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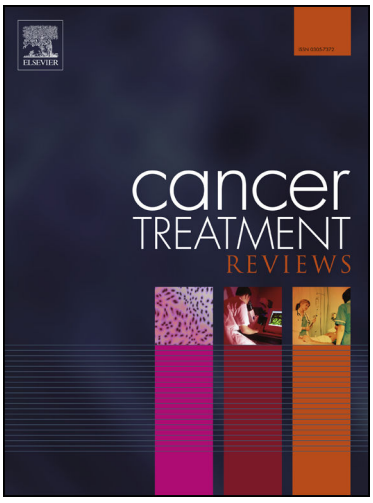

Tumour Review

New therapeutic targets in pancreatic cancer

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Title: New therapeutic targets in pancreatic cancer

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Highlights

- Pancreatic cancer has disappointing response to cytotoxic drugs and poor prognosis
- To date, no targetable driver genes have been recognized for pancreatic cancer therapy
- The genomic characterization should be the base for clinical trials development
- In clinical trials, drug combination strategy seems the most interesting approach

ABSTRACT

Pancreatic ductal adenocarcinoma(PDAC) is associated with poor survival. Of all newly diagnosed patients, only about 20% can benefit from a potentially curative surgical resection, the remaining 80% presenting with unresectable locally advanced(LAPC) or metastatic(MPC) disease. Currently, there are limited therapeutic options for LAPC and MPC patients. Furthermore, despite intensive research efforts to better understand the molecular bases of PDAC and the biological relevance of its tumor microenvironment, treatments still largely consist of classical cytotoxic chemotherapy agents.

Several studies of genetic and epigenetic sequencing have demonstrated the existence of 4 molecular PDAC subtypes, with heterogeneous genetic characteristics and different biological behaviour: squamous, pancreatic progenitor, immunogenic and aberrantly differentiated endocrine exocrine (ADEX). These distinct subtypes derive from alterations at multiple levels. Apart from the DNA repair pathway, however, none of these has so far been validated as a clinically relevant therapeutic target.

Also, PDCA is unique from an immunological perspective and many studies have recently tried to elucidate the role of intratumoral effector T-cells, RAS oncogene, immunosuppressive leukocytes and desmoplastic reaction in maintaining the immunological homeostasis of this disease. However, there still remains much to be learned about the mechanisms whereby the pancreatic immune microenvironment promotes immune escape of cancer cells. Furthermore, while therapies targeting the stroma as well as immunotherapies hold promise for the future, these are not yet standard of care.

This review aims to outline the state-of-the-art of LAPC and MPC treatment, highlighting data on the target therapies failure and current ongoing clinical trials on new promising therapeutic strategies.

Keywords: pancreatic cancer, targeted therapy, molecular subtypes

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INTRODUCTION

Pancreatic adenocarcinoma (PDAC) is the most common type of pancreatic cancer (PC) [1-3]. PDAC incidence is rising; it is expected to become the second cause of cancer-related death by 2030 and has a very poor prognosis[4]. More than 80% of patients have an advanced disease at diagnosis, and the 5-year overall survival rate is approximately 7% [5]. Poor survival is attributed to high aggressiveness, intrinsic chemotherapeutics resistance and lack of effectively targetable oncogenic drivers. Systemic chemotherapy is the mainstay of locally advanced (LAPC) and metastatic (MPC) patients treatment and single-agent gemcitabine had been the standard for more than two decades until first-line FOLFIRINOX and *nab*-paclitaxel/gemcitabine demonstrated better efficacy[6-9]. Targeted therapies play a limited role in PDAC management[10,11]. Therefore, new therapeutic approaches with meaningful impact on patients survival are urgently needed.

Recently, substantial progress was made in the understanding of PDAC genetic background and molecular biology. Up to 4 molecular subgroups have been identified, each with distinct molecular signatures and potential specific therapeutic targets[12]. These valuable research efforts, however, have not yet been matched either by the successful development of novel agents or by the identification of predictive biomarkers that could increase the effectiveness of existing therapies. As a result, PDAC remains refractory to most currently available treatments[13]. Furthermore, the peculiar tumour microenvironment with the excessive desmoplastic stroma represents an important biological barrier for drug delivery and activity[11,13]. In this regard, however, targeting components of the tumour stroma that contribute to desmoplasia emerged as a potentially valid therapeutic approach[14].

This article aims to review the complex and heterogeneous molecular characteristics of PDAC and to discuss novel promising molecular targets and therapeutic agents.

MOLECULAR SUBTYPES OF PANCREATIC CANCER

Several studies of genetic/epigenetic sequencing revealed significant molecular heterogeneity among PDAC. *Collison et al.* considered three molecular subtypes: classical, quasi-mesenchimal, endocrine-like; then, *Moffit et al.* identified four different molecular entities: classical, basal-like, normal stromal and activated stromal [12,15]. Recently, *Bailey et al.* suggested the existence of four molecular subtypes with different biological features and prognostic relevance: squamous, pancreatic progenitor, immunogenic and aberrantly differentiated endocrine exocrine (ADEX) (the last two as subclasses of the pancreatic progenitor subtype)[16]. This classification was based on the differential expression of crucial transcription factors and downstream targets in lineage differentiation during pancreatic development. Recently, the Cancer Genome Atlas Research Network performed an integrated genomic, transcriptomic and proteomic characterization of PDAC that identified two main subtypes: basal like/squamous and classical/pancreatic progenitor[17].

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The Squamous subtype is characterized by alterations of gene networks involved in inflammation, hypoxia response, metabolic reprogramming, TGF-ß signaling, MYC pathway activation, autophagy, TP53 and KDM6A mutations, up-regulated expression of TP63 transcription factor (ΔNp63) and its target genes. ΔNp63 expression is sufficient to induce and sustain the transcriptional signature of the squamous lineage in human PDAC[18]; in addition, RNA-seq identified high expression of TP63 and its target genes as key features in adenosquamous pancreatic tumours. Furthermore, hypermethylation and down-regulation of genes involved in the pancreatic endodermal development can also lead to the loss of endodermal identity. Squamous subtype is considered an independent poor prognostic factor.

The Pancreatic progenitor subtype is characterised by high levels of a pivotal transcriptional network for pancreatic endodermal determination and it seems to be triggered by errors in the cells guiding pancreatic development. PDX1 is one of the main transcriptional regulators in the formation of all pancreatic cell types and it appears to play an oncogenic role; moreover, oncogenic KRAS expression in the pancreatic parenchyma leads to neoplasm with increased expression of PDX1[19].

ADEX is characterized by up-regulation of transcriptional networks involved in later stages of pancreatic development which define the differentiation of exocrine and endocrine lineages. These networks include transcription factors such as NR5A2, MIST1 and RBPJL and genes associated with endocrine differentiation and MODY. NR5A2 might play a role in the acquisition of the cancer stem cell phenotype and in the PC epithelial-to-mesenchymal transition (EMT), this possibly contributing to the worse clinical outcome[20].

The Immunogenic class is characterised by significant immune infiltrate, largely composed of B and T cells (including both $CD8^+$ and regulatory T cells) and up-regulation of PD-1 and CTLA-4 signaling. These data suggest a potential role for immune modulator agents in this specific class. A further sub-classification based on the specific composition of the immune infiltrate might have a prognostic value, but studies are needed to confirm this hypothesis[16].

Both squamous and immunogenic subtype are defined especially by the tumour microenvironment rather than the tumour cells. This aspect confirms the crucial role of microenvironment in PDAC.

POTENTIAL TARGETS IN PANCREATIC CANCER

PDAC is a genetically and biologically heterogeneous tumour. Recently, emerging evidences demonstrated that a number of cancer genes and signalling pathways are critically involved in the processes of PDAC tumourigenesis and progression and, as such, they may be potentially useful therapeutic targets[21].

Molecular pathways

a. Transmembrane Receptor Proteins and downstream signaling cascade

In the last decades, much of the efforts to characterise the key oncogenic signalling pathways of PDAC focused on growth factors and growth factor receptors analysis. The receptor tyrosine kinases (RTKs)

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activate many pathways, including Ras/MAPK, PI3K/AKT, PLCγ/PKC, and JAK/STATs.

Activating mutations of KRAS are seen in over 90% of PDAC.

The phosphoinositide 3 kinase/AKT/ mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway is frequently activated in PDAC. This pathway is crucial in many cancer-associated activities and its activation is associated with poor prognosis[22]. Increased AKT activity has been identified in ~60% of PDAC samples, with amplification of the *AKT2* oncogene occurring in 10%–20% of cases[23].

Numerous RKTs play an important role in PC, including the epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), insulin-like growth factor receptor (IGFR), tropomyosin receptor kinase (TRK),vascular endothelial growth factor receptor (VEGFR) and PDGFR.

EGFR: EGFR overexpression is detected in up to 90% of PDAC and plays an important role in PDAC recurrence and liver metastasis development. Clinical data suggested that EGFR up-regulation might be associated with a more aggressive tumour behaviour and higher rates of disease recurrence after surgery[24].

FGF/FGFR: The fibroblast growth factor (FGF)/FGFR pathway plays a key role in PDAC development and progression. FGFR1 and FGFR2 are overexpressed in PDAC and they are associated with advanced tumour stage and shorter survival. FGF and FGFR increased levels are associated with up-regulation of *inducible* Nitric Oxide Synthase (iNOS) and tyrosine protein nitration in tumour tissues, confirming the oxidative stress involvement in FGF pathway-mediated PDAC development[21].

IGF/IGFR: In PDAC, high expression of Insulin-like Growth Factor-1 (IGF-1) and IGF1R are associated with high tumour grade and poor survival[24]. The co-expression of IGF1R and EGFR is significantly associated with poor survival in PDAC. Furthermore, IGF-1 is abundant in PDAC patients serum, where it binds to insulin-like growth factor binding proteins (IGFBPs). Recent studies highlighted that high IGF-1/low IGFBP-3 concentrations might be associated with increased PDAC risk, advanced PDAC and poor outcome.

TRK: TRK gene fusions lead to constitutive, ligand-independent downstream pathways activation, tumour cells promotion, proliferation and survival. These alterations, as well as ROS1 fusions, are rare in pancreatic cancer; however, the real incidence is unknown since routine testing is not standard practice. A study on 47 resected PDAC samples revealed a 66% increased TRK receptor expression compared with normal adjacent tissue. Another work demonstrated a correlation between TrkB expression and increased rates of perineural invasion, positive margin and development of metastasis in resected PDAC [25,26].

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)/VEGFR: Angiogenesis is a crucial event in tumour development and progression. VEGF is an angiogenic polypeptide that promotes endothelial cell proliferation and survival by binding to VEGFR-1 and VEGFR-2. Increased expression of VEGF mRNA was reported in PDAC samples this correlating with high micro-vessel density and disease progression[24].

b. Other pathways

WNT/β-CATENIN: The Wnt/beta-catenin pathway is involved in many cellular functions such as stem cell regeneration and organogenesis. Wnt pathway aberrant activation has been documented in up to 65% of

PDAC. A recent study showed that Wnt signaling enrichment resulted in increased PDAC development and aggressiveness[27,28].

NOTCH: Evidence suggest that Notch plays important oncogenic roles in pancreatic tumourigenesis. Recently, the Notch signaling pathway has been found to directly up-regulate Snail-1 and Slug, thereby inducing epithelial-to-mesenchymal transition (EMT).

ROUNDABOUT (ROBO) RECEPTORS/ SLIT GLYCOPROTEIN LIGANDS (SLIT): ROBO/SLIT have been linked to cell adhesion, proliferation and survival. Mutated SLIT–ROBO genes are described in approximately one-third of PDAC patients and are frequently silenced by methylation[29,30].

TRANSFORMING GROWTH FACTOR BETA (TGF-β): TGF-β acts as tumour suppressor gene in non-malignant clones, but it can promote angiogenesis and EMT in cancer cells and it is indeed one of the most important EMT-inducing factors[27]. TGF-β signaling regulates the transcription of target genes through a cascade of events involving SMAD2, 3 and 4 [24].

HEDGEHOG (Hh): The Hh signaling pathway has a critical role in embryonic development and maintenance of adult tissues. Its dysregulation has been highly implicated in tumourigenesis and its overexpression has been found in 70% of PDAC[31], where it promotes tumour growth and metastasis[32]. Interestingly, overexpression of sonic Hh (sHh) ligand is absent in the healthy pancreas but increases dramatically from PanIN stages to invasive adenocarcinoma[31]. Furthermore, several reports demonstrated that Hh pathway activation induces stem cell markers and is involved in EMT enhancement[33].

NEUREGULIN-1 (NRG1): NRG1 is a ligand that interacts with ERBB3 and ERBB4 RTK, stimulating the downstream signaling pathways. In PDAC, NRG1 fusion acts as an oncogenic driver, leading to greater expression of the NRG1 EGF-like domain and promoting the affinity with ERBB2/ERBB3 receptor complexes. Recent data showed the efficacy of ERBB inhibition therapy (e.g afatinib and erlotinib) in NRG1-rearranged PDAC [34].

Tumour-Suppressor Genes

Tumour-suppressor genes encode for proteins which generally restrain cell proliferation. Loss of tumour-suppressor function, via mutation or chromosome rearrangement, leads to deregulated cell growth. Tumour suppressor genes which are commonly mutated in sporadic PDAC and can represent useful therapeutic targets include Ink4A, p53 and SMAD4.

TP53:TP53 gene is mutated in 50–75% of PDAC. Mutations of TP53 arise in later-stage PanINs. Lack of p53 activity results in increased rates of genomic aberrations, contributing to PDAC heterogeneity and chemotherapy resistance.

SMAD4 (DPC4): Mutations of SMAD4, a key signal transducer of TGF-β, are seen in approximately 50% of PDAC[24]. SMAD4 loss occurs late in the process of PanIN progression to carcinoma and influences tumour-stroma interactions[1]. Available data about SMAD4 and its role as a biomarker in PDAC are discordant. Some studies showed improved overall survival (OS) after surgery in patients with SMAD4

expression, while loss of SMAD4 was described as a marker of a more aggressive phenotype with higher potential for metastatic disease progression. Conversely, other studies reported an inverse relation between SMAD4 expression and survival outcomes[27].

DNA Repair Factors

Particularly interesting in terms of potential therapeutic implications are BRCA and mismatch repair (MMR) gene mutation.

BRCA: Germline mutations of BRCA1 or BRCA2 cause a deficiency in DNA damage repair (DDR). DDR mutations lead to chromosomal instability and tumourigenesis through lack of repair or mis-repair of DNA damage [35]. A number of studies have shown that PDAC is the third most common cancer associated with these mutations after breast and ovarian cancers[36]. The lifetime-risk for PDAC in BRCA2 mutation carriers is estimated to be 3.5–10 times higher than that in the general population. In BRCA1 mutation carriers this risk appears to be lower (about 3.1 times higher than in the general population)[37].

MMR DEFICIENCY: The MMR system plays a pivotal role in the repair of DNA sequence mismatches during replication. Defects in the MMR system (dMMR) causes errors in DNA replication, leading to high burden of mutations especially involving microsatellites (short tandem repeats that are prone to DNA replication errors) and the resulting MSI phenotype. The prevalence of dMMR/MSI in PDAC has been reported to range from 1 to 2 % and it has been associated with better survival rates[38].

EMT

EMT is a multistage trans-differentiation process which allows highly polarized epithelial cells to undergo multiple biochemical changes to attain a mesenchymal phenotype. During EMT, epithelial cells lose their epithelial markers (E-cadherin, occludin, claudin, and laminin-1) and gain mesenchymal markers (N-cadherin, vimentin, and fibronectin). EMT is classified into three major types; type 3 EMT occurs in carcinoma cells and is considered to be an important event at different stages (dissemination, invasion, intravasation and extravasation) of the metastasis process.

Extracellular Matrix (ECM)

The PC microenvironment plays an important role in terms of tumour growth, invasion, and chemotherapy resistance. It is characterized by dense and firm desmoplasia and extensive immunosuppression[31]. In PDAC, only 10%-20% of the tumour volume is represented by the epithelial/tumour cell component, whereas the remaining volume is constituted by stromal cells, including cancer-associated fibroblasts (CAF), immune cells, endothelial cells, and abundant ECM[27,39].

In particular, CAFs can promote tumour progression and metastatic diffusion by facilitating tumour cell migration and invasion. There are at least two functional CAF entities: the myofibroblasts, characterized by enhanced ECM production and α-smooth muscle actin (αSMA) expression, and the secretory CAFs,

involved in the activation of NF-κB and STAT1 transcription factors. Myofibroblasts contributes to tumour stiffness, hypoxia and avascularization, whereas tumours with prevalence of secretory CAFs are more aggressive, immunosuppressive and chemotherapy-resistant, due to increased proliferation, vascularization, recruitment of MDSCs, stemness induction [40,41].

Furthermore, hyaluronic acid (HA), the major component of normal ECM, is significantly increased in several solid malignancies and has been implicated in tumour progression, treatment resistance, and poor prognosis. HA polymers bind to and trap water molecules, influencing tissue architecture, malleability, and ECM integrity[42]. Tumour stiffness is enhanced and interstitial fluid pressure increases. These factors enhance resistance to treatment[39].

Cancer Stem Cells

Cancer stem cells (CSCs), a minor subpopulation of tumour cells, are crucial in tumour initiation, progression and therapeutic resistance. Pancreatic CSCs present cell surface markers including CD24, CD44, CD133, ESA, c-Met, CXCR4 and ALDH1 [43] and share a lot of characteristics with normal stem cells like self-renewal capacity and quiescence. Many pathways (Wnt/β-catenin, sHh and Notch) are known to regulate stem cell self-renewal. CSCs non-dividing G0-state protects them from the cytotoxic potential of chemotherapeutic drugs and represent the biological basis of late tumour relapse following treatment. The mechanisms by which CSCs become drug resistant are largely unknown. It is very likely, however, that drug resistance is mediated by ATP Binding Cassette (ABC) drug transporters, quiescence, detoxifying enzymes, DNA repair ability and anti-apoptotic proteins overexpression[24]. Also, CSCs have an advantage in evading immune detection and elimination. Accumulating evidence indicates that CSCs express low levels of T-cell activation co-stimulatory molecules and high levels of T-cell inhibitory molecules including PD-L1[43]. Moreover, CSCs exhibit metastasis ability, even if the exact relationship between CSCs and metastasis is not clear yet. This might be secondary to the close association between CSCs and cancer cell EMT as suggested by the presence of common signaling pathways, such as Wnt/β-catenin and Notch axis.

CLINICAL TRIALS AND FUTURE PERSPECTIVES

Several trials have been conducted and many others are on going to investigate the role of various innovative drugs in PDAC either as monotherapy or in combination with chemotherapy (FIGURE 1, TABLES 1,2).

Transmembrane receptor proteins and downstream signaling cascade inhibitors

a. Mitogen/extracellular signal-related kinase **(MEK) inhibitors (MEKi)**

Trametinib is an orally bioavailable, allosteric, reversible and selective inhibitor of MEK1/2. It inhibits MEK-dependent ERK phosphorylation and MEK1/2 activation by preventing Raf phosphorylation of MEK on S217. A randomized, double blind, phase II trial evaluated first-line gemcitabine plus trametinib versus (vs) gemcitabine plus placebo in 160 MPC patients. No significant difference in OS (8,4 vs 6,7 months) and

progression free survival (PFS) (16,1 vs 15,1 weeks) was observed between the treatment arms[44].

A phase II study conducted by *Bodoky G et al*. investigated the efficacy and safety of selumetinib, an oral, potent, allosteric, highly selective ATP-uncompetitive MEK1/2 inhibitor, vs capecitabine in LAPC and MPC patients who failed first-line gemcitabine therapy, without demonstrating significant OS and PFS differences[45].

Another phase II trial enrolled 24 MPC first-line therapy progressed patients to receive trametinib and GSK2256098, an oral focal adhesion kinase (FAK) inhibitor. Treatment was well tolerated but no significant efficacy was demonstrated[46].

The potential synergistic role of MEKi and cycline-dependent kinase4/6 inhibitors (CDK4/6i) was investigated[47]. An ongoing phase I/II study will evaluate the role of ribociclib plus trametinib in LAPC or MPC (NCT02703571).

IGFR Inhibitors

Ganitumab is an anti-IGF1R monoclonal antibody (mAb) preventing the binding of IGF-1 and IGF-2 to their receptors. In a randomized, phase 2 trial with gemcitabine plus ganitumab vs gemcitabine plus conatumumab vs gemcitabine plus placebo, 125 MPC patients were enrolled and 40 were treated with first-line ganitumab plus gemcitabine. Treatment was well tolerated and showed numerical improvement in OS (HR:0.67;p=0.12) and PFS (HR:0.65;p=0.072) compared to gemcitabine plus placebo[48,49].

The GAMMA Trial, a double-blind, phase 3, randomized study, assessed the efficacy and safety of first-line ganitumab plus gemcitabine. This 3-arm study (gemcitabine+placebo vs gemcitabine+ganitumab 12 mg/kg vs gemcitabine+ganitumab 20 mg/kg) was discontinued prematurely after the results of a pre-planned futility analysis. Median OS (mOS) was 7.2 months in the placebo arm, 7.0 months in the low-dose ganitumab arm and 7.1 months in the high-dose ganitumab arm; similarly, no differences were observed in median PFS (mPFS) (3.7 months, 3.6 months and 3.7 months)[50,51].

The CARRIE trial was a randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy of first-line nab-paclitaxel/gemcitabine in combination with istiratumab (a mAb targeting IGF-1R and ErbB3) compared to nab-paclitaxel/gemcitabine plus placebo in MPC patients with high free serum IGF-1 levels. 88 patients were enrolled; the study failed to show mOS or mPFS improvement in favour of the investigational arm (mOS:8.9 months, mPFS:3.6 months) as compared to the control arm (mOS:11.7 months, mPFS:7.3 months). Similar results were reported for the group of patients with high free IGF-1 serum levels and Heregulin-positive tumours[52].

b. mTOR inhibitors (mTORi)

A phase II study evaluated the efficacy of single-agent everolimus in patients with gemcitabine-refractory MPC. Although well-tolerated, everolimus showed only minimal clinical activity[53].

A Hellenic Cooperative Oncology Group phase I/II study investigated the combination of gemcitabine with temsirolimus in LAPC and MPC patients; this association resulted feasible with manageable side effects but

it didn't show any significant clinical efficacy[54] .

c. TRK inhibitors

Encouraging results were obtained in trials exploring TRK inhibitors. In 2018, a study grouped 55 patients previously enrolled in a protocol with larotrectinib: a phase I study involving adults, a phase I/II study involving children and a phase 2 study in adolescents and adults. These patients had several types of solid tumors with TRK fusion positive molecular profile (only 1 patient had PC). The overall response rate (ORR) was 75% (95%CI:61-85) according to the independent review and 80% (95%CI:67-90) according to investigator assessment. The only PC patient achieved a partial response (PR). Median duration of response and PFS were not reached [25].

Two phase I studies evaluated the safety and efficacy of entrectinib, a TRKA/B/C, ROS proto-oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK) tyrosine kinases inhibitor, in patients with different solid tumours, including PC. Entrectinib was well tolerated; in 3 NTRK1/2/3-rearranged solid tumours, ORR was 100% (CI95%:44-100); in 7 ALK-rearranged solid tumours, ORR was 57% (CI95%:25-84) and in 14 ROS1-rearranged, ORR was 86% (CI95%:60-96). mOS and mPFS were not reached [55].

Other pathways inhibitors

a. NOTCH inhibitors

Various agents targeting the NOTCH pathway were investigated in PDAC: demcizumab, an anti-DLL4 antibody; tarextumab, a Notch2/3 receptors inhibitor; RO4929097 and MK-0752, two gamma secretase inhibitors.

The YOSEMITE trial was a double blind, three-arm, randomized, phase 2 study where MPC patients were randomly allocated to first-line therapy with gemcitabine and nab-paclitaxel plus either placebo or demcizumab according to two different schedules. Demcizumab was well tolerated but it didn't provide significant differences in mPFS and mOS[56-58].

The role of tarextumab in combination with first-line gemcitabine plus nab-paclitaxel was evaluated in a randomized, placebo-controlled, phase II study that recruited 177 patients. The addition of tarextumab to nab-paclitaxel and gemcitabine didn't improve OS. In addition, a potential negative effect on PFS and ORR was shown in the subgroup of patients with Notch-3 expression <25%ile[59].

A Phase II Study of RO4929097, a potent and selective inhibitor of γ-secretase enzyme, preventing the proteolytic cleavage required to activate Notch, was conducted in previously treated MPC. Eighteen patients were recruited but enrollment was stopped after discontinuation of further development of RO4929097 by the Sponsor. Three (25%) of 12 evaluable patients achieved stable disease (SD). The 6-month survival rate was 27.8% (95%CI:9.7–53.5) with a mOS of 4.1 months (95%CI:2.7–5.8 months) and a mPFS of 1.5 months (95%CI:1.3–1.6 months)[60].

A phase I multicenter study enrolled 44 MPC patients who received gemcitabine and MK-0752 as first- or second-line treatment. One patient achieved a confirmed PR and 13 patients had SD [61].

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b. TGF-β inhibitors

A phase Ib/II multinational trial in LAPC and MPC patients who were candidates for first-line gemcitabine chemotherapy investigated the efficacy of galunisertib, the first orally bioavailable small-molecule inhibitor of the type I TGF-β receptor (ALK5) serine/threonine kinase that specifically downregulates the phosphorylation of SMAD2, blocking the activation of the TGF-β pathway. Patients were randomised in a 2:1 ratio to receive gemcitabine plus galunisertib or placebo. The primary endpoint was met, with mOS of 8.9 months in the galunisertib arm and 7.1 months in the placebo arm (HR=0.79; 95%CI:0.59–1.09; posterior probability HR<1=0.93) [62].

Further exploration of TGF-β inhibitors in PC is ongoing in a phase I study evaluating galunisertib in combination with the anti- PD-L1 durvalumab(NCT02734160).

c. Hn inhibitors

A multicenter phase Ib study evaluated in naïve LAPC and MPC the combination of FOLFIRINOX with IPI-926, a potent and specific inhibitor of Smoothened (Smo) transmembrane protein, whose inhibition leads to repression of Hh pathway malignant activation, resulting in decreased desmoplasia and improved chemotherapy delivery to PC. ORR was 67% and patients receiving IPI-926 maintenance showed further declines in CA19-9 levels even after FOLFIRINOX discontinuation. Unfortunately, the study closed prematurely after a separate phase II trial of IPI-926 plus gemcitabine indicated a detrimental effect of this combination[63,64].

Another Hn inhibitor, vismodegib, was studied in combination with gemcitabine in a randomised, placebo-controlled, phase Ib/II trial but combination therapy didn't show any improvement in OS, PFS and ORR over standard treatment[65].

d. CDK4/6i

Several preclinical studies demonstrated anti-tumor activity of CDK4/6i [66-68]. In particular, in PDAC models palbociclib lead to ECM disruption, tumour cell apoptosis and quiescence, inihibion of metastatic spread and tumour progression[69]. The role of CDK4/6i is currently under evaluation in phase I, II and III studies.

DNA repair factors inhibitors: Poly ADP ribose polymerase inhibitors (PARPi)

Preliminar evidence of disease control with olaparib was provided by the results of a multi-tumour type phase 2 study which included 23 BRCA1-2 mutant PDAC patients[70].

Recently, the results of the international, randomized, double-blind, placebo-controlled phase III POLO trial of olaparib maintenance after≥16 weeks of first-line platinum-based chemotherapy were published. MPC patients harbouring germline BRCA mutations were randomized 3:2 to maintenance olaparib (90 patients) or placebo (61 patients). mPFS (primary endpoint) was improved with olaparib (7.4 months vs 3.8 months with

placebo, HR=0.53,p=0.004), irrespective of the response to induction chemotherapy; safety was consistent with its known adverse event profile[71].

The RUCAPANC trial investigated the efficacy and safety of rucaparib in refractory, BRCA1/2-mutant LAPC and MPC. Four out of 19 patients enrolled achieved a response; two PR and one CR were confirmed (ORR=15.8%). The disease control rate (CR, PR, or SD for≥12 weeks) was 31.6% in all patients and 44.4% in those who had received one prior chemotherapy regimen. However, despite an acceptable safety profile, enrolment was stopped as prespecified in the protocol because of an insufficient ORR among the first 15 patients[72].

An ongoing phase 2 study (NCT03140670) is evaluating the role of rucaparib maintenance in BRCA1-2 or PALB2 mutated PDAC after platinum-based treatment.

A multicentre single-arm phase II trial evaluated the ORR of veliparib in patients with previously treated BRCA1/2- or PALB2-mutant PDAC. No confirmed ORR were seen: one (6%) unconfirmed PR was observed at 4 months with disease progression (PD) at 6 months; four patients (25%) had SD, 11 (69%) had PD. mPFS was 1.7 months (95%CI:1.57-1.83) and mOS was 3.1 months (95%CI:1.9-4.1) [73].

Pishvaian et al. conducted a phase I/II trial of veliparib plus FOLFOX6 in MPC. The phase II part of the study included a treatment-naïve and a refractory patient cohort and recruitment was limited to patients with pathogenic germline or somatic DDR mutation (*BRCA1/2, PALB2, ATM*), and/or a family history suggestive of a breast or ovarian cancer syndrome (FH+). Veliparib plus FOLFOX resulted safe and well tolerated; the primary endpoint of ORR≥25% was reached and platinum-naïve, FH+ and DDR mutation positive patients had an ORR of 58%[74].

Veliparib was also evaluated in combination with FOLFIRI vs FOLFIRI alone for second-line treatment in a randomized phase II trial. While the trial didn't have a biomarker-driven recruitment strategy, nearly 30% of patients had DDR gene abnormalities, including 9% with homologous recombination deficiency (HRD). Veliparib increased toxicity but didn't improve OS[75].

A phase 2 study of veliparib plus or minus gemcitabine and cisplatin vs gemcitabine and cisplatin alone in LAPC and MPC is ongoing(NCT01585805).

Immunotherapy

In contrast to other solid tumours, immunotherapy has not shown brilliant results in PDAC so far. This is possibly due to the immune suppressive tumour microenvironment (with stromal infiltration of myeloid-derived suppressor cells, and tumour-associated macrophages) and overall low mutational load[76-77]. In clinical trials, neither ipilimumab nor nivolumab showed objective response[78,79]. However, pembrolizumab was associated with interesting ORR in MSI-H PDAC patients[80].

Anti-CTLA4 inhibitors and anti-PD-1 inhibitors are currently being investigated in combination with standard gemcitabine chemotherapy in clinical trials[81-84].

Interesting results are rising from the combination with vaccines, as in the case of GVAX, whole-cell vaccine composed of irradiated and allogeneic PC cells genetically engineered to secrete granulocyte-

macrophage colony-stimulating factor, which stimulates dendritic cell activation and T-cell priming [85-87]. 2,3-dioxygenase (IDO) up-regulation is one mechanism of resistance to immunotherapy since it inhibits T-cells response. An IDO inhibitor, indoximod, showed a 37% ORR at the interim analyses of a phase 2 trial in combination with gemcitabine and nab-paclitaxel[88].

A phase Ib trial was conducted in borderline-resectable and LAPC patients to assess the efficacy of the CCR2 inhibitor, PF-04136309, with FOLFIRINOX; an ORR of 49% was reported[89].

A phase 2 clinical trial evaluating the efficacy of PF-04136309 in combination with gemcitabine and nab-paclitaxel in MPC patients is in progress(NCT02732938).

ECM

Ibrutinib, a Bruton's tyrosine kinase inhibitor, showed inhibition of mast cells and tumour progression in a mouse model of b-cell tumourigenesis. Moreover, it was proven to be highly effective in limiting PDAC growth in transgenic mice and patient-derived xenograft disease models[90,91]. Unfortunately, the RESOLVE trial, a randomized, double-blind, placebo-controlled study of ibrutinib with nab-paclitaxel and gemcitabine in the first-line treatment of patients with MPDAC showed no improvement in OS or PFS in the intent-to-treat population[92].

The pegylated recombinant human hyaluronidase (PEGPH20) was first investigated in naïve PDAC patients in the phase 2 HALO 202 trial. PEGPH20 in combination with gemcitabine and nab-paclitaxel improved PFS only in patients with high HA expression[93]. Further to the results of subgroup analyses, recruitment into the ongoing phase 3 trial has been limited to patients with HA-high tumours *(NCT02715804)*.

PEGPH20 efficacy was investigated also in the SWOG S1313 trial, a phase Ib/II study of modified FOLFIRINOX plus PEGPH20 vs FOLFIRINOX alone in MPC patients, but the addition of PEGPH20 to FOLFIRINOX was detrimental (mOS: 14.4 months in the standard arm vs 7.7 months in the combination arm)[94].

Pamrevlumab, a mAb targeting the connective tissue growth factor, showed encouraging preclinical results[95,96]. Therefore, a phase 2 randomized study of gemcitabine and nab-paclitaxel +/- pamrevlumab in treatment-naïve LAPC patients was designed to evaluate resection rates and OS. Among patients who completed 6 cycles of treatment, 78% in the investigational arm and 17% in the control arm were resectable, while 44% and 17%, respectively, underwent resection[97]. An international phase 3, randomized, double-blind trial to evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab plus gemcitabine plus nab-paclitaxel versus placebo plus gemcitabine plus nab-paclitaxel for unresectable LAPC is ongoing (NCT03941093).

CSCs inhibitors

Preclinical evidence showed that napabucasin, an anti-STAT3, sensitizes cancer cells to chemotherapy drugs, including nab-paclitaxel and gemcitabine. 37 MPC patients were enrolled in a phase Ib study of napabucasin + gemcitabine and nab-paclitaxel. Out of 29 evaluable patients, 27 (93%) achieved disease control, while 23

(79.3%) had tumour regression. PR was reported in 10 (34.5%) patients[98]. Based on these results, a phase III study has been launched (CanStem111P test) where patients are randomized to receive standard gemcitabine plus nab-paclitaxel or the same treatment plus napabucasin[99].

Conclusion

Despite the recent increased number of treatment options, PC still shows modest response to conventional cytotoxic drugs and a dismal prognosis. This is partly due to the unique characteristics of the tumour microenvironment which is poorly immunogenic and largely composed of a highly desmoplastic stroma. Also, activation of oncogenic signalling pathways and frequent EMT dysregulation likely contribute to PDAC biological aggressiveness. While sophisticated studies allowed dissecting the genomic complexity of PC and the functional relevance of the surrounding stroma, no driver tumour genes or stromal elements have yet been validated as useful therapeutic targets. With the only exception of olaparib for BRCA mutant patients, the mainstay of treatment for advanced PDAC remains cytotoxic chemotherapy with targeted therapies and immune modulatory strategies yielding disappointing results so far.

PDAC is projected to become the second leading cause of cancer-related death by 2030. This alarming projection should prompt researchers to pursue further analysis of the mechanistic bases of treatment response/resistance and investigation of potentially game-changing treatment options. The available genomic data should be the base for development of biomarker-driven clinical trials. In the Era of precision medicine the optimal therapeutic management should be guided by high-sensitive and high-specific available biomarkers, able to define the biomolecular cancer cell profile. One of the major hurdles is that the PDAC biomolecular profile is spatial and temporal heterogeneous. In this regard, large studies are needed to validate new biomarkers for clinical application, investigating the most appropriate procedure to identify and to follow the dynamic biomarker-state.

Finally, combination treatment strategies including chemotherapy, targeted therapy, immunotherapy and stromal targeting drugs represent the most promising line of research.

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FIGURES

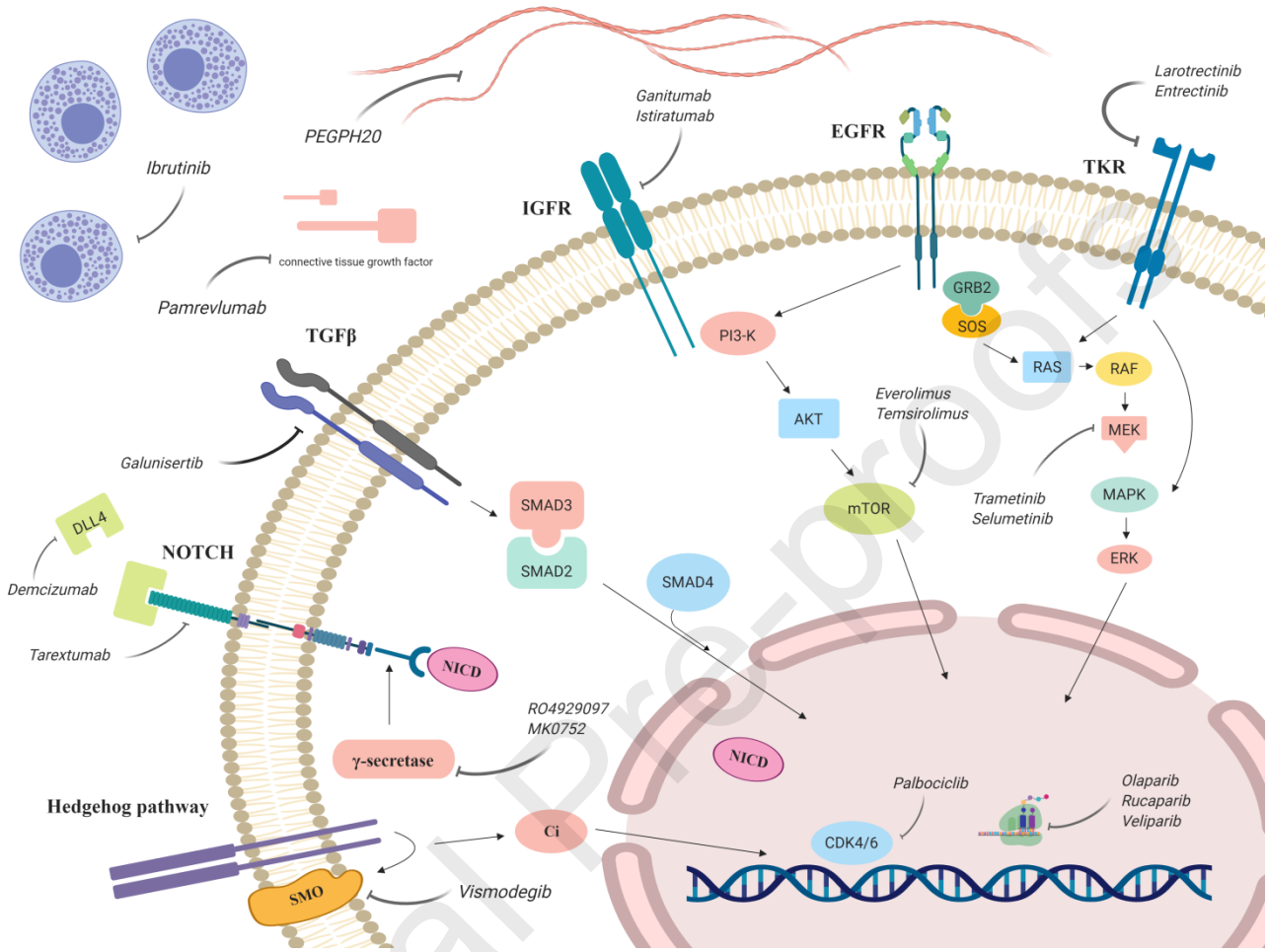

FIGURE 1. Potential targets and drugs for pancreatic cancer treatment

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TABLES

MECHANISM OF ACTION	DRUG ASSESSED	PHASE OF STUDY	TREATMENT ARMS	TREATMENT LINE	REFERENCES
MEK1/2 inhibitors	1. trametinib	II	gemcitabine + trametinib vs gemcitabine + placebo	I line	[44]
		II	Trametinib + GSK2256098	II line	[46]
	2. selumetinib	II	Capecitabine vs selumetinib	LA and MPC after gemcitabine based treatment	[45]
IGFR1- inhibitors	1. ganitumab	III	gemcitabine + placebo vs gemcitabine + ganitumab 12 mg/kg vs gemcitabine + ganitumab 20 mg/kg	I line	[50]
		II	gemcitabine + ganitumab vs gemcitabine + conatumumab vs gemcitabine + placebo	I line	[48]
	2. istiratumab	II	Gemcitabine + Nab-paclitaxel + istiratumab vs Gemcitabine + Nab-paclitaxel + placebo	First line	[52]
mTOR inhibitors	1. everolimus	II	everolimus	Second line	[53]
	2. temsirolimus	I-II	temsirolimus + gemcitabine	LAPC, first line	[54]
TRK inhibitors	1. larotrectinib	I/II-II	larotrectinib	Locally advanced or metastatic tumours after standard treatment	[25]
	2. entrectinib	I	entrectinib	All lines for advanced tumours	[55]
NOTCH inhibitors	1. demcizumab (anti-DLL4 antibody)	II	Gemcitabine + Nab-paclitaxel + placebo vs Gemcitabine + Nab-paclitaxel + demcizumab (single 70 day truncated course of demcizumab) vs Gemcitabine + Nab-paclitaxel + demcizumab (two 70 day truncated course of demcizumab)	First line	[58]
	2. tarextumab (Notch2/3 receptors inhibitor)	II	Gemcitabine + Nab-paclitaxel+ tarextumab vs Gemcitabine + Nab-paclitaxel + placebo	First line	[59]
	3. RO4929097 (γ-secretase inhibitor)	II	RO4929097	After first line	[60]

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	4. MK-0752 (γ-secretase inhibitor)	I	MK-0752	First and second line	[61]
TGF-β inhibitors	Galunisertib	Ib-II	Galunisertib + gemcitabine vs gemcitabine + placebo	First line	[62]
Hedgehog inhibitors	1. IPI-926	II	IPI-926 + gemcitabine	First line	[64]
		Ib	IPI-926 + FOLFIRINOX	LAPC and first line	[63]
	2. Vismodegib	Ib-II	Gemcitabine + vismodegib vs gemcitabine + placebo	First line	[65]
Poly ADP ribose polymerase inhibitors	1. Olaparib	III	olaparib vs placebo	Maintenance after first line	[71]
		II	Olaparib	Previous gemcitabine treatment	[70]
	2. rucaparib	II	Rucaparib	LAPC and MPC after 1-2 chemotherapy regimens	[72]
	3. veliparib	II	Veliparib	Second-third line	[73]
		II	Veliparib+ mFOLFIRI vs Mfolfiri	Second line	[75]
		I-II	Veliparib + FOLFOX	All lines	[74]
Immunotherapy	1. Ipilimumab (anti-CTLA4)	II	Ipilimumab	All lines	[78]
		Ib	Gemcitabine + ipilimumab	First and further lines (previous gemcitabine for first line prohibited)	[82]
		Ib	ipilimumab vs ipilimumab + GVAX	After first line (previous gemcitabine-based treatment mandatory)	[87]
	2. Tremelimumab (anti-CTLA4)	I	Gemcitabine + tremelimumab	First line	[81]
	3. Nivolumab (anti-PD1)	I	Nivolumab	All lines	[79]
	4. Pembrolizumab (anti-PD1)	II	Pembrolizumab	After first line	[80]

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	5. GVAX (vaccine)	II	GVAX → 5FU based CHT + RT	Adjuvant	[85]
	6. Indoximod (anti-IDO)	II	Indoximod + gemcitabine + nab-paclitaxel	First line	[88]
	7. PF-04136309 (anti-CCR2)	Ib	PF-04136309 + FOLFIRINOX	Borderline resectable and LAPC	[89]
ECM inhibitors	1. Ibrutinib (Bruton's tyrosine kinase inhibitor)	II	Ibrutinib + gemcitabine + nabpaclitaxel	First line	[92]
	2. PEGPH20 (pegylated recombinant human hyaluronidase)	II	PEGPH20 + nab-paclitaxel + gemcitabine vs nab-paclitaxel + gemcitabine	First line	[93]
		Ib-II	PEGPH20 + FOLFIRINOX vs FOLFIRINOX	First line	[94]
	3. Pamrevlumab (anti-connective tissue growth factor)	II	Gemcitabine + nab-paclitaxel + pamrevlumab vs gemcitabine + nab-paclitaxel	LAPC	[97]
Cancer Stem Cells inhibitors	napabucasin	Ib	Napabucasin + gemcitabine + nab-paclitaxel	All lines for advanced disease	[98]

TABLE 1. SELECTED PANCREATIC CANCER CLINICAL TRIALS

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MECHANISM OF ACTION	DRUGS	PHASE	SETTING	TRIAL IDENTIFICATION NUMBER
Mek1/2 inhibitor + CDK4/6 inhibitor	trametinib + ribociclib	I-II	LAPC and MPC	NCT02703571
TGF-β inhibitor + anti-PD-L1	galunisertib + durvalumab	I	Second and third line	NCT02734160
PARP-inhibitors	1. rucaparib	II	Maintenance in BRCA1-2or PALB2 mutated MPC after platinum-based therapy	NCT03140670
	2. gemcitabine and cisplatin with or without veliparib or veliparib alone	II	LAPC and MPC	NCT01585805
Anti-CCR2	PF-04136309 + gemcitabine + nabpaclitaxel vs gemcitabine + nabpaclitaxel + placebo	II	First line MPC	NCT02732938
ECM inhibitors	1. PEGPH20 + gemcitabine + nab-paclitaxel vs gemcitabine + nab-paclitaxel + placebo	III	First line MPC	NCT02715804
	2. Pamrevlumab + gemcitabine + nab-paclitaxel vs placebo + gemcitabine + nab-paclitaxel	III	LAPC	NCT03941093
Cancer stem cells inhibitor	Napabucasin + gemcitabine + nab-paclitaxel vs gemcitabine + nab-paclitaxel	III	First line MPC	NCT02993731

TABLE 2. Selected ONGOING CLINICAL TRIALS

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