerous cells is directed towards those repair mechanisms specifically involved in fixing DNA damage caused by anticancer drugs. Targeting DNA repair processes presents a promising consideration in targeted therapies for cancers, including PDAC (39) (*Figure 2*).

Gemcitabine is not only strongly implicated in discerning new standards of combination chemotherapy modalities in PDAC, but it is also recognized as a DNA damaging agent. Therefore, consideration of DNA damage repair inhibitors is important, as such agents could complement the effects of gemcitabine, allowing such DNA damage to remain in PDAC cells, eventually leading to apoptosis (40). Two ways of preventing the repair of such DNA damage are (I) blocking the function of cell cycle regulators to allow cancer cells with DNA damage to continue through the cell cycle process and (II) stopping the process of DNA repair directly. In PDAC, cell cycle inhibitors such as CHK1, WEE1, and ATR kinase inhibitors have shown varying levels of potential when tested in combination with gemcitabine. CHK1 inhibitors have presented as relatively ineffective (41), while WEE1 and ATR kinase inhibitors have shown some promising results in inhibiting tumor growth in xenograft models, but such research is still in its early phases (42-44). Relative to these cell cycle inhibitors, poly adenosine diphosphate-ribose polymerase (PARP) inhibitors target PARP proteins, which have DNA repair as one of their cellular functions. BRCA proteins play an important role in DNA damage repair (40). *BRCA1/2* gene mutations are commonly implicated in cases of familial PDAC, which make up 5–17% of PDAC cases (45). When *BRCA1/2* genes are mutated, homology-directed DNA repairs are compromised, and PARP acts as a substitute mechanism to maintain genomic integrity; consequently, the cells become very sensitive to PARP inhibitors. Olaparib (a PARP inhibitor), both alone and in combination with gemcitabine, has shown effectiveness in improving OS in PDAC patients having the *BRCA* mutation (46,47). Olaparib has also shown promising results in combination with bevacizumab in other cancers, whether the *BRCA* mutation was present or not, presenting possible relevance of this combination as a potential treatment in PDAC (48).

Another area of relevance of DNA damage repair inhibitors in developing therapies for PDAC involves its combination with radiotherapy. Utilization of radiation/chemoradiation has demonstrated potential for improving patient survival outcomes with regards to resectable as well as unresectable PDAC cases (49). Administration of chemoradiation preceding surgical resection has improved OS in patients with PDAC, although such survival benefit has been shown in limited contexts with smaller-scale studies (50-53). Given that radiotherapy results in DNA damage in cancer cells, utilizing DNA damage repair inhibitors to prevent these cells from repairing this damage can facilitate greater radiosensitization, making these cancer cells more vulnerable to radiotherapy (54,55). In PDAC xenograft models, several DNA damage repair inhibitors such as CHK1 inhibitors (AZD7762, MKK8776), ATR inhibitor (VE-822), PARP inhibitors (olaparib, veliparib) and WEE1 inhibitor (AZD1175), demonstrated sensitization effects to radiation/chemoradiation (44,56-60). The combination approach of radiotherapy with DNA damage repair inhibitors is in the early phases of PDAC clinical studies.

KRAS pathway inhibitors

Activating *KRAS* mutation is the most frequent mutation (>95%) in PDAC, and it is associated with the initiation, progression, and maintenance of PDAC (16). KRAS is a small GTPase that cycles between active GTP-bound and inactive GDP-bound forms. *KRAS* mutation occurs at three primary locations: glycine-12 (G12), glycine-13 (G13), or glutamine-61 (Q61). Activating *KRAS* mutation results in many oncogenic signaling pathways, including the MAPK pathway and the PI3K-AKT-mTOR pathway. PDAC is particularly addicted to *KRAS* mutation, further emphasizing the importance of KRAS and its related pathways as potential targets in this disease.

Therapies that directly target KRAS have been challenging to study and evaluate, one reason being the structure of the KRAS protein, which has a smooth surface, which in turn is not complimentary towards inhibitors directly binding to its surface (61). Other challenges associated with direct targeting of the KRAS protein include its similarity to a large number of other proteins involved with GDP/GTP binding, which makes specific targeting of KRAS more difficult, as well as the high affinity of KRAS for GDP/GTP and the high cellular concentrations of GDP/GTP, which diminish the efficacy

of a potential direct KRAS inhibitor (62). Consequently, research involving KRAS pathway inhibitors has focused on targeting downstream effector pathways, such as MAPK and PI3K-AKT pathways (63).

Regarding the MAPK pathway, MEK inhibitors have been more widely evaluated relative to RAF and ERK inhibitors, as MEK kinases have critical functions in regulating and promoting cancer cell proliferation and tumorigenic growth (64). RAF inhibitors, such as vemurafenib and dabrafenib, proved challenging to implement in cancer treatment modalities because RAF inhibition has been demonstrated to be overcome by developed resistive mechanisms and/or paradoxical activation of downstream kinases by alternative mechanisms (65,66). Research involving ERK inhibitors has been more limited in scope, although a study reported promising antitumor effects of these inhibitors along with inhibition of autophagy in pancreatic cancer preclinical models (67). MEK inhibitors, specifically trametinib, have shown potential in PDAC. In a phase II clinical trial, trametinib combination with gemcitabine presented a 1.7-month improvement in OS compared with gemcitabine monotherapy in PDAC patients (68). In a preclinical PDAC study, trametinib demonstrated additive antitumor response in combination with nab-paclitaxel plus gemcitabine chemotherapy (69).

PI3K-AKT signaling is greatly implicated in the development and survival of cancerous cells, so this pathway presents a pertinent target for cancer treatments (70,71). PI3K inhibitors, such as BKM120 and BAY 80-6946, have been evaluated in solid tumors in clinical contexts (72,73). Additionally, MK-2206, an AKT inhibitor, has demonstrated pertinence regarding PDAC targeted therapies (74,75). AKT inhibition in combination with gemcitabine has shown promising outcomes in preclinical PDAC models (76). Recently, Awasthi *et al.* demonstrated that the standard chemotherapy response of PDAC can be enhanced through dual targeting of PI3K and MAPK signaling by MK-2206 and trametinib, respectively (77). Thus, PI3K-AKT pathway inhibition has the potential to be complementary towards enhancing other forms of PDAC targeted therapies (70).

An alternate approach to target the KRAS pathway uses kinases and activators upstream of the KRAS protein. The Met kinase activates KRAS and its subsequent downstream pathways, and it is often overexpressed in many cancers including PDAC (78,79). Onartuzumab, a Met inhibitor, demonstrated potential as an inhibitor of the KRAS pathway; however, further research is needed to establish Met inhibitors as being therapeutically effective in this disease (80).

Anti-stromal therapies

The PDAC microenvironment, the desmoplastic stroma, is composed of a heterogeneous variety of cell types, such as PSCs, fibroblasts, endothelial cells, immune cells, as well as non-cellular extracellular matrix (ECM) components such as collagen and growth factors (81). PDAC cells release several factors that stimulate the stroma, and stromal cells release several mitogenic/oncogenic substances that stimulate PDAC progression, invasion, and therapy resistance (82). This tumor microenvironment not only creates a hypoxic environment that is detrimental to chemotherapy delivery and radiotherapy but also releases growth factors and cytokines which further the growth of the desmoplastic stroma (81,82). Further, PDAC epithelial and stromal compartments interact to potentiate tumor aggressiveness. Thus, the therapeutic potential of targeting this dense desmoplastic stroma was evaluated in advancing PDAC therapy (81).

The Sonic hedgehog (Shh) pathway induces PSCs to become activated, which promotes greater growth of the stroma microenvironment. A preclinical study using the Shh pathway inhibitor saridegib (IPI-926) in combination with gemcitabine demonstrated promising results (83). Although phase 1 studies showed that this combination was somewhat tolerable, issues regarding toxicity arose in later clinical trials as its immense effects on depleting the stroma did not improve OS in long-term considerations (84,85). Given the complexity of the desmoplastic stroma, although it promotes PDAC growth in many ways, it also has functions that limit PDAC progression, such as restraining tumor growth. Therefore, an inordinate focus on the destruction of the desmoplastic stroma, using the Shh pathway inhibitor, can have repercussions with complete removal of the stroma, which could facilitate a more aggressive growth of this disease, thus decreasing OS. Therefore, future studies on anti-stromal therapies shifted their focus away from completely depleting the desmoplastic stroma (81).

Another pertinent consideration regarding anti-stromal targeted therapies focused on hyaluronan, a glycosaminoglycan present in the desmoplastic stroma ECM. Hyaluronan levels are much higher in PDAC tissues relative to healthy pancreatic tissues, and it has been correlated with aggressive tumor growth and therefore

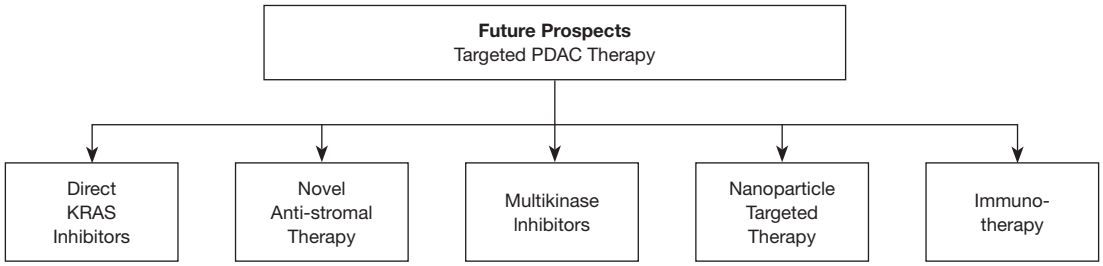

Figure 3 Future prospects of targeted therapies in the treatment of pancreatic cancer.

reduced OS (86). Depletion of hyaluronan with pegylated hyaluronidase (PEGPH20) showed some promise in PDAC, specifically in patients with higher levels of hyaluronan (87). Unfortunately, a recent randomized phase III trial of PEGPH20 plus NPT + Gem did not show any improvement in OS or progression-free survival (PFS) of PDAC patients (88).

Future prospects of targeted therapies for pancreatic cancer

Direct KRAS inhibitors

Based on the critical importance of the KRAS pathway in PDAC as well as difficulties associated with its direct and downstream targeting, there are ongoing efforts to have a direct inhibitor of this pathway (*Figure 3*). There are different variations of the oncogenic *KRAS* mutation, which differ in prevalence depending on the cancer type considered. For instance, G12D, G12V, and G12R *KRAS* mutation isoforms are more common in PDAC, whereas the G12C mutation isoform is more common in NSCLC but extremely rare in PDAC (16). Consequently, the drugs AMG-510 and MRTX-849 that are focused towards targeting the G12C *KRAS* mutation isoform are less applicable as direct KRAS inhibitors in PDAC (89,90). Recently, pan-KRAS inhibitors, such as BI-1701963 and BAY-293, which address all *KRAS* mutation isoforms more broadly, present greater applicability in PDAC. BI-1701963 and BAY-293 are inhibitors of the protein son of sevenless homolog 1 (SOS1), which activates KRAS, inclusive of its multiple oncogenic mutation isoforms. These direct KRAS inhibitors are emerging and receiving greater attention for clinical PDAC therapy.

Another approach utilizing direct KRAS inhibitors involves disruption of the localization of KRAS proteins to plasma membranes. One example of this approach is farnesyltransferase inhibitors (FTIs), as farnesyltransferase causes post-translational modification of KRAS that assists with its association with the plasma membrane and interactions with other activating proteins (91). In a phase III study, tipifarnib, an FTI, when evaluated in combination with gemcitabine, did not demonstrate any significant benefit (92). One possible reason for this ineffectiveness could be the presence of additional compensating lipid modification mechanisms, allowing for KRAS localization on plasma membranes regardless of FTIs (93). However, FTIs could present alternative treatment benefits with regards to inhibiting cytokine secretion which promotes inflammation and supports the tumor microenvironment (63). Other inhibitors that have been evaluated regarding the association of KRAS to the plasma membrane are deltarasin and salirasib. The protein phosphodiesterase 6 delta (PDEδ) helps the KRAS protein localize at the plasma membrane, so deltarasin, an inhibitor that blocks this interaction, was evaluated and showed promise in preclinical studies (94,95). Additionally, studies involving gemcitabine in combination with salirasib, which displaces Ras proteins from plasma membranes, have shown promising results, both in preclinical and clinical contexts (96). Therefore, additional research with the combination of gemcitabine with salirasib is needed to better assess the potential efficacy of salirasib as an inhibitor of KRAS.

Novel anti-stromal therapies

Based on the detrimental effects of initial anti-stromal therapies in PDAC, novel approaches have shifted their focus towards modulating the PDAC stroma in a more conservative, balanced manner (81). Additionally, exploring novel anti-stromal therapies is also imperative due to toxicities associated with initial anti-stromal therapies, including nausea and vomiting, muscle spasms, fatigue, and impaired or altered sense of taste (84,97).

Activated PSCs play an integral role in the PDAC stroma construction, as they are implicated in the deposition of ECM proteins such as collagen, laminin, fibronectin, and elastins, all of which bolster and contribute to the fibrotic stroma (81,98). Thus, therapeutic inhibition of PSCs activation has the potential to improve PDAC therapy. A novel approach involves analogs of fat-soluble vitamins, vitamins A and D. One characteristic feature of activated PSCs is their lack of cytoplasmic retinol containing lipid droplets. Loss of these lipid droplets enhances the activity of PSCs, which is further amplified as limited, impeded functionality of the pancreas and its secretions also diminishes levels of vitamins A and D. Vitamin A analogs have demonstrated reduced activity of PSCs, causing decreased PDAC cell proliferation (99). Vitamin D analogs have demonstrated high binding affinities to PSCs, which have many vitamin D receptors. Recent studies have shown the antitumor benefits of calcipotriol, a safe vitamin D analog, in combination with gemcitabine, with modulation of the PDAC stroma to be less reactive and more passive. Such reprogramming of the PDAC stroma has shown improved OS in mice with improvement in the delivery of chemotherapeutic drugs (100).

Recently, miRNAs are receiving more attention as novel anti-stromal therapies. A miRNA with potential relevance for PDAC is miR-21, which promotes fibrosis. As elevated amounts of miR-21 are implicated in PDAC tumors, they present potential diagnostic and therapeutic opportunities in this disease (101). Another miRNA, miR-29, has been implicated in PDAC. The loss of miR-29 has been reported in activated PSCs and fibroblasts causing increased ECM deposition and further stromal growth. Therefore, overexpression of miR-29 in activated PSCs has the potential to reduce stromal density and improve PDAC therapy (98). As miRNAs have shown promise in regulating fibrotic proteins and stroma to diminish tumor progression with little to no toxicity, miRNA-based targeted therapies have great potential for utilization in PDAC therapy.

Novel small-molecule inhibitors

Since many different signaling pathways are implicated in the progression of PDAC, consideration of agents that can inhibit multiple oncogenic pathways simultaneously represents a valuable approach to future targeted therapies. Evaluation of multikinase inhibitors for potential use in such therapies has demonstrated varying levels of efficacy.

MK2461, a multikinase inhibitor, has demonstrated efficacy in preclinical studies for its interference with interactions between PSCs and PDAC cells (102). MK2461 targets MET and PDGFRβ, both of which are present in PSCs and facilitate their interactions with other PDAC cells. Higher levels of MET and PDGFRβ in PSCs are implicated in increased PDAC progression (102). Since excessively high levels of MET expression indicate greater invasiveness and aggressiveness in PDAC, utilization of MK2461 has immense potential in future clinical studies, as this drug has shown attenuation of pancreatic tumor progression without significant toxicity effects (102). Evaluation of niraparib, a PARP inhibitor, has potential in PDAC patients where the disease possesses cellular difficulties regarding responsiveness in repairing DNA damage (103). CPI-613, a metabolic inhibitor, focuses on alterations of enzymatic activity involved in mitochondrial functions in tumor cells, presenting potential as a therapeutic agent because of its specific targeting of mitochondrial activity in tumor cells. CPI-613 is being evaluated in combination with FOLFIRINOX in PDAC patients as well, with important consideration placed towards the evaluation of a tolerable dose of CPI-613 (104). BEY-1107, a cyclin-dependent kinase (CDK) inhibitor, is currently under clinical investigation regarding its safety and efficacy in PDAC patients, both as a single agent as well as in combination with gemcitabine (105,106). Galunisertib is a therapeutic agent presenting strong selectivity and efficacy towards inhibition of TGFβ receptor 1 (TGFβR1). TGFβ is involved in tumorigenic growth and metastatic progression through multiple mechanisms such as cellular proliferation, angiogenesis, and stromal management, so TGFβ pathways present promising therapeutic targets (107). Galunisertib is currently being evaluated as monotherapy and in combination with gemcitabine in PDAC patients, presenting positive potential with only slight additional toxicity effects when administered concurrently with gemcitabine (108). Apatinib, a novel agent that inhibits VEGFR2, PDGFRβ and c-kit, is very promising in PDAC, as VEGFR2 plays a significant role in angiogenesis and metastasis in this disease (109-111). In addition to reducing tumor angiogenesis, apatinib also decreases tumor cell proliferation and induces apoptosis in PDAC cells (112). Also, apatinib is particularly appealing relative to previously considered antiangiogenic approaches, as it presents a greater capability towards improving OS in cancer patients (110). As a potential targeted agent for use in PDAC treatment modalities, further research and clarification are needed with regards to apatinib's applicability to PDAC patients.

Nanoparticle formulated targeted therapies

As the desmoplastic PDAC stroma presents a barrier to therapeutic agents, utilization of nanoparticles can lead to enhanced permeability, retention, and accumulation of anti-cancer drugs within tumors, conducive to increasing their efficacy (113). Nanoparticles have been used for improved delivery of chemotherapy drugs, combination treatments with multiple drugs, and small interfering RNA (siRNA)-derived therapeutics. siRNAs present potential for targeted treatment, as they safely facilitate suppression of gene expression, such as the *KRAS* gene, implicated in PDAC progression while not directly interfering with DNA. Nanoparticles can enable the delivery of siRNAs as therapeutic agents to PDAC cells and tumors.

Nanoparticle formulated targeted drugs have been shown to improve the efficacy of chemotherapeutic drugs, such as gemcitabine (114). EGFR-targeted nanoparticles in combination with gemcitabine improved treatment specificity and efficacy by delivering drugs near tumors, thereby improving cytotoxicity effects of gemcitabine at lower concentrations (115). Overall, nanoparticle-formulated targeted therapies present a direct mechanism that can improve not only the delivery of chemotherapeutic drugs to tumors but also their effectiveness in reducing tumor cell proliferation and tumor growth. Prabhuraj *et al.* demonstrated that administration of curcumin with gemcitabine via mesoporous silica nanoparticles (MSN) has additive antitumor effects in xenograft models and greater cytotoxicity in facilitating greater cell death among PDAC cells. As the application of curcumin presents enhanced effects of gemcitabine on PDAC, this also shows how the use of nanoparticles can complement existing chemotherapeutic agents (116).

Another combination therapy using nanoparticles, a Shh inhibitor, cyclopamine (CPA), and a chemotherapy drug paclitaxel (PTX) with a polymeric micelle formulation (M-CPA/PTX), has demonstrated improved antitumor response in PDAC preclinical studies by simultaneous remodeling of stroma by CPA and cytotoxic effects of PTX on tumor cells (117). These combination therapeutic strategies involving nanoparticles have a high potential for future PDAC therapy.

Immunotherapies

Immunotherapy approaches have faced significant challenges as potential targeted therapies for PDAC. Prominent stroma in the PDAC microenvironment presents a significant barrier to immunotherapies in multiple ways (118). The heterogeneous composition of the stroma with multiple cell types such as immunosuppressive myeloid cells and CAFs, prevents the development and activation of T-cells, creating a disadvantageous tumor microenvironment for immune responses to take effect (118). Beyond the stroma, T-regulatory cells (T-regs) tend to cause inhibitory effects localized at lymph nodes implicated with PDAC, limiting the efficacy of cytotoxic T-cells. Additionally, tumor-associated macrophages (TAMs) have been shown to facilitate tumor growth while also preventing cytotoxic T-cells from localizing into areas of tumors. The presence of $CD4^+$ and $CD8^+$ T-cells (which has shown the correlation with improvements in overall patient survival) into the PDAC microenvironment and subsequently the tumor itself are significantly limited by such inhibitory factors. Such immunosuppressive mechanisms in the PDAC microenvironment present immense challenges to potential targeted therapies involving immunotherapeutic considerations (118). Some approaches that have been utilized with immunotherapies include monoclonal antibody therapies, targeting immunosuppressive cells, adoptive cell therapy/transfer (ACT), and vaccines.

Targeting immune-checkpoint proteins, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) with ipilimumab and tremelimumab, or programmed cell death protein-1 (PD-1) with nivolumab has shown disappointing results as monotherapies in PDAC patients (119-121). Regardless, there is some potential for the combination of immune checkpoint inhibitors with other treatments such as chemotherapy and radiotherapy. Ipilimumab combination with gemcitabine has facilitated promising survival outcomes in PDAC patients (122,123), while tremelimumab, similarly, with gemcitabine, has demonstrated potential efficacy with manageable toxicity (124). Additionally, pembrolizumab, a PD-1 inhibitor, has shown considerable efficacy in combination with NPT + Gem (125). Another approach with immune checkpoint inhibitors in PDAC involves their administration with cancer vaccines, which has demonstrated some promise with improvements in greater T cell response (126).

Immunotherapy considerations present particular pertinence in tumors in which there are higher levels of microsatellite instability (MSI-H) facilitated by a defective DNA mismatch repair (dMMR) system, as such tumors are more vulnerable to and affected by immune system targeting. This is due to the increased prevalence of mutations in these cases, which in turn facilitates greater

amounts of antigen production, inflammatory response, and stimulation of T cells (127). In PDAC, however, the prevalence of MSI-H/dMMR is very low (<2%), indicating its limited applicability (128). Despite the rare occurrence of the MSI-H/dMMR phenotype in PDAC, it is recommended to test MSI-H and/or dMMR for advanced PDAC and treat patients who test positive with pembrolizumab as second-line therapy (129,130). Based on the limited data available about MSI-H/dMMR frequency in PDAC and the potential of immune-checkpoint inhibitors in this subgroup, future studies to improve MSI-H/dMMR detection methods might benefit select PDAC patients from immunotherapy.

Monoclonal antibody therapeutics aim to target something predominately expressed in PDAC which will, in turn, cause not only greater levels of cytotoxicity towards cancer cells but also block immunosuppressive signaling to enhance the activity of cells implicated in anti-tumor efficacy (131). One such target, mesothelin (MSLN), is overexpressed in almost all PDAC cells and implicated in adverse patient outcomes (132). Targeting MSLN using the antibody amatuximab showed demonstrable safety but it did not show any significant improvement in patient outcomes (133,134). However, other monoclonal antibody therapy targets, such as *KRAS* mutations, could be promising in future studies (131).

Direct targeting of immunosuppressive cells, such as T-regs, by chemotherapeutic drugs, such as cyclophosphamide and gemcitabine, has been attempted in PDAC (135). Although diminishing the presence of immunosuppressive cells does not necessarily impede PDAC progression directly, such therapeutic agents can enhance the anti-tumor functioning and efficacy of other modalities, such as CD40 agonists (136).

Utilizing ACT as an immunotherapy modality also shows promise in PDAC, as genetically engineered T-cells through ACT methods enhance anti-tumor activity by supporting the functioning of $CD4^+$ and $CD8^+$ T-cells (131). However, some difficulties in ACT-based immunotherapy approaches are the high degree of patient-centered personalization with genetic engineering, requiring immense time and effort, as well as the emergence of unanticipated resistances despite initial effective results (63).

Cancer vaccines GVAX and CRS 207 are currently under investigation for PDAC. The GVAX cancer vaccine utilizes genetically modified PDAC cells, while CRS 207 uses a recombinant bacterial basis using the *Listeria* bacterial strain (63,131). These vaccines have demonstrated safety in their use and improved survival when used in combination with each other (137). However, such survival benefit was of a lesser degree relative to standard chemotherapeutic regimens, so further research is needed to determine if such efficacy implicated in cancer vaccines can demonstrate more promising survival improvements in PDAC.

Conclusions

The prognosis and survival rate for patients diagnosed with PDAC remain particularly dire. The American Cancer Society reports that while the 5-year survival rate for patients diagnosed with all PDAC stages is dismal at 9%, it reduces to only 2.9% for patients with a stage 4 diagnosis. Unfortunately, PDAC patients are typically diagnosed at a late-stage, and approximately 50% of these patients receive a stage 4 diagnosis. Improving survival rates and remission for these patients is essential. Cytotoxic chemotherapy regimens, the current clinical standard of care for PDAC, have led to moderate improvement in OS; however, PDAC remission or cure is still elusive. Targeted therapies for PDAC are therefore potentially promising avenues that can lead to improved efficacy with reduced toxicity. Targeting specific molecular targets or oncogenes involved in PDAC progression may also enable better assessment of treatment response. Along with KRAS pathway inhibitors, other targeted therapies that have been investigated for PDAC treatment include antiangiogenic, DNA repair, and traditional anti-stromal therapies. Future considerations regarding PDAC targeted therapy are direct KRAS inhibitors, novel anti-stromal therapies, small molecule multikinase inhibitors, nanoparticle-based therapies, and immunotherapies. Overall, more research is essential for the development of novel targeted therapies with reduced toxicities that can lead to improved survival rates in PDAC patients and possible remission of this intractable disease.

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