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REVIEW



# Novel therapeutic strategies in pancreatic cancer: moving beyond cytotoxic chemotherapy

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**ABSTRACT**

**Introduction:** Prognosis of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) remains disappointing with a 5-year overall survival of only 3–5%. Compared to other cancers, the evolution in standard therapeutic options has been stagnant and polychemotherapy regimens (with well-known toxicity profile and resistance pattern) remain standard of care. Only for patients (5%-7%) with a breast cancer gene (BRCA) pathogenic germline variant, prognosis has improved by the use of olaparib (poly-ADP ribose polymerase (PARP) inhibitor).

**Areas covered:** This review covers emerging treatment strategies in the management of mPDAC. One of the main topics is the rigid and immunological cold tumor microenvironment (TME) of PDAC and the search for agents that impact this TME and/or engage the immune system. In addition, the use of next-generation sequencing (NGS) has elicited for some patients new targeted therapies directed at alterations in the RTK/RAS/MAPK pathway and the deoxyribonucleic acid (DNA) damage repair pathway. Other evolving treatment strategies are also discussed.

**Expert opinion:** The search for new, often combination, treatment strategies for mPDAC should be encouraged and implemented in early treatment lines given the significant decline of performance status of patients in later lines. NGS analysis should be used where available, although cost-effectiveness could be debatable.

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Metastatic pancreatic cancer; chemotherapy; immunotherapy; KRAS; targeted therapy

## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest cancers. Based on GLOBOCAN 2020 estimates, PDAC has ranked the 14th most common cancer in the world counting 495,773 new cases and causing 466,003 deaths (4.7% of all deaths caused by cancer) in 2020. Rates are four- to fivefold higher in high-income countries and there is a slightly higher prevalence in men (51–55% of cases) [1]. Unfortunately, it accounts for almost as many deaths (466,000) as cases (496,000) because of its poor prognosis and is the seventh leading cause of cancer-related death in both sexes, expecting to become the second leading cause by 2030 [2]. Combined 5-year overall survival (OS) is only 5–10%. Diagnosis is often made at an advanced stage due to vague symptoms in early disease, nonspecific diagnostic tests, and the lack of an established screening program. Subsequently, only 15–20% of PDAC are potentially resectable at diagnosis and these patients still have a recurrence rate of 85%, resulting in a 5-year OS of 20–30% after surgery [3]. Despite many efforts over the past years, progress in the standard of care treatment for locally advanced or metastatic PDAC (mPDAC), which still consists of polychemotherapy regimens, has been limited. Chemotherapy mostly consists of FOLFIRINOX (fluorouracil + folinic acid + irinotecan + oxaliplatin), Gemcitabine ± nab-paclitaxel, FOLFOX (fluorouracil + folinic acid + oxaliplatin), or nal-IRI +5FU (liposomal irinotecan + fluorouracil) [4–6]. Even with these established regimens, prognosis remains poor with median OS of approximately 12 months in mPDAC. Given the considerable toxicity of current regimens, further efforts to improve survival will not come from intensifying cytotoxic chemotherapy but through the addition of agents that synergize with existing therapies to achieve better anticancer effect. One of the potential reasons for the poor response to chemotherapeutic agents is the prominent desmoplastic tumor micro-environment (TME) of PDAC hindering the tumor intake of therapeutics. Potential beneficial strategies are aimed at agents that impact this desmoplastic TME. Furthermore, immunotherapy-based regimens have not yet proven to be of benefit in PDAC, attributed to immunological cold features due to a low tumor mutational burden, abundance of immunosuppressive cells as well as the desmoplastic TME. Agents that engage the immune system are therefore warranted. Altogether, to overcome these known resistance mechanisms, combination strategies with chemotherapeutic and immunotherapy agents are being explored [7–9].

Notwithstanding these efforts, there is still an unmet need for new treatments and predictive and prognostic biomarkers that can identify patients who are most likely to benefit from novel therapies or combinations. Despite the histological homogeneity of PDACs there is a complex genomic heterogeneity that precludes a one-size-fits-all treatment approach and more tailored medicine is therefore warranted. Comprehensive targeted genomic profiling has proven to be beneficial in guiding new targeted

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**Article highlights**

- Metastatic pancreatic ductal adenocarcinoma (PDAC) is known for its infaust prognosis. Standard of care chemotherapy regimens only reach a median OS of 12 months and come with significant toxicity.
- The desmoplastic tumor micro-environment (TME) of PDAC is known to hinder effectiveness of chemotherapy and is the focus new strategies. Examples are transforming growth factor-beta (TGFβ)-blockade and focal adhesion kinase inhibition (FAKi).
- Immunotherapy-based regimens have not yet proven to be beneficial in PDAC, attributed to immunological cold features as well as the desmoplastic TME. Combination strategies to engage the immune system such as therapeutic cancer vaccines and CD40 agonists are being explored.
- For a small group of patients with pathogenic germline BRCA1/2 mutation, the PARP inhibitor (PARPi) olaparib has been approved as maintenance treatment after first-line platinum-based therapy. More data are needed and underway to extend the use of PARPi in patients with non-BRCA mutated DNA damage repair genes.
- In the era of targeted therapy, other non-genetic molecular drivers are being explored.
- KRASG12C inhibitors have shown promising results in different types of solid tumors including PDAC harboring KRAS p.G12C mutation (1-2% of PDAC). Treatments targeting the more prevalent KRASG12 mutations are being explored.
- The minority of patients with KRAS wild-type PDAC may harbor alternative oncogenic drivers (i.e. fusions ALK, BRAF, FGFR2, MET, NRG1, NTRK1, NTRK3, RAF1, and ROS1) with the potential for tailored therapeutic opportunities. Two TRK inhibitors have, for example, received FDA approval for their use in solid tumors (including PDAC) with NTRK gene fusion.
- Other promising strategies currently being explored include autophagy, CDK4/6 inhibitors, and GSK-3β inhibition.

treatments and can detect two main categories of significant genomic targetable alterations: alterations in the RTK/Ras/MAPK signaling and predictive biomarkers for treatment in the deoxyribonucleic acid (DNA) damage repair pathway (for example Breast cancer gene (BRCA)-mutation). However, globally this has not yet become standard of care, in part due to the availability and costs restricting access to genomic and genetic analysis.

In this review, we discuss novel treatment strategies emerging in the management of mPDAC with a focus on non-cytotoxic systemic agents. In Figure 1, an overview of the different areas of interest is displayed.

## 2. Emerging strategies for PDAC

### 2.1. Desmoplastic tumour microenvironment

As mentioned upfront, the TME of PDAC is known to be highly desmoplastic, characterized by an abundance of activated stroma and progressive accumulation of extracellular matrix (ECM) proteins such as hyaluronic acid, altogether contributing to tissue structural rigidity and poor perfusion. These structural aberrations significantly reduce penetration of macromolecules, which hinders the tumor intake of therapeutics [10]. To modify this rigid TME, transforming growth factor-beta (TGFβ)-blockade has been analyzed, given its pleiotropic effects on stroma. TGFβ is produced by various cell types in PDAC such as cancer cells, cancer-associated fibroblasts (CAFs), immune cells, macrophages, and other stromal cells. TGFβ plays a pivotal role in the activation of pancreatic stellate cells (PSC), the most abundant fibroblast precursor in the pancreas and the chief organizers of the desmoplastic reaction, next to other sources of CAFs such as mesothelial cells and mesenchymal stem cells. As the expression of TGFβ increases throughout disease progression, so does the conversion of PSC into myofibroblasts, thus increasing fibrotic response [11,12]. Another feature of TGF-β is that it also contributes to a immunosuppressive TME in PDAC as it helps pancreatic cancer cells evade immune surveillance, leading to accelerated growth and metastasis [13]. NIS793 is an investigational recombinant human anti-TGFβ IgG2 monoclonal antibody (mAb) being evaluated as a single agent and in combination with other cancer therapies in adult patients with advanced malignancies, including mPDAC. The currently recruiting double-blind phase 3 cNIS794B12301 study is comparing NIS793 in combination with gemcitabine/nab-paclitaxel versus placebo with gemcitabine/nab-paclitaxel for first-line treatment of mPDAC. Primary outcome measure will be overall survival. Pamrevlumab, also a TGFβ mAb, is being investigated as neo-adjuvant treatment in combination with gemcitabine/nab-paclitaxel in an ongoing phase 3 trial for participants with locally advanced PDAC (NCT03941093).

Another strategy to tackle the rigid TME of pancreatic cancer, is through focal adhesion kinase inhibition (FAKi), along with standard chemotherapy and/or immunotherapy. Hyperactivated FAK activity has been identified as an important regulator of the fibrotic and immunosuppressive TME in PDAC, correlating with high levels of fibrosis and poor $CD8^+$ cytotoxic T-cell infiltration [14]. Moreover, FAK also plays a role in tumor cell signaling. Pancreas tumor animal models have shown a maximal synergetic effect when combining FAKi with a programmed cell death protein 1 (PD-1) antagonist and chemotherapy [14], supporting the hypothesis that FAKi's reduce stromal fibrosis and stimulate the immune response. A phase 1 study investigating the combination of defactinib, a selective orally active FAKi, with pembrolizumab and gemcitabine in refractory advanced PDAC, this combination appeared to be safe, had promising preliminary efficacy and showed biomarker activity in infiltrative T lymphocytes [15]. Also in the neoadjuvant setting, the sequential combination of chemotherapy, followed by anti-PD-1 and FAKi is being investigated (NCT03727880). This phase II study with primary endpoint being pathologic complete response (pCR) per tumor regression grade scores, will also allow comprehensive analysis of the TME and the implications of FAKi on it.

Combination with hyperthermia and/or radiotherapy are two other approaches to reduce resistance to standard systemic treatments. Raising the temperature of the tumor to approximately 40–44°C (mild hyperthermia) can improve drug delivery and dispersion, enhancing the effect of chemotherapy. The improved blood flow can also enhance radiation effect due to increased production of oxygen radicals. Moreover, hyperthermia inhibits DNA repair, augmenting tumor cell killing [16]. Currently, the first in-human (FIH), safety and preliminary efficacy study of whole-body hyperthermia (WBHT) treatment in advanced solid cancer patients or stage IV (TxNxM1) mPDAC patients is ongoing. 4 patients were treated without major side effects [17]. It is also believed that radiation therapy can alter the composition of the TME, affecting factors such as the tumor's

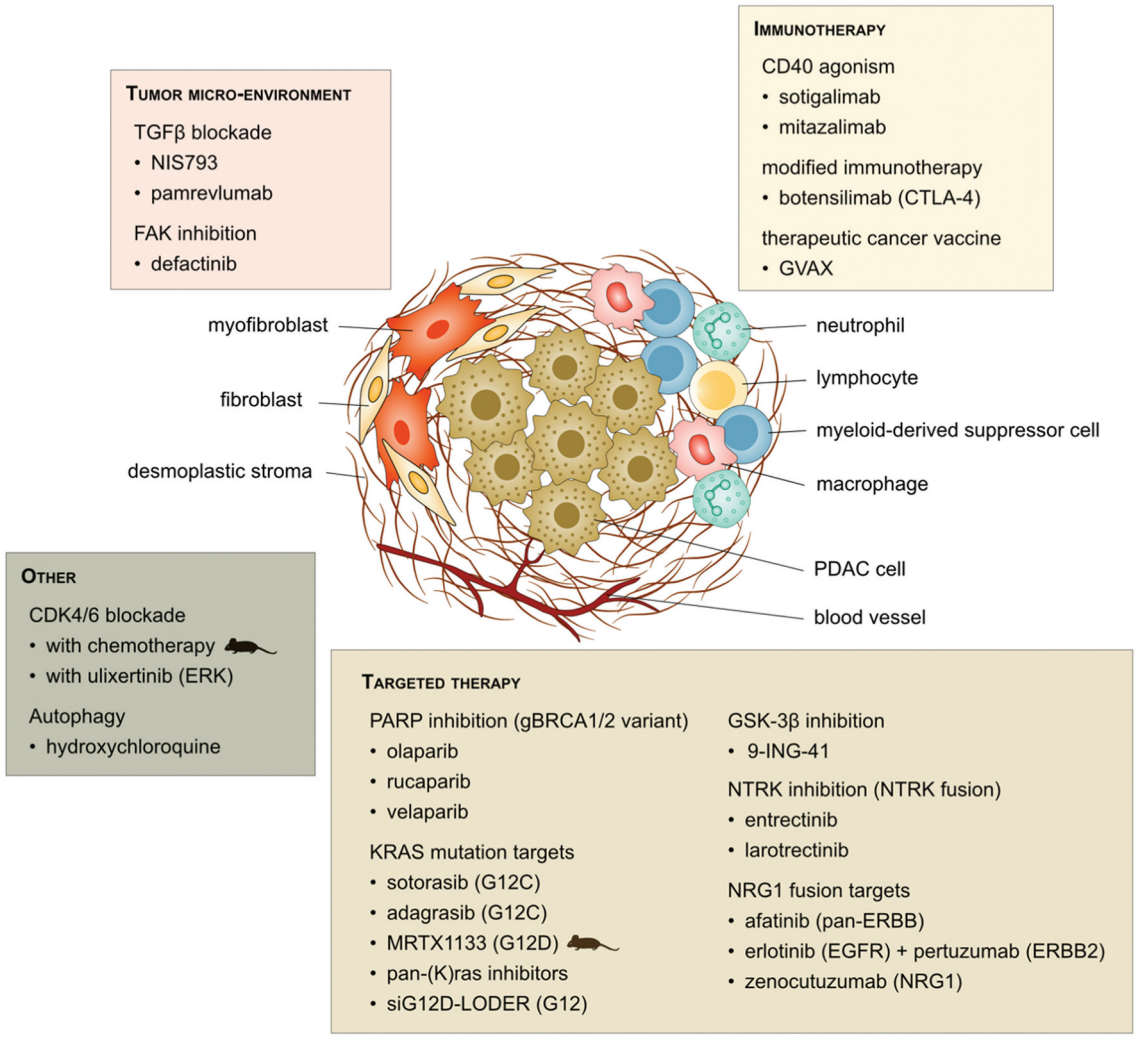


**Figure 1.** Schematic overview of novel therapeutic strategies in pancreatic ca.

Mouse indicates that the therapeutic strategy has only been researched in the preclinical setting. CD40, cluster of differentiation 40; CDK4/6, cyclin-dependent kinases 4 and 6; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; EGFR, Epithelial Growth Factor Receptor; ERBB, erythroblastic oncogene B; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; gBRCA1/2, breast cancer gene 1/2; GSK-3ß, glycogen synthase kinase 3; KRAS, Kirsten rat sarcoma viral oncogene homolog; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase; PARP, poly-ADP ribose polymerase; PDAC, pancreatic ductal adenocarcinoma; TGFß, transforming growth factor beta.

blood supply, immune response and extracellular matrix and therefore improving the response to systemic treatment. Chemoradiation strategies have been investigated in the locally advanced disease however its role remains controversial. In the metastatic setting, clinical data are lacking.

### 2.2. Immunotherapy

Over the recent years, immune checkpoint inhibitors (ICI) have been improving the outcome of patients with different types of cancer, particularly for patients with mismatch repair (MMR) deficiency. The minority (1%) of PDAC patients have MMR deficiency, and hence likely to benefit from ICI [18]. However, up to today, single agents or combined ICI have not proven clinical benefit for unselected (so mainly MMR proficient) PDAC patients. Multiple phase I and phase II trials have investigated the possible effect of single or combination antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1/PD-L1) in unselected PDAC, but no significant responses were reported [19–22].

This may be attributable to pancreatic cancer being classified as immunologically 'cold' compared to other tumors which may be attributed to several factors. Firstly, PDAC has a low tumor mutational burden (TMB) with subsequent low immunogenicity as a low TMB implies less neoantigens and therefore a low number of tumor infiltrating lymphocytes (TILs) [23,24]. Furthermore, lack of ICI response may be due to the TME of PDAC [25] which is characterized by the abundance of immunosuppressive cells, such as tumor-associated macrophages, myeloid-derived suppressor cells and regulatory T cells and along with limited infiltration of $CD8^+$ T cells. Finally, as mentioned above, PDAC has a dense desmoplastic stroma, consisting of high number of cancer-associated fibroblasts (CAFs), matrix metalloproteinases and hyaluronan which can amplify this immunosuppressive TME. In order to overcome these factors, various studies have looked at combining ICI's with each other, with chemotherapy or with local ablative therapies to achieve immunogenic cell death, neoantigen production and optimization of the TME.

#### 2.2.1. Combination strategies with chemotherapy

Chemotherapeutic agents such as nab-paclitaxel have been proven to hinder the immunosuppressive effects of CAFs as well as the desmoplastic stroma in which they reside [26,27]. This has led to a hopeful and previously unexplored treatment strategy combining chemotherapy and ICI as first-line treatment of mPDAC. Despite promising preclinical evidence, the Canadian Cancer Trials Group presented their results of a randomized phase II trial comparing gemcitabine/nab-paclitaxel with and without immune checkpoint inhibitors durvalumab and tremelimumab in 180 patients with mPDAC [9]. The addition of dual immune checkpoint inhibitors to gemcitabine/nab-paclitaxel unfortunately did not result in a significant improvement in OS, progression-free survival (PFS), or overall response rate (ORR) in an unselected population of patients with mPDAC. Only a trend to improved disease control rate (DCR) was seen. Correlative analyses to assess biomarkers that may predict immune sensitivity in this setting are underway.

#### 2.2.2. New strategies targeting the immune response

It seems that for checkpoint inhibitors to become useful in this type of cancer, something else must spark the immune response. CD40 agonists represent a strategy to do so, alongside their potential to augment the response to chemotherapy agents. CD40 is a cell-surface member of the tumor necrosis factor (TNF) receptor superfamily. Upon activation, CD40 can enhance the efficiency of dendritic cells to promote antitumor T cell activation and reeducate macrophages to destroy tumor stroma [28]. Preclinical studies have demonstrated that the combination of an agonistic CD40 monoclonal antibody with chemotherapy triggers T-cell-dependent tumor regressions and improves survival in animal models, which could be further augmented by addition of an anti-PD-1 mAb [7]. It is hypothesized that chemotherapy-induced release of tumor antigens, coupled with antigen-presenting cell activation and T-cell priming via agonistic CD40 mAb, can sensitize PDAC to ICI. Other than inducing a T-cell dependent antitumor immune response, CD40 agonists have also been found to redirect tumor infiltrating macrophages from the immunosuppressive M2 type to the tumoricidal M1 type which results in degradation of fibrosis in the stroma surrounding the tumor leading to enhanced efficacy of the chemotherapeutic agents [29,30].

Results from a phase Ib trial of patients with mPDAC, treated in first line with chemotherapy and a CD40 agonist mAb (sotigalimab) – with or without nivolumab – are promising [8]. In the dose-limiting toxicity-evaluable population ($n$ = 24 patients), the ORR was 54%. As a comparison, in a similar first-line metastatic patient population, the ORR of gemcitabine/nab-paclitaxel, with or without nivolumab, ranges from 18% to 23%. A randomized phase II study of gemcitabine/nab-paclitaxel with or without sotigalimab and with or without nivolumab in first-line mPDAC is under way (NCT03214250).

Mitazalimab is another agonistic, human monoclonal (IgG1) antibody targeting CD40 and is currently being investigated in the OPTIMIZE-1 (NCT04888312) study: a phase 1b/2 study assessing the safety and efficacy of mitazalimab in combination with mFOLFIRINOX in patients with mPDAC.

Simultaneously, newer generations of modified immunotherapy are also being investigated to improve response in cold tumors. For example, botensilimab, a CTLA-4 antibody with modifications in the Fc region, has been designed to have important efficacy and tolerability advantages over first generation immunotherapies. It empowers the immune system by activating existing T cells, priming and expanding new T cells, eliminating immunosuppressive regulatory T cells, and establishing memory cells for durable immunity. Furthermore, botensilimab is specifically engineered to avoid complement binding and complement-mediated toxicities including hypophysitis. In the C-800 study, as presented at ESMO GI 2022, botensilimab demonstrated remarkable activity in combination with balstilimab (PD-1 inhibitor) in microsatellite stable colorectal cancer, with a 24% response rate and 73% DCR in heavily pretreated patients [31]. A randomized, open-label, phase 2 trial of with botensilimab in combination with chemotherapy (gemcitabine/nab-paclitaxel) in pancreatic cancer has been initiated (NCT05630183).

Another promising strategy to enhance antitumor immune activity is the use of therapeutic cancer vaccines, often in combination with cytotoxic drugs. Cancer vaccines such as whole-cell vaccines, dendritic cells vaccines, and peptide vaccines can elicit the presentation of cancer antigens to the immune system with subsequent activation of cancer antigen-specific cytotoxic T lymphocytes (CTLs) in vivo and thereby provoking the anticancer immune response. The review by Schizas et al. [23] provides a complete overview of multiple investigated cancer vaccines in PDAC. However, drawbacks of these studies are the small numbers of patients, the long period of recruitment as well as a high drop-out rate due to tumor progression. Vaccine synthesis also comes with many difficulties and no definite biomarkers of immune response are established yet. One example is GVAX, an irradiated allogeneic whole tumor cell vaccine in which pancreatic cancer cells are engineered to express granulocyte–macrophage colony-stimulating factor (GM-CSF). In the phase II study by Wu et al. [32], GVAX was combined with ipilimumab in the maintenance setting of mPDAC. Unfortunately, this combination therapy did not improve OS compared to continuation of chemotherapy and even resulted in a numerically inferior survival. However, clinical responses and biological effects on immune cells were observed, including T-cell response and formation of tertiary lymphoid structures. Hence, it can be concluded that the quality of the immune response was insufficient to lead to disease control. Therefore, further studies of novel combinations with therapeutic cancer vaccines in the treatment of mPDAC are necessary to further increase immune response.

### 2.3. Targeted therapy

In the era of precision medicine, the increasing use of next generation sequencing (NGS) has led to our increasing knowledge on the genetic alterations and molecular drivers of PDAC, thus identifying potential actionable drug targets. The Know Your Tumour program was a large prospective trial/initiative which assessed pancreatic tumor samples for actionable mutations and hence identifying potential drug targets.

In this study, highly actionable mutations were identified in approximately a quarter of the patients [33].

### 2.3.1. DNA repair pathway

One of the hallmarks of cancer is genomic instability [34]. In certain instances, tumor cell defects in the repair of damaged DNA contribute to genomic instability. Synthetic lethality is a phenomenon whereby a disruption in a single gene (tumor suppressor gene or DNA repair gene) is compatible with cell survival, but the occurrences of several genetic events will result in cell death [35,36]. This concept is exploited by using poly-ADP ribose polymerase (PARP) inhibitors in patients with pathogenic germline BRCA1 or BRCA2 (gBRCA1/2) alterations. Approximately 4–7% of patients with PDAC harbor a pathogenic gBRCA1/2 variant; hence, the role of using a PARP inhibitor (PARPi) in the management of advanced PDAC has been assessed [37–39].

The PARP enzyme family is involved in several cellular pathways. PARP enzymes, PARP 1, PARP2 and PARP 3 play a pivotal role in the DNA damage repair pathway [40]. PARPi's hinder PARP enzymes and hence single strand breaks persist which results in the accumulation of double strand breaks, thus preventing DNA damage repair [41,42]. Normal cells can repair double-strand breaks via the homologous recombination repair pathway. However, malignant cells which harbor genetic alterations that result in homologous-recombination repair defects such as germline and somatic BRCA1/2 mutations, PALB2, ATM, CHEK2, RAD51, or Fanconi-anemia-related gene alterations are unable to repair these double strand breaks, and this leads to cell death. Other mechanisms of PARPi activity such as PARP1 trapping, activation of error-prone non-homologous end joining pathway, and impaired BRCA1 recruitment have been well described [41,43].

Several phase II studies evaluating different PARPi's (olaparib [44], rucaparib [45,46], and veliparib [47]) in patients with mPDAC and a pathogenic germline or somatic BRCA1/2 mutation have been published with variable but promising results (Table 1). Best responses were seen in patients with platinum-sensitive disease. Not all PARPi's appeared to be equally effective, which could be attributed to the ability of olaparib and rucaparib to trap PARP more efficiently. Rucaparib maintenance treatment also demonstrated activity in patients with a pathogenic gPALB variant, raising the possibility of a wider application of PARPi's beyond BRCA-mutated PDAC.

Building on these positive results, the POLO study was the first phase III double blind, placebo controlled randomized trial in which 154 patients with PDAC and a pathogenic gBRCA1/2 mutation were randomized 3:2 to olaparib or placebo as maintenance therapy if at least stable disease was reached after a minimal of 4 months of first-line platinum-based chemotherapy. The study met its primary endpoint PFS; median of 7.4 months in the olaparib arm versus 3.8 months in the placebo arm, hazard ratio 0.53; (95% confidence interval, 0.35 to 0.82; $P = 0.004$) [48]. This landmark trial resulted in the Food and Drug Administration (FDA) approval of olaparib in the maintenance setting for patients with gBRCA mutated mPDAC. However, OS was not statistically significant [49]. It is important to note that this trial has its limitations: the cessation of treatment after only 4 months of treatment is not the current standard of care and instead of using placebo as maintenance, chemotherapy maintenance would have been more appropriate. In summary, there is emerging data to support the use of PARPi in patients with PDAC with pathogenic gBRCA1/2 mutations.

Given that gBRCA1/2 mutations comprise only a small proportion of genes involved in DNA damage repair, the question remains whether these other genes could also benefit from PARPi. Concerning the other somatic (and rarely germline) mutations in DNA damage repair genes, namely ATM, BARD1, BLM, BRCA1, BRCA2, CHEK2, PALB2, RAD50 and RAD51C, it appears that these patients are often treated in the same way as BRCA-mutated patients, i.e. with platinum-based chemotherapy, especially FOLFIRINOX, as stated by the majority of an expert panel gathered by the European Society of Digestive Oncology (ESDO) [50]. Based on data from the Know Your Tumour Program, human recombinant deficiency is potentially predictive for response to platinum-base therapy, but not prognostic [51], but it should be noted that individual groups were small. As stated above, one of the phase 2 trials demonstrated activity of a PARPi (rucaparib) for patients with a pathogenic gPALB2 variant [45]. However, more data are needed to extend the use of PARPi to patients with non-BRCA mutated DNA damage repair genes.

Recently, there is also evidence to support combining PARPi's with other therapeutic agents such as anti-angiogenic agents and ICI. As previously mentioned, immunotherapy for PDAC offers little benefit. It has been suggested by Seeber et al. [52] that BRCA-mutant PDAC may benefit as they found an association between BRCA-mutation and high TMB along with higher PD-L1 expression. Moreover, there is interest in whether the immunogenicity in BRCA mutated patients could be augmented further. Preclinical studies have demonstrated that PARPi's modulate the immune microenvironment by increasing the TMB, genomic instability, and PD-L1 expression and activating the immune inflammatory stimulator of interferon genes (STING) pathway [53,54]. Also, after receiving PARPi treatment, accumulated chromosome rearrangements generate plenty of neoantigens and elevate the immunogenicity of tumor. Consequently, several (pre-)clinical studies in other solid tumors have shown preliminary efficacy with the combination of PARPi plus ICI [55].

Table 1. Overview of phase II studies evaluating different PARPi's in patients with mPDAC and a pathogenic germline or somatic BRCA1/2 mutation.

| PARPi | Year | n | Prior chemotherapy | RR | mPFS (months) | mOS (months) | Reference |
|---|---|---|---|---|---|---|---|
| Olaparib | 2015 | 23 | Gemcitabine | 21.7% | 4.6 | 9.8 | [44] |
| Rucaparib | 2018 | 19 | 1–2 prior regimens | 15.8% | / | / | [46] |
| Veliparib | 2018 | 16 | 1–2 prior regimens | 0% | 1.7 | 3.1 | [47] |

*PARPi= PARP inhibitor; n=number; RR= response rate; mPFS= median progression free survival; mOS= median overall survival.*

Three trials are currently underway to evaluate this further. The phase 1b/2 randomized PARPVAX study is enrolling patients with mPDAC that have not progressed on platinum chemotherapy to receive niraparib with either ipilimumab or nivolumab (NCT03404960). The POLAR trial (NCT04666740), a phase II maintenance trial in platinum-sensitive mPDAC, holds a single arm treatment of pembrolizumab with olaparib. Three different groups of patient populations will be investigated: those with core DNA damage repair gene mutations (g/sBRCA1/2, PALPB2), and those with non-core mutations but interestingly also a group where no mutation was identified but who had complete response or partial response to prior platinum-based therapy. SWOGS2001 (NCT04548752) is another ongoing phase II maintenance trial in platinum-sensitive mPDAC, but with only gBRCA1/2 patients and which is randomized to compare treatment with olaparib alone versus olaparib with pembrolizumab. We are awaiting with much curiosity the results from these trials.

### 2.3.2. Kras

As previously mentioned, genetic alterations but also non-genetic molecular drivers are being explored by use of NGS to identify potential actionable drug targets. The presence or absence of KRAS mutation could guide clinicians in search of a more tailored approach.

**2.3.2.1. KRAS mutation targets.** Activation of the MAPK pathway due to KRAS mutation as the main oncogenic driver (>90%) identified in PDAC with secondary drivers seen in cell cycle regulators such as TP53 (40–47%), SMAD4 (1–50%) and CDKN2A (5–50%) [56–59] is the leading mechanism of oncogenesis in PDAC. G12 (glycine in position 12) KRAS mutations account for more than 80% of cases, of which KRAS G12D is the most frequent one (41% of all KRAS mutations) [60]. KRAS has been an undruggable target for a long time (also in PDAC), but luckily, over the past few years promising developments have been made. As well in PDAC, efforts in targeting KRAS G12C have been made. CodeBreaK100 [61], the Phase I and II, first-in-human, open-label multicenter study investigating sotorasib in 129 patients with advanced solid tumors harboring the KRAS p.G12C mutation, included 12 patients with PDAC. Sotorasib (AMG 510) is a small molecule that specifically and irreversibly inhibits KRAS G12C (through a unique interaction with the P2 pocket) and is currently FDA approved in second-line treatment of KRAS G12C mutated NSCLC. Combined phase I/II data (38 patients) showed an ORR of 21% and DCR 84% with a meaningful PFS benefit of 3.98 months. More recently, the ongoing phase 1–2 KRYSTAL-1 trial (NCT03785249) [62] also reported beneficial outcomes for treatment with adagrasib, another KRAS G12C inhibitor, in non-colorectal cancer advanced gastrointestinal malignancies, including PDAC. Adagrasib contains some different pharmacokinetic (PK) properties compared to sotorasib such as a longer half-life (around 24 hours), extensive tissue distribution, dose-dependent PK, and the ability to penetrate the central nervous system. Until now, 12 patients with KRAS G12C-mutated PDAC (median 3 prior lines of therapy; median follow-up 8.1 months) have been enrolled in KRYSTAL-1, and of the 10 evaluable, 50% showed a partial response and all achieved disease control with adagrasib monotherapy, favoring this targeted approach. The median PFS reached 6.6 months (95% CI 1.0–9.7) and 50% were still receiving treatment at the time of data cutoff. Several promising combination therapy strategies targeting KRAS are currently being investigated in early phase clinical trials to overcome primary and acquired resistance to RAS inhibitors. These include combinations with other RTK-RAS pathway targets (EGFR, MEK, SOS1, SHP2, MTOR), chemotherapy, immunotherapy, and synthetic lethal targets.

However, since KRAS G12C represents only 1–2% of all PDAC, targeting the other more prevalent KRASG12 mutations should be pursued. For example, recent xenograft models demonstrated the potency of the KRASG12D-specific inhibitor MRTX1133 to inhibit KRAS-dependent signaling, modulate the immune tumor micro-environment and induce tumor regression [63]. MRTX1133 exhibited marked tumor regression (≥30%) in a subset of KRASG12D-mutant xenograft models, including eight of 11 (73%) pancreatic ductal adenocarcinoma (PDAC) models. Moreover, co-targeting KRASG12D with possible feedback/bypass pathways, as EGFR or PI3Kα, led to enhanced antitumor activity. Multiple mutant-selective KRAS inhibitors are currently being investigated in preclinical and clinical trials but also pan-(K)RAS inhibitors targeting a broad range of KRAS alterations are being explored [64].

Another RAS-targeting approach is to use RNA interference (RNAi). siG12D-LODER (Local Drug EludeR) is an encapsulated polymeric matrix encompassing a small interfering RNA targeting KRAS G12D and all additional G12X mutations (G12C, G12V…) that gets degraded slowly over 12–16 weeks. The siG12D-LODER is delivered endoscopically directly into the pancreas tumor. A first-in-human phase 1/2a study of patients with locally advanced PDAC who received a one-time dose of siG12D-LODER with ongoing chemotherapy demonstrated that the combination was well-tolerated and safe and exhibited promising potential efficacy with 10/12 patients achieving disease control and a median overall survival of 15.1 months [65]. Currently, a phase 2 study (NCT01188785) of siG12D-LODER with gemcitabine/nab-paclitaxel or FOLFIRINOX in borderline resectable or locally advanced PDAC is investigating this further and will examine the safety of combination with chemotherapy. This study will also analyze KRAS mutation status and monitor circulating free DNA and circulating tumor cells. However, whether RNA interference can also be applied in metastatic disease remains to be investigated.

**2.3.2.2. Glycogen synthase kinase-3 beta (GSK-3β).** Glycogen synthase kinase 3 alpha (GSK-3α) and GSK-3β have been associated with multiple cellular pathways that contribute to normal homeostasis, but also to tumor development, progression, and metastasis. In PDAC, oncogenic KRAS mutations drive overexpression of different downstream effectors, including GSK-3β which promotes tumor growth, survival, and chemoresistance and is correlated with shorter overall survival [66]. Inhibition of GSK-3β activity counteracts these mechanisms by impacting key targets like NF-κB, NFAT, Rb, TAK, GLI1, and TopBP1. As such, novel therapeutic approaches targeting GSK-3β or the signaling cascades that regulate its expression

have become interesting options for treating PDAC. Given the important role of GSK-3β kinases in regulating the response to DNA damage induced by chemotherapy, the combination of GSK-3 inhibitors with chemotherapy is of very interest [67]. In vivo and in vitro studies have also demonstrated an immunomodulatory role of GSK-3β as inhibition of its activity led to reduced levels of PD-1 and enhanced activity of cytotoxic T cells in the immune suppressive TME of PDAC [68], encouraging the combination of GSK-3β inhibitors with immunomodulatory agents as well. Early-stage clinical trials are currently studying small molecule inhibitors targeting GSK-3β beta, and interim results show favorable results. For example, the phase Ib/II 9-ING-41 study (NCT03678883), which is actively recruiting patients. 9-ING-41 is a small molecule potent selective GSK-3β inhibitor that downregulates nuclear factor kappa B (NF-κB) [68]. NF-κB activation is particularly important in cancer cells that have become chemo- and/or radio-resistant [69]. 9-ING-41 has significant in vitro and in vivo activity as a single agent and/or in combination with standard cytotoxic chemotherapies in a spectrum of solid tumors including PDAC and hematological malignancies. In the (currently open) third part of the trial, patients with previously untreated metastatic or locally advanced PDAC are randomized to receive 9-ING-41 with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel alone. More trials exploring the use GSK-3β inhibitors as single agent or in combination strategy are underway.

### 2.3.3. KRAS wild type

Compared to KRAS mutant ($KRAS^{MT}$) PDAC, KRAS wild-type ($KRAS^{WT}$) tumors represent a minority of PDAC (8–12% of all [70,71], up to 16% of patients younger than 50 years [72]) but they may harbor alternative oncogenic drivers with the potential for tailored treatments, making their identification a therapeutic opportunity [73]. Reports showing exceptional response to targeted therapy in PDAC harboring a variety of oncogenic alterations in $KRAS^{WT}$ tumors, encourage this strategy.

In fact, the activation of MAPK pathway is possible also in the absence of KRAS mutations. Singhi et al [71] demonstrated that the MAPK signaling is activated in about one third of KRAS wild-type PDAC. In their study, that investigated real-time targeted genome profile analysis in 3594 PDACs, 12% (445) were $KRAS^{WT}$, which is more than from previous analyses. 38% of those harbored recurrent genomic alterations with the potential to activate the RTK/RAS/MAPK pathway of which BRAF alterations were the most prevalent. Other frequent alternate drivers were found to be kinase fusions genes in FGFR2, RAF, ALK, RET, MET, NTRK1, ERBB4, and FGFR3 representing about 7.6% of genetic alterations of all KRAS wild-type PDAC. All these kinase fusions appeared to be mutually exclusive, and in parallel with BRAF, were not present in PDAC with KRAS alterations.

Fusco and colleagues [70] also characterized the landscape of targetable oncogene fusions detected in $KRAS^{WT}$ PDAC through a retrospective analysis of 100 PDAC at a single institution and validation of the results in two independent cohorts. A small set of fusion-positive cases treated with matched targeted therapy was also reported. After somatic molecular sequencing with NGS, 13/100 (13%) PDAC in their MCC100 cohort appeared $KRAS^{WT}$, of which 31% (4/13) had targetable oncogenic fusions. Of the 87 (87%) $KRAS^{MT}$ PDAC none (0%) had oncogenic fusions. The enrichment for targetable fusions among $KRAS^{WT}$ cases was validated through two independent cohorts (AACR GENIE and TCGA), with reported 19% and 20% fusions incidence. Fusions were identified in ALK, BRAF, FGFR2, MET, NRG1, NTRK1, NTRK3, RAF1, and ROS1 in the setting of $KRAS^{WT}$ PDAC.

The four targetable fusions in the dependent MCC100 cohort were an FGFR2-PAWR rearrangement, a PDZRN3-RAF1 rearrangement, an ATP1B1-NRG1 rearrangement, and a novel RDX-MET fusion that had not previously been reported. Many other case reports enclosing targeted treatment of $KRAS^{WT}$ PDAC with specific kinase fusion genes have been published, and some of these are also summarized in Table 2.

Neurotrophic Tyrosine Receptor Kinase (NTRK) fusions, present in less than 1% of all PDAC, is another group of possible targetable alterations. A single institution Canadian study [79] reviewing whole genome sequencing and Ribonucleic acid (RNA)-sequencing of 400 PDAC reported an overall prevalence of NTRK fusions of 0.8% (3/400), while in KRAS wild-type tumors, it was 6.25% (2/32). Pishvaian et al. [75] reported three cases receiving entrectinib, a TRK/ROS/ALK inhibitor, after discovery of NTRK (in 2) and ROS1 (in 1) fusions. All three patients demonstrated clinical benefit for periods much longer than expected with chemotherapy alone and the two patients with NTRK fusions exhibited clinically meaningful responses to therapy. O'Reilly et al. [76] reported the case of a 61-year-old woman with an NTRK1 gene fusion who experienced partial response on larotrectinib (TRK inhibitor), after two prior chemotherapy lines. Resistance to larotrectinib occurred after 6 months, associated with the emergence of an acquired BRAF mutation as a new oncogenic driver. Moreover, larotrectinib (November 2018) and entrectinib (August 2019) have received FDA approval for their use in patients with solid tumors (including PDAC) that have an NTRK gene fusion without a known acquired resistance mutation and are metastatic or not suitable for surgery, having progressed following treatment or have no satisfactory alternative therapy. This approval was based on clinical trials [80,81] that showed durable and clinically meaningful responses in patients with NTRK fusion-positive solid tumors, with good tolerance and a manageable safety profile. Loxo-TRK-14001 [81] ($n = 70$) included one pancreatic cancer patient who experienced a 30% reduction in tumor size on larotrectinib.

Targeting of neuregulin 1 (NRG1) fusions in $KRAS^{WT}$ PDAC is also being explored more in detail. NRG1 is a ligand of the ERBB3 and ERBB4 receptors and recruitment of EGFR and/or ERBB2 by activated ERBB3/4 leads to stimulation of downstream signaling pathways. As such, NRG1 fusion proteins are oncogenic drivers in multiple solid tumors, including pancreatic cancer. Heining et al. [78] reported clinically relevant, though short, responses with afatinib (pan-ERBB inhibitor) and erlotinib (EGFRi) plus pertuzumab (ERBB2 mAb) in patients with NRG1-rearranged PDAC. The ongoing global phase 2 part of the eNRGy study (NCT02912949) is investigating zenocutuzumab (MCLA-128; Zeno), a bispecific antibody targeting NRG1 fusion signaling, in NRG1 fusion positive (NRG1+) cancers including pancreatic cancers. So far, 10 in 51 patients included have pancreatic cancer and all of them are $KRAS^{WT}$. ORR in this cohort is reported to be 40% (4/10; 90% CI

Table 2. Overview of case reports with targeted treatment of KRAS$^{WT}$ PDAC with specific kinase fusion genes.

| Targetable fusion/rearrangement | Age Gender | Prior treatment | Targeting agent | Response |
|---|---|---|---|---|
| FGFR2-PAWR [70] | 48<br>F | FOLFIRI(NOX) | erdafitinib (FGFRi) | PR after 2 months |
| PDZRN3-RAF1 [70] | 81<br>M | Gem/Nab-P<br>Fluorouracil + leucovorin | trametinib (MEKi) | After 3 weeks<br>– Decrease pancreatic mass<br>– Increase liver/nodal disease |
| RDX-MET [70] | 80<br>M | Resection<br>Adj gemcitabine + capecitabine<br>Gem/Nab-P | crizotinib (c-METi) | Ongoing CR >12 months |
| EML4-ALK [74] | 35<br>M | FOLFIRINOX<br>Gemcitabine/nab-paclitaxel<br>SBRTWhippleGem/Nab-P | ceritinib (ALKi)<br>alectinib | CA 19.9 normalized and PR at 2 months |
| EML4 - ALK [74] | 32<br>F | FOLFIRINOX<br>Gem/Nab-P | crizotinib (ALKi) | SD at 15 months |
| STRN – ALK [74] | 34<br>M | FOLFIRINOX | gemcitabine + crizotinib<br>crizotinib (ALKi) | Radiographic response at 2 months |
| TPR-NTRK1 [75] | 51<br>M | FOLFIRINOX<br>Gemcitabine/cisplatin | entrectinib (TRK/ROS/ALKi) | Clinical benefit<br>PR for 8 months |
| TPR-NTRK1 [75] | 47<br>M | Gem/Nab-P<br>Chemoradiation | entrectinib<br>(TRK/ROS/ALKi) | Clinical benefit |
| SCL4A4-ROS1 [75] | 54<br>M | Gem/Nab-P ± Notch inhibitor<br>FOLFIRINOX<br>TACE | entrectinib<br>(TRK/ROS/ALKi) | SD for 7 months<br>(afterward liver resection) |
| CTRC-NTRK1<br>BRAF-V600E MT [76] | 61<br>F | Gem/Nab-P + ADI-PEG 20<br>FOLFIRINOX | larotrectinib (TRKi)<br>selitrectinib (TRKi)<br>dabrafenib (BRAFi) + trametinib (MEKi) | PR at 2 months<br>PD at 6 months<br>PD at 2 months<br>PD and death at 2 months |
| BRAF deletion +TP53 mutation [77] | 66<br>F | FOLFIRINOX<br>Gem/Nab-P | trametinib (MEK1/2 inhibitor) | PR at 2 months<br>PD at 6 months |
| ATP1B1–NRG1 [78] | 30<br>F | FOLFIRINOX | afatinib (pan-ERBBi) | PR at 7 weeks<br>PD at 3 months |
| ATP1B1-NRG1 [70] | 56<br>F | Resection<br>5 lines of chemo<br>HIPEC + mitomycin-C | afatinib (pan-ERBBi) | PD after 4 months |

5-FU/LV= fluorouracil + folinic acid; CR = complete response; F=female; FOLFIRNOX = fluorouracil + folinic acid + irinotecan + oxaliplatin; Gem/Nab-P = gemcitabine + nab-paclitaxel; HIPEC = hyperthermal intraperitoneal chemotherapy; M=male; PD = progressive disease; PR = partial response; SBRT = stereotactic body radiation therapy; SD = stable disease; TACE= transarterial chemoembolization.

15–70) with tumor-regression in 7/10 patients and disease control rate of 90% (90% CI 61–100). CA 19.9 decline of 50% is observed in all evaluable patients (9/9). Duration of response results is still pending. The results reflect a significant radiologic tumor and biomarker response in heavily pretreated metastatic KRAS$^{WT}$ NRG1+ mPDAC with minimal toxicity. Hence, Zeno is a promising novel targeted therapeutic option for patients with NRG1+ cancers and this strategy further emphasizes the possible role of targeted therapy in KRAS$^{WT}$ pancreatic cancer with oncogenic fusions.

The desirable benefit of precision oncology in KRAS$^{WT}$ PDAC has triggered many researchers to set up trials investigating the use of agents targeting molecular aberrations that are enriched in KRAS$^{WT}$ PDAC [73]. Even though only a minority of patients might be susceptible to a targeted treatment, every attempt to improve the dismal prognosis of mPDAC should be encouraged. The recommendation of Luchini et al. [73] to routinely determine KRAS mutational status in PDAC, followed by comprehensive molecular profiling of only the KRAS$^{WT}$ patients, could be a good alternative when access to large-panel next generation sequencing is not readily available.

## 2.4. Other promising treatment strategies

### 2.4.1. CDK4/6 therapy

As previously mentioned, KRAS mutation is the main initiator (>90%) of oncogenesis in PDAC with secondary ones in cell cycle regulators, including cyclin-dependent kinases (CDKs, CDK4 and CDK6, are serine/threonine kinases that modulate cell cycle entry and $G_1$ progression by phosphorylation of the retinoblastoma protein (RB1). Overexpression and altered regulation of CDK4/6 have been observed in multiple cancer, including PDAC (caused by loss-of-function mutations in p16 (IKN4A), encoded by CDKN2A (inactivated in > 80% of PDAC)). CDKNA2 mutation has also been linked to more aggressive progression of PDAC. Hence, the use of specific CDK4/6 inhibitors could be a promising novel approach in PDAC [82].

Three CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, are currently approved for treating advanced estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in association with endocrine therapy [83]. Meanwhile, preclinical data have also demonstrated the antiproliferative activity of CDK4/6 inhibitors in PDAC cell lines and patient-derived xenografts [84,85]. As single-agent treatment with CDK4/6 inhibitors has shown only modest responses in most tumor types, combination therapies are likely required. For PDAC, one of the suggested strategies is to combine CDK4/6 inhibitors with cytotoxic chemotherapy, especially gemcitabine, as the addition of CDK4/6 inhibitors exerts a synergistic effect with increased apoptosis and chemosensitivity leading to reduction of invasion and tumor progression [84]. Variable preclinical results of concomitant treatment with CDK4/6 inhibitors and gemcitabine or

5-fluorouracil (5-FU) have been reported [84,86]. On the other hand, combining CDK4/6 inhibitors with classical chemotherapy may also interfere with the cytotoxic effect of DNA-damaging agents or antimitotic drugs as CDK4/6 inhibitors arrest cells in G1, thereby protecting cells from damage during DNA replication or mitosis. Salvador-Barbero et al. [87] hypothesized that sequential inhibition of CDK4/6 kinases after chemotherapy may prevent proper recovery from these cytotoxic agents, thereby providing new therapeutic opportunities in combination with the current standard of care in PDAC. Therefore, the safety, benefit, and optimal sequence of CDK4/6 inhibitors in combination with gemcitabine- or 5-FU-based chemotherapy in PDAC should be further explored in clinical trials.

Another combination strategy is to use CDK4/6 inhibitors together with drugs targeting the downstream RAS pathway as the potential mechanism of escaping targeted blockade of oncogenic KRAS signaling in PDAC is through the upregulation of CDK4/6 signaling [88]. For example, a preclinical study in xenograft models [89] showed that the combination of MEK inhibition and CDK4/6 inhibition prevents tumor cell proliferation by promoting senescence-mediated growth arrest. In addition, the combined inhibition of CDK4/6 and MEK modulates the PDAC microenvironment, possibly increasing the sensitivity of PDAC cells to immune checkpoint blockade. Other combination strategies with CDK4/6 inhibitors have been preclinically investigated [90] but results of translation into clinical trials are to be awaited. For example, a currently ongoing phase-1 trial is looking at the combination of palbociclib with the ERK inhibitor ulixertinib in advanced mPDAC (NCT03454035).

Another interesting combination strategy is to combine CDK4/6 inhibitors with PARPi's. As previously mentioned, the PARP inhibitor olaparib improves outcomes of BRCA1/2 mutated PDAC patients [48]. PARP1 expression is controlled by the RB1/E2F axis and repressed by CDK4/6 inhibitors [91], and it has been suggested that this effect is much stronger during recovery from taxanes [87]. Therefore, CDK4/6 inhibitors could increase the sensitivity of PDAC cells to PARP inhibitors, but this hypothesis needs further investigation.

#### 2.4.2. Autophagy

Upregulated autophagy in pancreatic cancer cells can contribute to therapy resistance by allowing the cells to survive under stress conditions induced by treatments. Autophagy is a cellular process that captures, degrades, and recycles intracellular proteins and organelles in lysosomes. When autophagy is upregulated, cancer cells might utilize it to prevent the toxic accumulation of cellular waste products caused by therapies, reducing their effectiveness. Additionally, increased autophagy can enhance the cancer cells' ability to adapt to survive environmental stress, partly by maintaining metabolic function of mitochondria, making them more resilient to treatments. This connection between autophagy and therapy resistance is an active area of research, and targeting autophagy alongside therapies could potentially improve treatment outcomes [92,93]. Hydroxychloroquine (HCQ) is an inhibitor of autophagy that inhibits the fusion of the autophagosome to the lysosome. Karasic et al. [94] investigated in their open-label, randomized phase II trial the addition of HCQ to gemcitabine/nab-paclitaxel in patients with untreated advanced or mPDAC. However, the group receiving HCQ did not appear to have a better survival of 12 months, discouraging the routine use of HCQ with chemotherapy. The combination of HCQ with targeted therapy is also being investigated in ongoing clinical trials with various ERK/MAPK pathway inhibitors (Ulixertinib; Trametinib; Binimetinib) in combination with HCQ (NCT04145297; NCT03825289; NCT04132505).

## 3. Conclusion

Despite many efforts to discover new effective treatments for mPDAC, chemotherapy remains standard of care, often with significant toxicities and only 40–50% of patients reaching second-line treatment. Over the past years, immunotherapy has improved the prognosis of many other solid tumors, but unfortunately for PDAC, its role remains disappointing with many negative trials for immunotherapy in monotherapy but also in combination strategies [23]. The aggressive behavior of mPDAC and its resistance to chemotherapy but also immunotherapy can be mainly attributed to the highly desmoplastic TME with its typical structural rigidity, poor perfusion and low immunogenicity [10]. Targeting this typical rigid immunosuppressive TME is the focus of many ongoing phase 1/2 trials, for example using TGFβ-blockade or addressing focal adhesion kinase inhibition (FAKi). Mostly, this is done in combination with standard chemotherapy regimens and we are awaiting with much curiosity the results from these studies. To improve the antitumor immune response, cancer vaccines and CD40 agonists are being explored, but larger studies are needed to confirm their efficacy.

In the era of precision medicine, the use of NGS has improved our knowledge on the genetic alterations and molecular drivers of PDAC and has guided the identification of potential targeted therapies. For a small subset of patients with HRD, PARPi's can improve prognosis. The PARPi olaparib has shown efficacy (improved PFS) in the maintenance treatment of gBRCA1/2 mutated mPDAC, hence postponing the need to treat these patients with more toxic established chemotherapy regimens [48]. Many clinicians also believe in the wider use of PARPi's in the other non-BRCA mutated DDR genes, but more data are needed to confirm efficacy in this rare setting.

KRAS mutations are known to be the foremost oncogenic drivers in PDAC with secondary ones in cell cycle regulators. The efficacy of KRASG12C inhibitors has been shown in PDAC as well [61,62], but KRASG12C mutations represent only 1% of PDAC, so strategies to target the more prevalent KRAS mutations are needed and under way. Oncogenic KRAS signaling triggers the expression of GSK-3β and GSK-3β acts as a tumor promoter. By inhibition of GSK-3β, PDAC cell growth and survival can be impaired and drug sensitivity can be improved. As such, clinical studies evaluating the activity of GSK-3β inhibitors in monotherapy or in combination therapy in PDAC are being developed. The scarce group of $KRAS^{WT}$ PDAC often harbor alternative oncogenic drivers of the RTK/RAS/MAPK pathway (i.e.

fusions ALK, BRAF, FGFR2, MET, NRG1, NTRK1, NTRK3, RAF1, and ROS1) with the potential for tailored treatments, making their identification a therapeutic opportunity. If NGS is available, its analysis is recommended in every patient with mPDAC as it may hold an opportunity for tailored treatment, even if this only concerns a minority of patients. In centers/countries where NGS is not readily available, at least RAS mutation analysis is recommended, with additional NGS in those who are $KRAS^{WT}$. Other promising strategies currently being explored are for example autophagy and CDK4/6 inhibitors.

To conclude, in the pursuit of new hopeful therapeutic options for this patient group with dismal prognosis, at all times clinicians should be encouraged to refer patients with a good performance status for possible study inclusion.

## 4. Expert opinion

Chemotherapy will remain standard first-line (second-line) treatment for some time, but the goal will be for combination strategies to decrease resistance to chemotherapy. One of the main key areas to be addressed is the rigid and immunological cold TME of PDAC. New agents targeting this should be sought and combined with standard of care treatment.

Currently, treatment beyond second line for PDAC is often very individualized or is dependent upon clinical trials. Unfortunately, the performance status of patients with mPDAC in further lines of treatment is often too dismal to be included in these clinical trials. As such, strategies in earlier lines (often combination with standard of care treatments) should be encouraged.

NGS analysis has extended treatment options for some patients, but this is not readily available everywhere. In an ideal setting, every treating center should implement NGS analysis for their patients with mPDAC, but cost-effectiveness is still preventing this. The question is whether future research should be more focused on the overall population or whether it should focus more on individualized treatments. However, given the example of the rare occurrence of $KRAS^{WT}$ patients, the gain of more individualized treatments is debatable.

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**Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.**


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