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Recent advances in targeted therapy for pancreatic adenocarcinoma

INTRODUCTION

Pancreatic adenocarcinoma (PDAC) is a fatal disease with a 5-year survival rate of 8% and a median survival of 6 mo[1]. It ranks fourth among cancer-related deaths in the United States, and will become the number two cause within a decade[2]. In PDAC, several mutations in the genes are involved, with Kirsten rat sarcoma oncogene (*KRAS*) (90%), cyclin-dependent kinase inhibitor 2A (*CDKN2A*) (90%), and tumor suppressor 53 (*TP53*) (75%–90%) being the most common. Mothers against decapentaplegic homolog 4 (SMAD4) represents 50% (Table 1). In addition, the self-preserving cancer stem cells (CSCs), dense tumor microenvironment (fibrous accounting for 90% of the tumor volume), and suppressive and relatively depleted immune niche of PDAC are also constitutive and relevant elements of PDAC. They are considered significant clinical barriers to successful therapy development, making PDAC one of the most challenging diseases to treat. At present, only surgical resection is a potentially curative treatment for this refractory disease, which shows improvement in survival rates[3,4].

Conventional cytotoxic treatments, such as chemotherapy and radiation therapy, have not been successful in improving the chances of survival in pancreatic cancer patients. Since 2011, two combination regimens for metastatic pancreatic cancer have become the gold standard: 5-fluorouracil/leucovorin with irinotecan and oxaliplatin (FOLFIRINOX); and nab-paclitaxel with gemcitabine. With these approaches, response rates range from 23% to 31%, progression-free survival (PFS) rates are 5.5–6.6 mo, and overall survival (OS) is between 8.5 and 11 mo. Single-agent gemcitabine, and its combinations, have failed to provide the expected results, only achieving moderate life expectancy prolongation. However, most patients are diagnosed at the

unresectable stage. Therefore, the development of novel and effective therapeutic strategies is vital to improving treatments that are both targeted and personalized.

Imatinib ushered the era of targeted therapies for solid tumors in 2001. Since then, targeted therapies have been approved for renal, colorectal, gastroenteropancreatic neuroendocrine tumors, non-small cell lung cancer, and malignant melanoma[5-9]. There is only one United States Food and Drug Administration (FDA)-approved targeted therapy for PDAC-erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, combined with gemcitabine hydrochloride in patients with metastatic, locally advanced, or unresectable PDAC. However, the absolute benefit of gemcitabine plus erlotinib is also minimal (2 wk)[10].

In this review, we summarize current targeted therapies and clinical trials targeting dysregulated signaling pathways and components of the PDAC oncogenic process, analyze possible reasons for the lack of positive results in clinical trials, and suggest ways to improve them. We also discuss emerging trends in targeted therapies for PDAC: combining targeted inhibitors of multiple pathways. The PubMed database and National Center for Biotechnology Information clinical trial website (www.clinicaltrials.gov) were queried to identify completed and published (PubMed) and ongoing (clinicaltrials.gov) clinical trials (from 2003-2022) using the keywords pancreatic cancer and targeted therapy. The PubMed database was also queried to search for information about the pathogenesis and molecular pathways of pancreatic cancer using the keywords pancreatic cancer and molecular pathways.

TARGETED THERAPY

Targeted therapy highlights the association between tumor characteristics and individualized treatment response. Biomarkers and genomic mutations may serve as potential targets or prognostic indicators based on the expression of biomarkers. Overall, targeted therapies are based on three main approaches: inhibition of aberrant activation of oncogenes, interference with inactivation of tumor suppressor genes, and exploitation of biological functional defects in specific genes.

Most pancreatic tumors (about 95%) carry *RAS* mutations, the most common of which are *KRAS* alterations (85%)[11]. Mutations of *KRAS* and other genes, such as

inactivation of *CDKN2A* (in about 90% of PDAC cases) and SMAD4/DPC4 (approximately 55%), breast cancer susceptibility gene 2 (*BRCA2*), MutL homolog 1, or protease serine 1 alterations accumulate throughout the development of tumors. Approximately 50%-70% of PDAC cases carry mutations in the *TP53* gene, which occurs in late pancreatic intraepithelial neoplasia and leads to the malignant progression of PDAC[12]. As a result of these mutations, multiple critical processes-related signaling pathways are dysregulated, including apoptosis and cell proliferation. In addition, key molecules and pathways from the tumor and surrounding stroma, such as EGFR-mediated and pro-angiogenic pathways, influence the resistance of PDAC to therapy and are associated with a poor prognosis[13]. A total of 60 mutations in 12 different signaling pathways accompany the occurrence of aberrant ducts in PDAC[14], making targeted therapy a possible way to improve the efficacy of existing therapies (Table 2, Figure 1).

KRAS pathway and downstream signaling pathways
KRAS: *KRAS* oncogenic mutations can be observed in more than 90% of PDAC cases. Unfortunately, in mouse models, the resulting mitogen-activated protein kinase (MAPK) inhibition after *KRAS* inhibition (or direct blockade of downstream MEK) may further lead to the activation of protein kinase B alpha (Akt), EGFR, human epidermal growth factor receptor 2 (HER2), platelet-derived growth factor receptor α (PDGFRα), and AXL, resulting in the ineffectiveness of such drugs[15]. Therefore, the development of clinically effective *KRAS* inhibitors has been challenging. Initially, the strategy to target *KRAS* was to inhibit farnesyltransferase, as farnesylation is critical for RAS activation. A phase II trial (SWOG 9924) evaluated the efficacy of an oral farnesyltransferase inhibitor R115777 as first-line therapy for metastatic PDAC patients, but there was no clinical benefit[16]. A novel alternative strategy for targeting KRAS involves the use of exosomes, or small extracellular vesicles loaded with small interfering RNAs targeting *KRASG12D*, the most common KRAS mutation in PDAC[17], and was studied in a recent phase I trial (NCT03608631) that included patients with metastatic PDAC (mPDAC).

In addition, the KRASG12C mutation was identified in 2% of PDACs[18], and its molecular inhibitors ARS-1620 and sotorasib have shown preliminary antitumor efficacy in preclinical models[19] and patients with advanced solid tumors[20]. To date, only a small subset of patients carrying the KRASG12C mutation can be treated with FDA-approved sotorasib or adagrasib. The CRYSTAL-1 phase II clinical trial applied adagrasib to patients with KRASG12C-mutated pretreated solid tumors, and 1 PDAC patient achieved a partial response. Phase I/II trials (NCT03785249 and NCT04330664) evaluating the effectiveness of adagrasib are ongoing.

Given the difficulty of directly targeting KRAS, therapies targeting its major downstream effector pathways are in development, including the RAS/rapid accelerated fibrosarcoma (RAF)/MEK/extracellular signal-regulated kinase (ERK) and phosphatidylinositol-3 kinase (PI3K)/phosphoinositide-dependent kinase-1/Akt signaling pathways[21].

RAF/MEK/ERK MAPK pathway: Mitogen-activated extracellular kinases are a component of the RAS/RAF/MEK/ERK pathway and play a key role in proliferation, apoptosis, differentiation, and angiogenesis[22]. ERK1/2 MAPK is phosphorylated and activated after RAF serine/threonine kinase phosphorylates and activates MEK1 and MEK2. Activated ERK subsequently modulates the activity of approximately 160 substrates including transcription factors, protein kinases, phosphatases, and regulators of apoptosis[23]. However, several phase II studies of MEK inhibitors did not show efficacy as monotherapy for PDAC including CI-1040[24], selumetinib[25], pimasertib[26], and trametinib[27]. Most likely, the unsatisfactory results were caused by feedback activation and crosstalk between pathways, resulting in the activation of PI3K/mammalian target of rapamycin (mTOR)/Akt[28].

Mirzoeva et al[29] demonstrated the utility of the combinatorial effect of EGFR plus MEK inhibitors in the epithelial molecular subtype of PDAC. In addition, Brauswetter et al[30] identified specific molecular isoforms with KRAS G12C mutants that responded better to MEK inhibition than the more common G12D variant. Therefore, outcomes can be improved by identifying molecular subtypes and appropriate combination therapy to select the right targeted therapy for the right patient.

However, even considering the abovementioned issues, the MEK inhibitors' therapeutic effect is still unsatisfactory. It was shown in a phase I trial that afatinib combined with selumetinib, an inhibitor of MEK, had limited anticancer activity in patients with *KRAS*-mutated solid tumors including pancreatic cancers[31]. Similarly, the results of a phase II trial of selumetinib and MK-2206 (Akt inhibitor) in combination with modified FOLFIRINOX showed that the combination was less effective than FOLFIRONIX in PDAC patients, but had more significant toxicity[32]. The THREAD trial evaluated the efficacy of trametinib and hydroxychloroquine in PDAC patients at different stages of PDAC (NCT03825289).

Currently, approximately 10 clinical trials of MEK1/2 inhibitors targeting PDAC (selumetinib, cobimetinib, and trametinib) are underway, and it is crucial to evaluate the results before considering them for the clinical treatment of PDAC patients.

Furthermore, cobimetinib (MEK inhibitor) or GDC-0994 (ERK1/2 inhibitor) alone only transiently suppresses the MAPK pathway in *KRAS* mutant cancer cell lines[33,34]. Alternatively, co-targeting MEK and ERK with these drugs demonstrates significant antitumor activity in cancer cells and tumor models with dysregulated MAPK pathways. However, in the clinical setting, combining cobimetinib and GDC-0994 in clinical settings is no longer recommended due to overlapping adverse events (AEs)[35]. Overall, developing inhibitors targeting this pathway is promising, but further research is needed to find more appropriate combinations while reducing AEs.

KRAS wild-type PDAC: As mentioned above, most patients with PDAC have *KRAS* mutations. In the small subset of patients with *KRAS* wild-type (WT) PDAC, other mutations, such as neurotrophic receptor tyrosine kinase (NTRK) and neuregulin 1 (NRG1), can initiate PDAC tumorigenesis and be targeted. The incidence of NTRK fusions is 0.3%[36]. Chromosomal rearrangements in the *NTRK* gene family promote the expression of chimeric rearranged promyosin receptor kinases[37]. It is possible that these chimeric proteins signal through the same MAPK and PI3K/Akt pathways as normal TRK proteins and are involved in tyrosine kinase crosstalk[38]. Therefore, a promising approach for targeted therapy is to address fusions of tropomyosin receptor kinase genes 1, 2, or 3 (*NTRK1, 2, 3*).

In solid tumors with *NTRK* gene fusions, regardless of tumor type, larotrectinib, and other TRK inhibitors have shown significant and durable antitumor activity (overall response rate 75%, 95% confidence interval [CI]: 61%-85%)[39]. The latest American Society of Clinical Oncology-Gastrointestinal data reconfirmed that larotrectinib is recommended for a variety of gastrointestinal tumors (including pancreatic cancer) carrying *NTRK* fusion mutations[40]. A pooled analysis of clinical trials (NCT02122913, NCT02637687, NCT02576431, NCT02097810, NCT02568267, EudraCT, and 2012-000148-88) revealed that the selective TRK inhibitors larotrectinib and entrectinib were effective against solid tumors (including PDAC) harboring *NTRK* gene fusions (79% response rate for larotrectinib; 57% for entrectinib). Larotrectinib and entrectinib have received FDA's breakthrough designation targeting NTRK fusion-positive solid tumors[41,42]. Next-generation TRK inhibitors, such as selitrectinib and repotrectinib, are being developed to address on-target resistance[43]. Among them, second-generation TRK inhibitor LOXO195 achieved efficacy in 2 patients with NTRK fusion-positive solid tumors, who had disease progression after larotrectinib therapy[44].

NRG1 fusions are rare oncogenic drivers, found in approximately 0.2% of all solid tumors[36]. These fusions trigger hyperactivation of ERBB3/HER3, which drives tumor growth and cancer cell survival. Seribantumab is a fully humanized anti-HER3 immunoglobulin G2 (IgG2) monoclonal antibody (mAb) that inhibits tumor growth in NRG1 fusion-driven preclinical models. CRESTONE is a phase II trial of seribantumab in patients with locally advanced or metastatic solid tumors with NRG1 fusions. Preliminary data suggest that seribantumab induces durable responses with a favorable safety profile. These data support the continued evaluation of seribantumab in the CRESTONE study (NCT04383210).

Tyrosine kinase receptor pathway
EGFR: EGFR is highly expressed in 30%-50% of PDACs[45-47]. Interestingly, EGFR signaling input is required for pancreatic carcinogenesis even in the presence of an oncogenic *KRAS* mutation[48,49]. The small molecule erlotinib, a selective inhibitor of EGFR tyrosine kinases, is the first approved targeted therapy in PDAC. In a phase III

trial of metastatic PDAC, the combination of gemcitabine and erlotinib improved median OS (mOS) significantly by 0.33 mo (about 10 d) in the entire study population[10].

Nimotuzumab, an anti-EGFR mAb, showed significantly prolonged OS in combination with gemcitabine *vs* gemcitabine monotherapy in a phase II trial (median PFS 3.2 mo *vs* 5.5 mo, hazard ratio [HR] 0.55, *P* = 0.0096; median OS 5.2 mo *vs* 8.6 mo, HR 0.66, *P* = 0.034)[50]. A phase III trial (NCT02395016) showed that nimotuzumab in combination with gemcitabine improved OS and PFS in patients harboring *KRAS* WT with locally advanced or metastatic pancreatic cancer, with significantly longer median OS in the nitrozumab-gemcitabine group (10.9 mo *vs* 8.5 mo, HR = 0.50, 95%CI: 0.06-0.94; *P* = 0.025). In addition, median PFS was 4.2 mo in the trial group compared with 3.6 mo in the control group (HR = 0.56, 95%CI: 0.12-0.99; *P* = 0.013)[51].

Positive trends have been reported for the EGFR inhibitors matuzumab (phase I)[52] and panitumumab in combination with gemcitabine and erlotinib (phase II)[53]. By contrast, the combination of cetuximab and gemcitabine failed to improve OS, with an mOS of 6.3 mo and PFS of 3.4 mo in the combination arm, compared with 5.9 and 3 mo, respectively, in the gemcitabine monotherapy arm[54].

Trastuzumab, a humanized Ab against HER2, has not yet improved the prognosis of pancreatic cancer in clinical trials. The 12-wk PFS rate for trastuzumab in combination with capecitabine was 23.5%, with a median OS of 7.0 mo[55]. Another recombinant humanized mAb against HER2, pertuzumab, has been used to treat solid tumors including pancreatic cancer. Two pancreatic cancer patients showed partial responses with stable disease for 15.3 mo in 1 patient[56]. Afatinib, a second-generation irreversible inhibitor of ERBB receptors (both EGFR and HER2/neu), is approved as monotherapy for the first-line treatment of non-small cell lung cancer (NSCLC) with EGFR mutations and treatment of lung squamous cell carcinoma after failure of platinum-based chemotherapy. A phase II trial conducted by the "Arbeitsgemeinschaft Internistische Onkologie" was designed to evaluate whether the gemcitabine/afatinib combination was more effective than gemcitabine alone in metastatic PDAC. However, adding afatinib to gemcitabine did not improve therapeutic efficacy and was more toxic. Median OS in the combination group was 7.3

and 7.4 mo in the gemcitabine group. The median PFS was identical in both groups (3.9 mo *vs* 3.9 mo). In addition, AEs were more frequent in the combination group, especially diarrhea (71% *vs* 13%) and rash (65% *vs* 5%)[57].

Vascular endothelial growth factor: Overexpression of vascular endothelial growth factor (VEGF) in PDAC is associated with tumor progression and poorer prognosis[58,59]. However, angiogenesis-targeted therapy is clinically ineffective in pancreatic cancer patients. The reason may be that dense stromal tissue with reduced vascular density impedes the delivery of effective drugs. Moreover, the withdrawal of antiangiogenic agents after therapy may be associated with increased tumor aggressiveness and invasion, offsetting the potential therapeutic benefits offered by antiangiogenic agents[60].

Multiple clinical trials of antiangiogenic agents have been conducted to treat PDAC, yet the results have been overwhelmingly disappointing. For PDAC patients, it has shown improvement in PFS in a few clinical trials[61], but no significant prolongation in OS has been observed. Humanized monoclonal antibodies such as bevacizumab have an affinity for circulating VEGF-A, but phase II and III studies have shown no survival advantage for bevacizumab in combination with gemcitabine and erlotinib[61-64]. A meta-analysis concluded that bevacizumab plus gemcitabine treatment elicited only a moderate response rate without survival modifications[65]. Other VEGF inhibitors, such as axitinib and aflibercept, provide no survival advantage[66-69]. Likewise, sorafenib (an inhibitor of VEGFR and RAS/RAF/MAPK signaling) had no additional value for patient survival over gemcitabine[70].

The promising drug in the field is currently anlotinib. Anlotinib is a novel oral tyrosine kinase inhibitor that targets VEGFR, fibroblast growth factor receptor, PDGFR, and c-kit. Compared to the placebo, it improved PFS and OS in a phase III trial in patients with advanced NSCLC[71]. A phase II trial of anlotinib, toripalimab, and nab-paclitaxel in patients with locally advanced/metastatic pancreatic cancer is underway (NCT04718701). A first-in-human phase I study of AK109, an anti-VEGFR2 Ab, in patients with advanced or metastatic solid tumors, including 2 patients with pancreatic cancer (2/40), showed a controlled safety profile and promising antitumor

activity (NCT04547205). Two phase II studies of AK109 in combination with AK104 (anti-PD-1/cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] bispecific Ab) are being evaluated in patients with multiple solid tumors (NCT05142423, NCT04982276).

Insulin-like growth factor receptor 1: Insulin-like growth factor receptor 1 (IGF-1R), a transmembrane receptor tyrosine kinase, is overexpressed in pancreatic cancer. Activation of IGF-1R is associated with decreased apoptosis, cancer cell proliferation, and angiogenesis[72,73]. Yet the use of gemcitabine and a single IGF-1R inhibitor alone has not achieved satisfactory clinical results. A phase III clinical trial of the IGF-1R mAb ganitumab showed no improvement in patient survival[74].

A previous study showed that the simultaneous blockade of IGF1R and EGFR/HER2 synergistically inhibited pancreatic tumor growth and eliminated the activation of IRS-1, Akt, and MAPK phosphorylation. Based on this, combining these two inhibitors may prevent drug-resistance reactions caused by monotherapy[75]. A phase I/II study of gemcitabine and erlotinib in combination or not with MK-0646, an IGF1R inhibitor, in advanced pancreatic cancer showed that the combination of MK-0646 with gemcitabine plus erlotinib was tolerable and improved OS but not PFS compared with gemcitabine plus erlotinib[76]. Istiratumab (MM-141), a quadrivalent bispecific Ab recognizing IGF-1R and ERBB3, provided promising results in preclinical studies[77], but its phase II clinical trial was negative[78].

PI3K/Akt/mTOR pathway

The overexpression of Akt is found in more than 40% of PDAC cases[79,80]. PI3K/Akt/mTOR, as a critical pathway in many aspects of cell growth, survival, and apoptosis, plays an essential role in the occurrence and development of various tumors including PDAC[81]. Dysregulation of this pathway may lead to tumor resistance to chemotherapy[82,83]. It has been documented that activation of Akt is associated with a poor prognosis[84,85]. Inhibition of Akt signaling induces apoptosis and limits tumor growth[86].

Alkyl phospholipid perifosine acts as an inhibitor of Akt and PI3K phosphorylation[87]. Combining perifosine with gemcitabine exhibits synergistic

effects on pancreatic cancer cells expressing high levels of phosphorylated Akt, primarily inhibiting tumor migration/invasion and inducing tumor cell apoptosis[88].

Clinical activity of everolimus (mTOR inhibitor) in patients with gemcitabine-refractory pancreatic cancer was limited, with a median PFS of 1.8 mo and median OS of 4.5 mo[89]. Combining everolimus with capecitabine achieved appropriate efficacy, with a mean OS of 8.9 mo (95%CI: 4.6-13.1) and median PFS of 3.6 mo (95%CI: 1.9-5.3)[90]. Temsirolimus is another mTOR inhibitor tested in locally developed or metamorphosic conditions[91,92]. A phase I/II trial evaluating sirolimus, a selective inhibitor of mTOR, enrolls patients with advanced pancreatic cancer (NCT03662412). In addition, other drugs targeting this pathway have been developed such as PI3K inhibitors, BKM120 and BYL179 (NCT02155088); RX-0201 (Akt antisense oligonucleotide inhibitor); and BEZ235 (combined inhibitor of PI3K and mTOR)[93,94].

Poly (ADP-ribose) polymerase pathway
Germline *BRCA* mutation is an autosomal dominant mutation associated with an increased risk of breast, gynecologic, colorectal, and pancreatic cancers. In families with germline *BRCA2* mutations, the relative risk of pancreatic cancer is 3.5% (95%CI: 1.9–6.6)[95]. Mounting evidence has demonstrated that *BRCA1/2* mutant breast and ovarian cancers are susceptible to DNA damage-related therapies, including poly (ADP-ribose) polymerase inhibitors (PARPis) and platinum-based drugs[96].

Clinically, PARPis have shown significant efficacy against other refractory *BRCA*-mutated solid tumors[97-100]. Olaparib is a PARPi that was effective in a single-arm phase II trial[98]. Veliparib, another PARPi, has modest activity in patients with previously platinum-treated germline *BRCA1/2* mutation-positive pancreatic cancer[101]. The RUCAPANC study, which evaluated the PARPi rucaparib, was discontinued during the interim analysis due to a lack of patient response[102].

A phase II trial of niraparib, a highly specific PARP-1 and PARP-2 inhibitor, is currently being conducted in metastatic PDAC patients with somatic or germline defects in multiple DDR genes (NCT05442749). A randomized phase II trial (PARPVAX) of niraparib (nira) *vs* an immune checkpoint inhibitor, nivolumab (nivo, PD-1 mAb) or ipilimumab (ipi, CTLA-4 mAb), has been evaluated in a non-genomic

selected, advanced PDAC patient population that has received at least 16 wk of platinum-based therapy without progression (NCT03553004). Another similar trial showed that compared to nira/nivo, nira/ipi prolonged median PFS as maintenance therapy for advanced PDAC patients with no progressive disease after first-line platinum-based chemotherapy, with an mPFS of 1.9 mo (95%CI: 1.8-1.9) for nira/nivo and 7.6 mo (95%CI: 4.0-11.1) for nira/ipi (NCT03404960).

A prospective phase III trial (POLO, NCT02184195) evaluated olaparib in metastatic PDAC patients with *BRCA* mutations[103]. The results indicated that metastatic PDAC patients with germline *BRCA1* or *BRCA2* mutations were significantly less likely to progress after taking olaparib. The trial included 154 patients with germline *BRCA* mutations whose tumors had not progressed after 16 wk of platinum-based induction chemotherapy. They were randomly assigned: 92 to receive olaparib and 62 to placebo. PFS was significantly longer in the olaparib group compared with the placebo group (median PFS: 7.4 mo *vs* 3.8 mo, HR = 0.53; *P* = 0.004). There was no difference in OS between the placebo and olaparib groups, despite the fact that some patients in the placebo group received PARPis as follow-up therapy. The risk of disease progression was reduced by 47% in the olaparib group, and patients treated with olaparib were at least twice as likely to be disease progression-free at 6, 12, 18, and 24 mo as those receiving a placebo. Based on this, National Comprehensive Cancer Network guidelines included olaparib as recommended maintenance therapy for PDAC patients with germline *BRCA1/2* mutations, good performance status, metastatic disease, and no disease progression after 4-6 mo of first-line chemotherapy. In addition, the safety of olaparib was also validated in the POLO trial, where patients' health-related quality of life was assessed and found to remain unchanged with no clinically meaningful deterioration. Grade ≥ 3 or higher AEs occurred in 39.6% of the olaparib group and 23.3% of the placebo group; 5.5% and 1.7% of patients discontinued treatment due to AEs, respectively[99,104].

Multidrug combination therapy is also a promising strategy. Antiangiogenic agents act synergistically with PARP inhibitors, resulting in increased levels of hypoxia and downregulation of homology-driven repair genes[105]. This combination will be further investigated in a phase II trial, including patients with mPDAC

(NCT02498613). In addition, an ongoing phase II trial is evaluating the efficacy of olaparib in combination with pembrolizumab (an immunotherapy cancer drug) in patients with *BRCA*-mutated pancreatic cancer (NCT04548752). A phase II trial evaluating talazoparib in patients with advanced cancer and DNA repair variants is ongoing (NCT04550494).

RET pathway

Genetic abnormalities in the RET proto-oncogene have been reported in PDAC. In phase I trials for pancreatic and biliary tract cancer, vandetanib (a multitargeted tyrosine kinase inhibitor of EGF, VEGFR, and RET) was evaluated in combination with gemcitabine and capecitabine. A 78% disease control rate (> 2 mo), 3 partial responses, and 15 patients with stable disease were observed in this trial[106]. A subsequent phase II trial of vandetanib in combination with gemcitabine *vs* gemcitabine monotherapy has shown that the combination did not improve OS in advanced PDAC (8.83 mo *vs* 8.95 mo, HR = 1.21, 80.8%CI: 0.95-1.53; *P* = 0.303)[107]. In addition, LOXO-292, a selective RET inhibitor, is being investigated in a phase I study (NCT03157128).

Tumor suppressor pathway

TP53 tumor suppressor pathway: Contrary to the role of proto-oncogenes, the role of a tumor suppressor is to suppress tumorigenesis. *TP53* is the most frequently inactivated suppressor in PDAC, and *TP53* gene alterations are found in approximately 70% of PDAC patients[108,109]. *p53 is a transcription factor that regulates the expression of* multiple genes. Its biological functions include inhibiting cell proliferation by inducing p21 expression, promoting tumor cell apoptosis, maintaining gene stability, and inhibiting tumor vascularization by stimulating B-cell lymphoma 2-associated X protein expression[110,111]. *TP53* reactivators include Zn2+ chelators such as COTI-2, cys-targeting agents such as APR-246 and CP-31398, and other proteins that assist in *p53* resilience, inhibit abnormal *p53* aggregation, or stabilize *p53*[112].

A clinical trial of COTI-2 is ongoing in patients with *TP53* mutant PDAC (NCT02433626). In addition to reactivation, inhibition of Mouse double minute 2 homolog (MDM2) is another emerging strategy for targeting *TP53*-mutated tumors. The p62-NRF2-MDM2 axis is involved in tumor progression and programming[113], and MDM2 antagonizes *p53* through direct interaction or ubiquitin-dependent degradation[114]. Therefore, inhibition of MDM2 may increase *p53* activity and suppress *p53*-mutant cancers[115]. Recent studies have confirmed the efficacy of MDM2 inhibitors, such as Nutlin, MA242, SP141, and MI-319, *in vitro* and *in vivo*[116-119]. MANTRA-2 is a phase II trial evaluating the clinical benefit of Milademetan, a selective MDM2 inhibitor, in MDM2 amplified (copy ≥ 12) TP53-WT solid tumors and is currently recruiting (NCT05012397).

Transforming growth factor/β SMAD4 pathway: Another tumor suppressor gene associated with the pathogenesis of pancreatic cancer is the *SMAD4* gene, and approximately 40% of PDAC patients carry *SMAD4* mutations[109]. In normal cells, the product of this gene (a 64-kDa protein) plays a role in transforming growth factor beta (TGF-β)-mediated signal transduction, gene transcription, and growth arrest. The TGF-β/SMAD4 signaling pathway mediates tumor-stromal interactions and the epithelial-stromal transition. Evidence suggests that TGF-β inhibitors, including trabedersen and galunisertib, reduce tumor metastasis and invasion in animal models[120,121]. A randomized phase II trial showed that galunisertib in combination with gemcitabine improved OS compared with gemcitabine alone[122]. The combination of galunisertib and durvalumab (programmed death-ligand 1 mAb) has also been studied in metastatic PDAC patients[123]. The sponsor has since terminated further studies of galunisertib due to limited clinical activity. Instead, a new generation of TGF-β pathway inhibitors, such as TGF-βR inhibitors and TGF-β-checkpoint traps, are under development[124,125]. NIS793, a human IgG2 mAb TGF-β antagonist, is in a phase III trial to evaluate the efficacy of NIS793 in treatment-naïve patients with mPDAC (NCT04935359). Furthermore, TGF-β levels are reduced in fibroblasts due to blockade of the angiotensin type III receptor[126,127]. Thus the angiotensin receptor blocker losartan was tested in a preclinical model of pancreatic

cancer and subsequently tested in combination with FOLFIRINOX in a phase II trial[128], which enabled R0 resection in 69% (30/49) of patients with locally advanced disease[129]. A randomized phase II trial evaluating losartan in combination with FOLFIRINOX and stereotactic body radiotherapy in neoadjuvant setting is ongoing (NCT03563248).

Dysfunctional CDKN2A and CDK4/6 inhibitors: *CDKN2A* is a multifunctional gene that creates p16 and p19, arrests the cell cycle at the G1/S checkpoint through a CKD4/6-regulated mechanism[130], and the proteins bind to MDM2 to block the reduction in *p53* levels[131]. Approximately 60% of PDAC patients carry *CDKN2A* mutations, with an odds ratio of 12.33, indicating that germline mutations in *CDKN2A* are associated with a high risk of developing PDAC[108,109]. CDK4/6 is a potential target for *CDKN2A*-deficient tumors[132,133]. The CDK4/6 inhibitors ribociclib and palbociclib have shown safety and efficacy in metastatic breast cancer and liposarcoma[134,135]. Additionally, CDK4 inhibitors are efficacious in preclinical models of PDAC[136-139], and a related clinical trial (NCT02501902) is ongoing. Researchers have concluded that CDK4/6 inhibitors alone exert limited antitumor effects and can show greater promise when used in combination with other targeted agents[140]. Mechanistically, CDK4/6 inhibitors block DNA repair mechanisms and increase the sensitivity of PDAC cells to PARPis[141]. PDAC cells are more sensitive to immune checkpoint blockers when CDK4/6 and MEK are inhibited jointly[142]. A phase I clinical trial of palbociclib in combination with the PI3K/mTOR inhibitor gedatolisib in advanced PDAC patients is ongoing (NCT03065062).

Nuclear factor kappa B pathway

Nuclear factor kappa B (NF-κB) is a protein complex involved in cell proliferation, cell adhesion, apoptosis, and inflammatory responses[143]. Overexpression of the NF-kB pathway is reported in approximately 70% of pancreatic cancers[144,145]. Curcumin is a potent inhibitor of this pathway, and its effects have been demonstrated in several *in vitro* and *in vivo* pancreatic cancer models[146,147].

Nafamostat mesilate (NM) is a synthetic serine protease inhibitor that inhibits NF-κB activation[148]. NM infusion with gemcitabine for inoperable advanced pancreatic cancer was evaluated in a phase I/II study. The median OS and 1-year survival rates were 10 mo and 40%, respectively[149]. Subsequently, a phase II study of NM/gemcitabine adjuvant chemotherapy showed that gemcitabine combined with local arterial perfusion adjuvant chemotherapy with NM is safe and may be an option in the adjuvant setting after curative surgery for pancreatic cancer[150].

STROMA TARGETS

PDAC is characterized by dense fibrous stroma representing up to 90% of the tumor volume. Desmoplasia means excessive proliferation of fibrotic tissue with a modified extracellular matrix providing a protumorigenic environment[151,152]. Pancreatic stellate cells play a major role in stromal responses, and they are closely associated with pancreatic cancer cells[153,154], controlling matrix synthesis, cell growth, migration, and invasion through a diverse set of signaling cascades. In addition, hepatocyte growth factor (HGF) from stromal cells was associated with the growth, angiogenesis, and invasiveness of pancreatic cancer[155]. The pro-fibroproliferative response is accompanied by a relatively avascular tumor microenvironment, followed by hypoperfusion and hypoxia in the cancerous tissue, which leads to the generation of more aggressive tumor subclones[156], altered tumor metabolism, increased glycolysis[157], and decreased chemotherapeutic drug concentrations. Therefore, stroma-specific therapeutic strategies can be developed. One way is to directly target specific components of the extracellular matrix, such as matrix metalloproteinases (MMPs), and the other is to target specific signaling pathways that promote the development of the tumor stroma, such as the Sonic Hedgehog (SHH) pathway.

SHH pathway

Hedgehog signaling is an essential pathway for proliferation and survival in embryonic development. In response to hedgehog ligand binding to PATCHED 1 receptor protein in target cells, a signaling cascade is triggered, eliminating the

inhibitory effect of Smoothened (SMO), which then enhance tumor progression, metastasis, and tumorigenesis[158].

Combined with gemcitabine, cyclopamine, an SMO antagonist, was shown to reduce metastatic potential in the GEMM (KPC) model of PDAC[159]. A phase II trial of vismodegib (a second-generation SMO inhibitor) combined with gemcitabine had a PFS benefit (4 mo *vs* 2.5 mo; *P* = 0.30) but did not improve OS (6.9 mo *vs* 6.1 mo; *P* = 0.84)[160]. These results are consistent with another clinical trial (NCT01088815)[161]. In addition, a phase I trial (NCT00878163) enrolled metastatic PDAC patients to evaluate the combination of vismodegib and erlotinib. Although the combination was well tolerated and 20% of patients exhibited stable disease, there was no significant tumor shrinkage effect[162]. Overall, the clinical trials with vismodegib did not meet expectations. Thus, the clinical development of this drug has been discontinued. In another phase II trial, saridegib (an SMO inhibitor) plus gemcitabine had a survival disadvantage (NCT01130142). Nevertheless, when combined with FOLFIRINOX, there was clinical activity with an objective response rate of 67%[163]. The clinical development of this drug was also halted.

The reasons for the disappointing results of hedgehog inhibition could be arising SMO mutations under therapy and compensatory feedback loops leading to a (hyper) activation of the PI3K pathway or downstream targets of the hedgehog pathway (*e.g.,* Gli2)[164,165]. This suggests that targeting both the Hedgehog pathway and PI3K pathway could be used for treating pancreatic cancer, as shown in medulloblastoma[166].

Hyaluronic acid
Hyaluronic acid (HA) is a glycosaminoglycan that is abundantly present in the extracellular matrix and contributes to the dense desmoplastic stroma surrounding the tumor. The degradation of HA by hyaluronidase may help disrupt the stroma and enhance drug delivery to the tumor[167]. Recombinant human hyaluronidase (PEGPH20) has been studied in mouse models of pancreatic cancer and was found to degrade HA, reduce interstitial fluid pressure, increase vascular permeability, and

enhance doxorubicin delivery to tumors. In combination with gemcitabine, PEGPH20 inhibits tumor growth and prolongs survival[167].

The HALO 202 trial examined improvements in PFS in patients with untreated metastatic PDAC. In this phase II trial, 269 patients were randomized to treatment with PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) *vs* nab-paclitaxel/gemcitabine (AG). The mPFS was significantly improved in the PAG arm for 6 mo *vs* 5.3 mo in the AG arm (HR = 0.73; *P* = 0.045). In patients with > 50% of HA staining, the PAG group had a higher objective response rate (45% *vs* 31%) and a longer mOS (11.5 mo *vs* 8.5 mo, HR = 0.96, 95%CI: 0.57-1.61)[168]. The HALO109-301 phase III clinical trial evaluating PEGPH 20 (NCT02715804) was terminated due to unsatisfactory results. In a phase II trial (SWOG S1313) of modified FOLFIRINOX (mFOLFIRINOX) plus PEGPH20 compared with mFOLFIRINOX monotherapy. Ramanathan *et al*[169] reported an inferior OS when PEGPH20 added to mFOLFIRINOX (7.7 mo [95%CI: 4.6-9.3 mo] *vs* 14.4 mo [95%CI: 10.1-15.7 mo]). Several phase I/II trials of PEGPH20 combined with programmed cell death protein 1 mAbs and other drugs are currently recruiting patients (NCT03634332, NCT03193190). There may soon be new treatment paradigms for this disease based on the randomized phase III trials of PEGPH20.

MMPs

MMPs can disrupt the extracellular matrix and basement membrane, thus contributing to tumor invasion, angiogenesis, and metastasis[170]. Marimastat is an MMP inhibitor demonstrating single-agent activity and safety in PDAC patients[171]. However, when combined with gemcitabine, marimastat did not show any clinical benefit or survival advantage, with mOS of 165.5 d in the combination group compared with 164 d in the gemcitabine monotherapy group and 1-year survival rates of 18% and 17%, respectively[172]. Similarly, tanomastat, an MMP inhibitor, did not show any clinical benefit in PDAC compared with gemcitabine[173]. The study ended after a second interim analysis (median OS of 3.74 mo for tanomastat *vs* 6.59 mo for gemcitabine). Andecaliximab, an mAb targeting MMP9, demonstrated favorable safety and clinical activity in a phase I trial in combination with gemcitabine and nab-

paclitaxel in advanced PDAC patients, with an mPFS of 7.8 mo (90%CI: 6.9-11.0), an objective response rate of 44.4% and a median duration of response of 7.6 mo[174].

Connective tissue growth factor

Connective tissue growth factor (CTGF) is overexpressed in PDAC and is a profibrotic mediator. In a preclinical study, FG-3019, an mAb against CTGF, increased the effectiveness of gemcitabine, resulting in a significant tumor response[175]. A phase II clinical trial for advanced PDAC showed that FG-3019 in combination with gemcitabine and erlotinib was well tolerated, with median PFS and OS of 3.7 and 7.4 mo, respectively[176]. Based on the results of a phase II trial, gemcitabine plus nab-paclitaxel, in combination with FG-3019 or placebo, showed significant improvement in median PFS in the group using FG-3109 (18.4 mo *vs* 10.4 mo) (NCT02210559). In early 2018, FDA granted a fast-track designation to FG-3019 (pamrevlumab) for treating patients with locally advanced, unresectable PDAC. An ongoing phase III, randomized, double-blind trial is enrolling patients with locally advanced, unresectable PDAC to evaluate the efficacy of receiving gemcitabine in combination with pamrevlumab (NCT03941093).

HGF/c-MET pathway

HGF and its receptor c-MET are vital to the onset and progression of pancreatic cancer. HGF, present on pancreatic stellate cells, increases stromal production and interacts with its ligand, c-MET, on pancreatic cancer cells. This process is vital to the proliferation and migration of pancreatic cancer cells[177].

Among c-MET-targeted therapies, the most advanced clinical development is tivantinib, a c-MET inhibitor in phase III development for various malignancies[178]. A randomized phase II study has been conducted to evaluate the efficacy of tivantinib in combination with gemcitabine in patients with unresectable locally advanced or metastatic untreated pancreatic cancer (NCT00558207). Recently, an HGF-neutralizing Ab, YYB101, has been developed with encouraging preclinical results and has been tested in clinical trials in patients with refractory solid tumors[179]. In

addition, NK4, an intramolecular fragment of HGF that targets the HGF/c-MET axis, has demonstrated promising results *in vitro* and *in vivo*[180,181].

Cabozantinib, a small molecule inhibitor targeting c-MET and VEGFR-2, is evaluated in a randomized phase II study in several solid tumors, including metastatic pancreatic cancer (NCT01466036). In addition, anti-MET antibodies (emibetuzumab and onartuzumab) have been successfully used in preclinical models of pancreatic cancer[182,183].

CSCs

CSCs are a unique subset of cells with the potential for self-renewal and differentiation, which can lead to carcinogenesis, progression, metastasis, and drug resistance. Pancreatic CSCs were first described by Li *et al*[184]; they identified a subpopulation of pancreatic cancer cells expressing CD44, CD24, and epithelial surface antigen (ESA) (CD44+ CD24+ ESA+). CSCs with this phenotype form pancreatic tumors when injected into the tail of orthotopic immunocompromised mice[185]. Wnt/β-catenin, Notch, and activation of the Janus kinase/signal transducer and transcription (JAK/STAT) pathways play a central role in developing pancreatic CSCs[186].

Notch pathway

The Notch pathway is an evolutionarily conserved pathway important in mammalian pancreas organogenesis. Upregulation of Notch has been found in PDAC and increases tumorigenesis. Evidence suggests that crosstalk between phytochemicals, microRNAs, and Notch signaling regulates the self-renewal division of CSCs[187]. The intracellular domain of Notch induces proliferative signaling and differentiation by altering gene transcription. The Notch pathway interacts with the Hedgehog, *KRAS*, and NF-κB pathways[93,188,189].

Since Notch signaling is activated by γ-secretase, γ-secretase inhibitors have been developed as therapeutic agents for the treatment of PDAC. A single-arm phase II trial of the γ-secretase inhibitor RO4929097 was discontinued due to intolerable toxic effects. The 6-mo survival rate is 27.8%, the mOS is 4.1 mo, and median PFS is 1.5

mo[190]. A phase I trial of MK-0725 (a γ-secretase inhibitor) and gemcitabine for PDAC patients, achieved 13 stable disease and one partial response of 19 evaluable patients[191]. Tarextumab is a fully human IgG2 Ab targeting Notch2 and Notch3 receptors[192]. The results of a randomized phase II study evaluating tarextumab in combination with gemcitabine and nab-paclitaxel in patients with untreated metastatic PDAC were suboptimal, without improvement in OS, PFS, or ORR[193].

WNT pathway

The WNT pathway is important in cell differentiation and proliferation. In preclinical mouse models, abnormal WNT signaling leads to pancreatic cancer[194].

Vantictumab is an mAb that blocks WNT signaling. Preclinical studies have shown that this Ab reduces cancer stem cell frequency and increases the activity of chemotherapy[195]. The safety and tolerability of vantictumab combined with nab-paclitaxel and gemcitabine are being investigated in a phase Ib dose-escalation study (NCT02005315).

Ipafricept inhibits WNT signaling by acting as a decoy receptor while binding and sequestering WNT ligands. The combination of ipafricept and gemcitabine and nab-paclitaxel was well tolerated in a phase Ib study for patients with untreated stage IV pancreatic cancer, with a median PFS of 5.9 mo and a median OS of 9.7 mo[196].

JAK/STAT pathway

JAK/STAT pathway has been found in pancreatic cancer[197,198]. Abnormalities in the JAK/STAT pathway directly leads to increased cell transformation, cell proliferation, apoptosis, and angiogenesis. Additionally, STAT3 inhibition results in increased sensitivity to chemotherapy (mainly gemcitabine) and delays tumor progression in PDAC patients[199]. PDAC cell death and proliferation increases when STAT3 inhibitors are administered with chemotherapeutic agents. A phase III trial of evaluating STAT3 inhibitors on PDAC when co-administered with standard chemotherapy regimens has been completed (NCT02231723), but results have not yet been uploaded.

Itacitinib, a selective JAK1 inhibitor, combined with nab-paclitaxel and gemcitabine was evaluated in a phase Ib/II study in patients with advanced solid tumors including locally advanced/metastatic pancreatic cancer patients[200]. The combination therapy demonstrated acceptable safety and clinical activity[201]. However, after an interim analysis of the phase III JANUS 1 and 2 trials of ruxolitinib (JAK1/2 inhibitor) in combination with capecitabine showed no additional clinical benefit of ruxolitinib compared to capecitabine (NCT02117479, NCT02119663), the sponsor prematurely terminated this study on itacitinib on February 11, 2016.

Napabucasin is an investigational, oral agent hypothesized to inhibit multiple oncogenic pathways. Several clinical trials have been initiated to evaluate the safety and efficacy of the drug in various gastrointestinal malignancies[202]. Single-arm phase Ib/II study with napabucasin and nab-paclitaxel plus gemcitabine recruited 59 patients with mPDAC. According to published abstracts, the combination regimen was well tolerated. Among the 50 patients evaluated, the disease control rate was 92%, with 2 complete remissions (4%) and 26 partial responses (52%)[203]. Of all 59 patients enrolled, the 1- and 2-year OS rates were 46% and 13%, respectively. These results led to the further investigation of this treatment combination in the ongoing phase III CanStem111P trial (NCT02993731).

Momelotinib is a JAK1/2 inhibitor with additional activity against TANK-binding kinase 1[204]. Momelotinib was safe and well tolerated in a phase I dose-escalation trial of momelotinib combined with gemcitabine and nab-paclitaxel in patients with previously untreated metastatic PDAC (NCT02101021). However, there was no OS or PFS benefit *vs* gemcitabine plus nab-paclitaxel in the context of suboptimal engagement of the target. This study does not support momelotinib as a first-line treatment for pancreatic cancer[205].

CSC may be an important target for treatment, but there is still a question of whether targeting them is the best way to counteract their ability to progress, expand and resist treatment in the host environment[206]. Future studies should focus on clonal evolution, especially on monitoring CSC during cancer progression and after treatment.

AUTOPHAGY

An autophagy process primarily involves degrading damaged organelles or proteins[207] and enables cells to recycle cellular contents as an internal fuel source during cellular recycling. This process is necessary for pancreatic cancer cells to overcome nutritional deficiencies.

Hydroxychloroquine (HCQ) was one of the first autophagy inhibitors to enter clinical trials. However, HCQ alone did not show significant antitumor effects[208]. According to a randomized phase II study, gemcitabine/nab-paclitaxel with or without HCQ did not improve OS (11.1 mo *vs* 12.1 mo; *P* = 0.44) or PFS (5.7 mo *vs* 6.4 mo; *P* = 0.25)[209]. In a randomized phase II trial, there was a significant improvement in Evans Grade histopathology and carbohydrate antigen 19-9 response after adding HCQ in the preoperative setting. OS and DFS were not different between groups in this study, nor were AEs or R0 resections[210].

In a recent study, *KRAS* inhibition and ERK inhibition increased autophagic flux in PDAC[211]. Thus, autophagy inhibitors synergistically act with ERK inhibitors in inhibiting PDAC driven by *KRAS* mutations[211]. A synergistic antiproliferative effect was observed when autophagy inhibition was combined with MEK1/2 inhibition in PDAC cells as well as patient-derived xenograft models[212]. According to these studies, inhibiting autophagy genetically or pharmacologically may enhance the antitumor effects of other antitumor drugs such as ERK inhibitors and MEK inhibitors in PDAC. Several promising studies have evaluated the combination of autophagy inhibitors and MEK (NCT04132505, NCT03825289) or ERK inhibitors (NCT04386057) in patients with locally advanced or metastatic cancer[213-215].

OTHER TARGETS

Adenosine has been identified as an essential regulator of tumor proliferation, survival, and migration. Inhibition of adenosine receptors has been shown to modulate immune responses within the tumor microenvironment, thereby enhancing antitumor effects[216]. Several clinical trials evaluate the safety and efficacy of adenosine A2 receptor antagonists in combination with immunotherapy or cytotoxic

therapy in patients with advanced solid tumors including PDAC, Ciforadenant (NCT03454451), and NIR178 (NCT03207867).

Accumulating clinical evidence suggests that overexpression of urokinase-type plasminogen activator (uPA) or its cell surface receptor is closely associated with worse clinicopathological features and poor prognosis in PDAC patients[217]. RHB-107, the only known agent targeting the uPA pathway, was effective in a phase II clinical trial in patients with locally advanced unresectable pancreatic cancer (NCT00499265). RHB-107, combined with gemcitabine, significantly improved 1-year survival by 17% in patients with unresectable PC. In 2017, RHB-107 received an Orphan Drug Designation from the FDA for PDAC adjuvant therapy.

CONCLUSION

Despite the advances in the last 20 years, pancreatic cancer remains a devastating malignancy with limited options for effective treatment. As mentioned above, the self-preserving CSCs, dense tumor microenvironment, and suppressive and relatively depleted immune niche of PDAC are considered significant clinical barriers to successful therapy development, making it one of the most challenging diseases to target.

Targeting individual molecules is not a good approach. In the currently known studies on the mechanisms of ineffectiveness or resistance of targeted therapies, it is suggested that inhibition of one pathway may lead to activation or compensatory upregulation of others, *e.g.*, inhibition of the PI3K/Akt/mTOR pathway may lead to tumor escape *via* the MAPK pathway. This suggests to us that, in fact, most clinical trials have also demonstrated that monotherapy of targeted drugs is not feasible. Therefore, combining targeted inhibitors of multiple pathways may be the future targeted therapy research's primary direction. At the same time, in addition to considering drug efficacy, we must consider that a multidrug combination implies a superposition of AEs and toxicity.

Based on the characteristics of pancreatic cancer - dense fibrous stroma, accounting for 90% of the tumor volume, and excessive proliferation of fibrous histochemistry, drugs are not easy to reach the tumor interior. Investigating targeted or cytotoxic

drugs that are more accessible to the tumor, or using more efficient delivery methods, such as local arterial delivery, may improve efficacy.[7]

Most of the studies conducted to date have been designed based on gemcitabine activity. Given that gemcitabine is no longer the reference drug, future studies should focus on targeted therapy with either nab-paclitaxel or FOLFIRINOX as the control group, which may improve the results achieved. Furthermore, most studies showed[7] promising results in preclinical evaluations, but the vast majority failed to proceed to more advanced clinical studies due to the lack of positive results. This suggests that better preclinical models should be developed to accurately reflect the tumor characteristics and environment in humans, thereby making clinical trials more relevant to preclinical studies.

PDAC is a very complex entity, joining different molecular particularities and in a dynamic manner, not in a static one. As some guidelines already stated and can be concluded from de data shown here, is very important to spread the genetic and transcriptomic profiling of every PDAC to capture the vulnerabilities of the tumor as far as possible as the way to improve therapeutic results. In conclusion, developing the targeted drug for pancreatic cancer has a long way to go. The complex interactions within targeted biological pathways, the pharmacokinetics of targeted drugs, predictive markers of the targeted drug benefit, and the combined application of targeted drugs still require extensive and in-depth studies.

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Figure Legends

Figure 1 Overview of targeted therapy strategies for pancreatic adenocarcinoma. The figure summarizes the systemic therapeutic targets and corresponding drugs for pancreatic cancer, including treatment strategies for many aspects such as signaling pathways and gene mutations in tumor cells, and molecules in the extracellular environment, and extracellular matrix. " — |"indicates "targeting"; Akt: Akt serine/threonine kinase; BTK: Bruton's tyrosine kinase; CDK4/6: Cyclin-dependent kinase 4/6; CSC: Cancer stem cell; CTGF: Connective tissue growth factor; DC: Dendritic cell; EGFR: Epidermal growth factor receptor; ERK: Extracellular-regulated protein kinase; HGF: Hepatocyte growth factor; IGF-1R: Insulin-like growth factor receptor; JAK: Activation of the Janus kinase; *KRAS*: Kirsten rat sarcoma oncogene; MEK: Mitogen-activated protein kinase; MMP: Matrix metalloproteinase; mTOR: Mammalian target of rapamycin; Notch: Notch receptor; PARP: Poly (ADP-ribose) polymerase; NRG1: Neuregulin 1; NTRK: Neurotrophic receptor tyrosine kinase; PEGPH20: Pegylated recombinant human hyaluronidase PH20; PI3K: Phosphatidylinositol 3-kinase; PSC: Pancreatic stellate cell; RAF: Rapid accelerated fibrosarcoma; SMAD4: Mothers against decapentaplegic homolog 4; SHH: Sonic hedgehog pathway; SMO: Smoothened; STAT: Signal transducer and transcription; TGF-β: Transforming growth factor-β; VEGFR: Vascular endothelial growth factor receptor.

Table 1 Molecular targets for pancreatic cancer treatment

Target	Frequency of mutation/expression, %
KRAS	95
VEGF	93
Sonic hedgehog	70
Notch3	69-74
TP53	70
NF-kB	70
IGF-1R	64
CDKN2A	60
EGFR	43-69
Akt/mTOR	40
SMAD	40
BRCA1/2	1-3
NRG1 fusion	0.5

NTRK fusion	0.3

Akt: Akt serine/threonine kinase; *BRCA1/2*: Breast cancer susceptibility gene 1/2; *CDKN2A*: Cyclin-dependent kinase inhibitor 2A; EGFR: Epidermal growth factor receptor; *KRAS*: Kirsten rat sarcoma oncogene; IGF-1R: Insulin-like growth factor receptor; mTOR: mammalian target of rapamycin NF-κB: Nuclear factor kappa B; Notch3: Notch receptor 3; NRG1: Neuregulin 1; NTRK: Neurotrophic receptor tyrosine kinase; SMAD: Mothers against decapentaplegic homolog; *TP53*: Tumor suppressor 53; VEGF: Vascular endothelial growth factor.

Table 2 Clinical trials evaluating the impact of chemotherapeutic agents against specific targets

Target	Study treatment		Phase	Population	No. of patients	mPFS	mOS	Ref.
EGFR	GEM + Erlotinib		III	Locally advanced or metastatic	285	3.75	6.24	Moore *et al*[10], 2007
	GEM + Placebo			PDAC	284	3.55	5.91	
EGFR	GEM + Nimotuzumab		IIb	Locally advanced or metastatic PC	96	5.1	8.6	Schultheis *et al*[50], 2017
	GEM + Placebo				96	3.4	6	
EGFR	GEM + Nimotuzumab		III	K-Ras wild-type, locally advanced	46	4.2	10.9	Qin *et al*[51], 2022)
	GEM + Placebo			or metastatic PC	46	3.6	8.5	
ERB2	GEM + Afatinib		II	Metastatic PC	79	3.9	7.3	Haas *et al*[57], 2021
	GEM + Placebo				40	3.9	7.4	
VEGF	GEM + axitinib		II	Advanced PC	69	4.2	6.9	Spano *et al*[67], 2008
	GEM				34	3.7	5.6	
VEGF	GEM + axitinib		III	Advanced PDAC	314	4.4	8.5	Kindler *et al*[68], 2011
	GEM + Placebo				316	4.4	8.3	
VEGF	GEM + aflibercept		III	Metastatic PC	271	3.7	6.5	Rougier *et al*[69], 2013
	GEM + Placebo				275	5.1	7.8	

PARP	Veliparib	II	BRCA-mutated PDAC	16	3.1	1.7	Lowery et al[101], 2018
PARP	Olaparib Placebo	III	gBRCA1 or BRCA 2 mutation and metastatic PC	92 62	7.4 3.8	18.9 18.1	Golan et al[103], 2019
PARP	Cisplatin and GEM + Veliparib Cisplatin and GEM	II	Untreated gBRCA/PALB2+ PDAC with measurable stage III to IV PDAC	27 23	10.1 9.7	15.5 16.4	Sohal et al[40], 2020
RET	GEM + Vandetanib GEM + Placebo	II	Locally advanced or metastatic PC	72 70	NA	8.83 8.95	Middleton et al[107], 2017
Hedgehog	GEM + Vismodegib GEM + Placebo	II	Metastatic PC	53 53	4 2.5	6.9 6.1	Catenacci et al[160], 2015
Hyaluronic acid	mFOLFIRINOX + PEGPH20 mFOLFIRINOX	II	Metastatic PDAC	55 59	4.3 6.2	7.7 14.4	Ramanathan et al[169], 2019
MMP	GEM + Marimastat GEM + Placebo	NA	Advanced PC	120 119	NA	5.51 5.47	Bramhall et al[172], 2002
MMPs	Tanomastat GEM	III	Advanced or Metastatic PDAC	138 139	1.68 3.5	3.74 6.59	Moore et al[173], 2003
NOTCH	RO4929097	II	Previously treated metastatic PDAC	18	1.5	4.1	De Jesus-Acosta et al[190], 2014

NOTCH	GEM + Tarextumab	II	Untreated metastatic PC	89	3.7	6.4	Hu et al[193], 2019
	GEM + Placebo			88	5.5	7.9	
Wnt	GEM and nab-paclitaxel + Ipafricept	Ib	Untreated stage IV PC	26	5.9	9.7	Dotan et al[196], 2020
Autophagy	GEM and nab-paclitaxel + Hydroxychloroquine	II	Advanced PC	55	5.7	11.1	Karasic et al[209], 2019
	GEM and nab-paclitaxel			57	6.4	12.1	

EGFR: Epidermal growth factor receptor; ERBB2: Erb-B2 receptor tyrosine kinase 2; GEM: Gemcitabine; mFOLFIRINOX: Modified fluorouracil plus leucovorin, oxaliplatin and irinotecan; MMPs: Matrix metalloproteinases; mOS: Median overall survival; mPFS: Median progression-free survival; NOTCH: Notch receptor; PARP: Poly (ADP-ribose) polymerase; PC: Pancreatic cancer; PDAC: Pancreatic adenocarcinoma; RET: Ret proto-oncogene; VEGF: Vascular endothelial growth factor.

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