Current and Emerging Therapies in Metastatic Pancreatic Cancer

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Abstract

Targeted therapies and immunotherapy have changed the face of multiple solid malignancies, including metastatic melanoma and lung cancer, but no such therapies exist for pancreatic ductal adenocarcinoma (PDAC) despite the knowledge of key mutations and an increasing understanding of the tumor microenvironment. Until now, most clinical studies have not been biomarker driven in this highly immunosuppressive and heterogeneous cancer. Ongoing basic and translational studies are better classifying the disease in hopes of identifying critical pathways that distinguish the unique PDAC subtypes, which will lead to personalized therapies. In this review, we discuss the current treatment options for metastatic pancreatic cancer and highlight current ongoing clinical trials, which aim to target the stroma and the immune microenvironment either alone or in combination with standard chemotherapy. Identifying biomarkers and key resistance pathways and targeting these pathways in a personalized manner in combination with chemotherapy are likely to yield a more immediate and durable clinical benefit. Clin Cancer Res; 23(7): 1670–8. ©2017 AACR.

See all articles in this CCR Focus section, “Pancreatic Cancer: Challenge and Inspiration.”

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer for which little progress has been made over the past decades, with 5-year survival at 7% (1), and is projected to be the second leading cause of cancer-related death in the United States by 2030 (2). Even for early-stage disease, recurrence is high. Although recent combination therapies for metastatic PDAC have improved the median overall survival (mOS) by up to 5 months, the overall prognosis remains little changed, and novel therapies are desperately needed (3, 4). A majority of patients at diagnosis are deemed unresectable, as the disease remains symptomatically silent during the early stages, and no effective screening test exists.

A multitude of clinical trials have failed to demonstrate efficacy likely due to the aggressive nature of PDAC, attributed to a potent immunosuppressive tumor microenvironment (TME) in which many distinct cells appear to collaborate toward tumor growth and metastasis (5). Understanding the intricate pathways that are critical in these collaborative interactions is key to the design of innovative clinical trials in hopes of improving outcomes. This review will first summarize current standard-of-care treatments in metastatic PDAC and discuss modifications of approved regimens, which aim to decrease the rates of adverse events while aspiring to maintain efficacy. Next, the review will focus on current ongoing clinical trials, which appear to have appealing preclinical scientific merit and will hopefully lead to a change in the current standard of care. Some of these trials aim to combine chemotherapy with novel agents, including gene therapy to reconstitute wild-type p53; an enzyme to decrease the density of the tissue matrix by digesting hyaluronan (HA); and inhibitors of cytokines, which manipulate tumor-associated macrophages (TAM). Other therapies include combinations that do not include a chemotherapy backbone and intend to increase tumor-infiltrating lymphocytes by combining cytokine inhibitors with immune checkpoint blockade (ICB; Table 1). Other novel and upcoming trials include biomarker-targeted antibodies, including bispecific antibodies, either alone or in combination with ICB. Other immunologic approaches, such as vaccine therapy and CAR T cells, are not the focus of this article. This review summarizes ongoing, active accruing clinical trials and the preclinical data available to justify these studies in metastatic pancreatic adenocarcinoma when queried in ClinicalTrials.gov. Due to space limitation for this review, not all clinical trials are discussed, but many are listed in Supplementary Table S1.

Current Clinical Practice

Gemcitabine

Studies aiming to improve pancreatic cancer therapy are almost always conducted in the metastatic setting. From a historical perspective, gemcitabine was the first agent approved by the FDA for the treatment of pancreatic cancer and was approved based on an improvement in clinical benefit. In 1996, the FDA approved gemcitabine hydrochloride for patients with locally advanced or metastatic disease who were previously treated with 5-fluorouracil (5-FU). Gemcitabine showed definitive efficacy in a pivotal phase III study in subjects with untreated advanced pancreatic cancer in comparison with 5-FU, prolonging median survival (4.4 to 5.6 months) and 12-month survival (2% to 18%) rates, and improved a composite score of clinical benefit (comprising pain, functional status, and weight measurements; ref. 6). This small improvement in survival foreshadowed the great difficulty that haunted the field for the next 15 years.
Table 1. Selected ongoing clinical trials in metastatic pancreatic adenocarcinoma

<table>
<thead>
<tr>
<th>Clinical trials identifier</th>
<th>Study title</th>
<th>Stage</th>
<th>Phase</th>
</tr>
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<tbody>
<tr>
<td>NCT02352337</td>
<td>Randomised Phase II Study in Metastatic Pancreatic Cancer Evaluating FOLFIRINOX +/- LV5FU2 in Maintenance Versus FIRGEM in First-line</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>NCT02620800</td>
<td>Study of 5-Fluorouracil (5-FU), Nab-paclitaxel, Bevacizumab, Leucovorin, and Oxaliplatin in Patients With Metastatic Pancreatic Cancer (FABLOx)</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>NCT02551991</td>
<td>A Randomized, Open-label Phase 2 Study of Nanopiposomal Irinotecan (Nal-IRI)-Containing Regimens Versus Nab-Paclitaxel Plus Gemcitabine in Patients With Previously Untreated, Metastatic Pancreatic Adenocarcinoma</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>NCT02184915</td>
<td>A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients With gBRCA Mutated Metastatic Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>NCT02826486</td>
<td>A Phase II, Multicenter, Open-label Single Arm Study to Assess the Safety and Efficacy of the Combination of BL-8040 and Pembrolizumab in Patients With Metastatic Pancreatic Cancer, the COMBAT Study</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>NCT02777710</td>
<td>A Dose Escalation Phase I Study With an Extension Part Evaluating the Safety and Activity of an Anti-PD1 Antibody (DURVALUMAB) Combined With a Small Molecule CSF-1R Tyrosine Kinase Inhibitor (PEXIDARTINIB) in Patients With Metastatic/Advanced Pancreatic or Colorectal Cancers</td>
<td>III/IV</td>
<td>I</td>
</tr>
<tr>
<td>NCT02732938</td>
<td>Philb2 Study of P1-04136309 in Combination With Gem/Nab-P in First-line Metastatic Pancreatic Patients (CCR2)</td>
<td>IV</td>
<td>II/II</td>
</tr>
<tr>
<td>NCT02715804</td>
<td>A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination With Nab-Paclitaxel Plus Gemcitabine Compared With Placebo Plus Nab-Paclitaxel and Gemcitabine in Participants With Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma</td>
<td>IV</td>
<td>III</td>
</tr>
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Abbreviations: BRCA, breast cancer; CCR2i, CC-chemokine receptor 2 inhibitor; FOLFIRINOX, 5-fluorouracil, irinotecan, and oxaliplatin; nab-paclitaxel, albumin-bound paclitaxel.

Gemcitabine combinations

Multiple phase II and III studies evaluated the addition of other agents to gemcitabine, with almost universal failure to show improvement in survival despite improved response rates (RR) and progression-free survival in some studies (7). Notable failures included the addition of 5-FU, capcitabine, oxaliplatin, and cisplatin, each failing to improve survival compared with gemcitabine alone (8–14). The first clear benefit for a gemcitabine combination in a phase III study was the addition of erlotinib, an EGFR receptor tyrosine kinase inhibitor, which prolonged median survival by 10 days when added to gemcitabine and was approved by the FDA for this indication but rarely used in the clinic for its limited benefit (15).

Seventeen years after gemcitabine was approved, addition of nab-paclitaxel to gemcitabine (gem/nab-p) resulted in a near 2-month survival benefit and is a regimen that is widely used (4). Nab-paclitaxel is a 130-nm albumin-bound formulation of paclitaxel, which is hypothesized to have greater plasma and tumor delivery, impact on stroma, and cytotoxic activity compared with the traditional cremophor-based paclitaxel (16). The MPACT trial demonstrated superiority for gem/nab-p compared with gemcitabine alone in a large randomized phase III study, with improved RR (23% vs. 7%), prolonged median progression-free survival (mPFS) (5.3 vs. 3.7 months), and prolonged mOS to 8.5 months compared with 6.7 months (4). This regimen has increased toxicity compared with single-agent gemcitabine and may not be suitable for elderly and poor performance status (PS) patients who were not represented in the phase III clinical trial. Although most subjects required a dose modification of nab-p (41% with dose reduction and 71% with dose delays), this did not seem to compromise efficacy (17). An alternative gem/nab-p regimen includes omission of treatment on day 8 while maintaining full dose, which in our clinical practice is well tolerated by patients over 70 years who have a good PS. However, this modification has not been evaluated in a comparative study and should be reserved for subjects who are ineligible for the standard regimen utilized in the MPACT trial.

FOLFIRINOX

FOLFIRINOX is an alternative regimen for healthy individuals in the first-line setting. In a phase II to III randomized trial in patients with ECOG 0 or 1, FOLFIRINOX (fluorouracil 400 mg/m² as a bolus followed by 2,400 mg/m² given as a 46-hour continuous infusion, irinotecan 180 mg/m², and oxaliplatin as 85 mg/m², every 2 weeks) resulted in an 11.1-month OS compared with 6.8 months with gemcitabine—a 4.3-month survival benefit over gemcitabine alone [hazard ratio (HR), 0.57; 95% confidence interval (CI), 0.37–0.89; P < 0.001; ref. 3]. mPFS and objective RR both favored FOLFIRINOX compared with gemcitabine alone: 6.4 months and 31.6% compared with 3.3 months and 9.4% in the group, respectively (P < 0.001). One-year OS was 48.4% in the FOLFIRINOX arm versus 20.6% in the gemcitabine arm (3). Although FOLFIRINOX is clearly superior to gemcitabine monotherapy, treatment is reserved for patients with excellent PS due to its adverse event profile, which includes fatigue, bone marrow suppression with 45.7% grade 3 or 4 neutropenia, 12.7% diarrhea, and 9.0% sensory neuropathy (3). A follow-up of the PRODIGE 4/ACCORD 11 study indicated that efficacy was only mildly affected in the 81% of the 242 patients who required dose reduction (mOS, 10.9 vs. 11.1 months; ref. 18).

Due to poor tolerability of FOLFIRINOX in a significant proportion of patients, regimens with reduced doses of irinotecan and bolus fluorouracil, or omission of bolus fluorouracil, and addition of pegylaspin on day 3 or 4, commonly referred to as modified FOLFIRINOX, or “mFOLFIRINOX,” are widely...
used. mFOLFIRINOX omitting bolus 5-FU resulted in an RR of 30%, mPFS of 8.5 months, and mOS of 9.0 months in the 36 patients tested in the metastatic setting (19). A prospective, single-arm phase II study tested the regimen with 25% dose reduction of bolus fluorouracil and irinotecan and found the RR, mPFS, and mOS to be 35.1%, 6.1 months, and 10.2 months, respectively, which was comparable with that reported in the original PRODIGE 4/ACCORD 11 trial (20). With the caveat of comparing distinct trials and limited number of patients, mFOLFIRINOX, although better tolerated, may not be equivalent to full-dose FOLFIRINOX when compared for efficacy, and it appears that the dose-reduced forms have a shorter mOS. For patients who do not have a robust PS or are intolerant to gem/nab-p, there may not be a choice but to use the dose-reduced regimen. Prophylactic administration of pegylated filgrastim in the absence of severe leukocytosis and pretreatment with palonosetron, aprepitant, and dexamethasone likely contribute to a decrease in adverse events (20). Pretreatment with atropine also appears to help with the cholinergic symptoms associated with irinotecan. Other FOLFIRINOX modifications are described elsewhere (21).

Maintenance therapy
In our clinical experience, FOLFIRINOX or gem/nab-p are used indefinitely until disease progression or patient preference for discontinuation. Peripheral neuropathy and myelosuppression are common initial adverse events that require dose modifications. Ongoing clinical trials are evaluating the potential to switch to maintenance therapy after disease stabilization on combination therapy (Table 1; NCT02352337, NCT02184195).

Therapy after progression
As first-line therapy has become more effective, a larger group of patients are able to proceed to additional therapies after progression. Earlier studies suggested that there may be a benefit to utilizing 5-FU–based combinations after first-line therapy with gemcitabine, with combination 5-FU and oxaliplatin showing benefit in some studies (22–24), but not in others (25). In 2015, combination nanoliposomal irinotecan and 5-FU was the first regimen approved by the FDA for second-line therapy in PDAC (26).

Nano-liposomal irinotecan and 5-FU
The NAPOLI-1 study was an international phase III clinical trial comparing combination nanoliposomal irinotecan, leucovorin, and infusional 5-FU (5-FU/nal-p) with leucovorin and infusional 5-FU alone and with nal-p alone after failure of gemcitabine-based therapy. The combination regimen was significantly better than single-agent 5-FU, prolonging mOS from 4.2 to 6.1 months (HR, 0.67; P = 0.012; ref. 26). There is some toxicity, particularly neutropenia and diarrhea, but for appropriate patients who have progressed on gemcitabine-based therapy, it is the new standard of care in the second-line setting. There are no approved agents for use beyond second-line therapy in advanced PDAC.

Clinical trials
Patients and clinicians are strongly encouraged to consider participation in clinical trials, as there are limited options and there is a need to improve outcomes. In the first-line setting, there are numerous opportunities for clinical trials, of which a majority are designed to build on established chemotherapy backbones, most commonly gem/nab-p. Because a majority of patients will have short PFS, even with aggressive first-line therapy, a search for second-line clinical trials should be initiated at the time of starting therapy. A search in ClinicalTrials.gov for active clinical trials in metastatic PDAC using defined search terms identified 259 trials, a selection of which are included in Supplementary Table S1. Notable trials from this selected list are further discussed in this review (Table 1).

Combination chemotherapies
With the success of two- and three-drug combinations, there has been interest in utilizing more aggressive regimens, often with a lower individual dose of chemothermy to improve tolerability and potentially increase cytotoxicity. The FABLOX trial is an ongoing study evaluating metronomic chemotherapy with 5-FU, nab-p, bevacizumab, leucovorin, and oxaliplatin in untreated PDAC (NCT02620800). After evaluating tolerability in a phase I study, the phase II portion hopes to improve 1-year survival (27).

Chemotherapy with targeted therapies
Addition of targeted therapies to gemcitabine, including cetuximab or bevacizumab, failed to add any additional benefit (28, 29). Insulin-like growth factor 1 receptor (IGF-1R) is overexpressed in PDAC and may be associated with tumor growth and metastasis (30). In the GAMMA trial, a first-in-human, randomized trial of the IGF-1R antibody, ganitumab failed to improve survival in combination with gemcitabine over gemcitabine alone (31). However, subgroup analysis revealed that subjects with high serum levels of IGF-1R ligands (including IGF-1) may have benefited from the addition of ganitumab. These findings led to the ongoing randomized phase II CARRIE study, which is evaluating the efficacy of MM-141 (istiratumab), compared with placebo, when combined with gem/nab-p in the first-line treatment of metastatic PDAC (NCT02399137). Istratumab is a novel bispecific tetravalent antibody that blocks both IGF-1R and ErbB3 receptors, thereby blocking the adaptive PI3K/AKT/mTOR signaling pathway (32). Results from the GAMMA study have led to a biomarker-driven clinical trial that is limited to subjects with high levels of circulating IGF-1.

Targeting the TME
Immunotherapy
In contrast to advances in other solid tumor malignancies, such as melanoma and lung, bladder, kidney, and specific colon cancer subtypes, pancreas cancer has for the most part been resistant to ICB and is considered to be poorly immunogenic (33–35). Of the monotherapy ICBs tested, ipilimumab resulted in one delayed response (of the 27 treated), whereas none of the 14 patients treated with BMS-936559, a programmed death-ligand 1 (PD-L1)–directed IgG4 monoclonal antibody, experienced an objective response (36, 37). On the other hand, treatment with 10 mg/kg every 2 weeks with MED4736 (durvalumab), an Fc-optimized monoclonal antibody directed against PD-L1, resulted in responses in two of 25 patients and a disease control rate of 21% (38). Although these findings are encouraging, microsatellite instability status or the duration of response in patients who benefited was not reported. Due to the limited number of patients treated in these two trials, no firm conclusions can be made except that responses with ICB remain limited at best, and immunotherapy...
in pancreatic cancer should be reserved for clinical trials. The one exception may be in patients whose tumors are microsatellite unstable for which responses have been reported and for whom ICB-containing clinical trials should be sought (39). Mechanisms for this relative resistance to checkpoint inhibitors are under study, but a clear explanation has not emerged, as discussed by Johnson and colleagues in this CCR Focus (40).

Various alternative strategies to impact the immune system include novel approaches that aim to manipulate TAMs, monocytic cell egress from the bone marrow, and tumor lymphocyte infiltration, amongst others, and are discussed below.

Stromal fibroblasts—CXCR4 and immunotherapy

As seen in patients, antibodies to CTLA-4 or PD-L1 alone failed to control tumor growth in KPC mice (LSL-K-rasG12D, LSL-P53R172H/+; Pdx-Cre), a well-established genetically engineered mouse model of PDAC (4). However, conditional depletion of fibroblast-associated protein-expressing carcinoma-associated fibroblasts or inhibition of the chemokine receptor CXCR4 in KPC mice treated with anti-PD-L1 resulted in a modest tumor response (~15%) in short-term experiments. Tumors from mice treated for 24 hours with this combination had an increased accumulation of CD3+ T cells and Foxp3+ regulatory T cells (Treg) within the tumor, suggesting that Tregs do not completely block presumed T-cell function in controlling tumor growth (41). However, further experiments need to be performed to determine whether there is a sustained increase in T-cell infiltration and the role of Tregs in pancreas cancer when both CXCR4 and PD-L1 are inhibited. Based on these and unpublished findings, combination therapies that target CXCR4 and PD-1/PD-L1 are being tested in the clinic (Table 1). The most advanced is CXCessoR4, a phase I/II study testing this combination with ulocuplumab (anti-CXCR4) and nivolumab (anti-PD-1) in solid tumors, which includes a PDAC cohort (NCT02472977). Results from this study are eagerly awaited to assess the feasibility of pursuing this axis in a non–chemotherapy-based regimen. Other similar combinations include COMBAT/KEYNOTE-202, a single-arm phase II study, which is testing BL-8040, a short synthetic peptide that functions as a CXCR4 antagonist, with pembrolizumab in metastatic PDAC (NCT02826486). BL-8040 has been used in combination with chemotherapy in relapsed/refractory acute myeloid leukemia and required daily subcutaneous dosing due to a short half-life (42). Because most PDAC patients are treated chronically in the outpatient setting, this may pose a logistical challenge if administration of BL-8040 is not permissible at home or a formulation allowing less frequent dosing is not available. Other combination studies with BL-8040 are also planned. Currently, there is no compelling evidence to envision a chemotherapy-free regimen for PDAC in the very near future. Addition of chemotherapy to CXCR4/ICB may be necessary to overcome the highly immunosuppressive TME, given that gemcitabine-containing regimens deplete suppressive Tregs as measured in peripheral blood and within the tumor and may have effects on CD8+ T-cell expansion, making gemcitabine an ideal choice when considering chemotherapy combinations (43–45).

Stromal architecture—pegylated recombinant human hyaluronidase (PEGPH20)

PDACs are highly desmoplastic, where neoplastic, immune, and stromal cells reside in a dense extracellular matrix (ECM), of which HA is an abundant component (Fig. 1). HA is a large linear glycosaminoglycan, which is an integral architectural component of many tissues including PDAC, and high expression is associated with poor survival (46, 47). In a preclinical study using an autochthonous mouse model of PDAC, Provenzano and colleagues demonstrated that PDAC tissue from live mice whose HA content was high exhibited an unusually high interstitial fluid pressure and low vascularity (48). Other studies have suggested that tumor hypovascularity in part compromises delivery of chemotherapeutic agents, such as gemcitabine (49). Treatment with hyaluronidase decreased both tumor HA content and interstitial fluid pressure, re-expanded microvasculature, and led to a survival benefit in mice (48). These preclinical data supported clinical trials with PEGPH20. Interim analysis of an open label, randomized phase II study of PEGPH20 with nab-paclitaxel and gemcitabine in the first-line setting showed an improved RR and a trend toward OS benefit in patients whose tumors scored high for HA (52% vs. 24%; P = 0.038; and 12 vs. 9 months; HR, 0.62, respectively), whereas no statistically significant benefit was observed in overall RR in patients whose tumors scored low for HA (50). These results then led to the current ongoing phase III biomarker-driven combination study of hyaluronidase with gemcitabine and nab-paclitaxel in patients with tumors that score high for HA. Due to an imbalance in thromboembolic events observed in the phase II study within the PEGPH20 arm, patients at high risk for thromboembolism are excluded, and enoxaparin prophylaxis has been instituted. If the encouraging phase II results hold in the larger phase III study, the prevalence of high-HA PDAC tumors will determine the impact of this regimen in PDAC. Because venous thromboembolism (VTE) in PDAC is highly prevalent and is...
associated with both short- and long-term mortality, excluding patients with VTE may result in a further sub-selection of PDAC patients who are likely to have a better prognosis (51, 52). Understanding the underlying mechanism by which PEGPH20 increases the risk of thrombosis may identify strategies to avoid VTE and thereby improve outcome for a greater number of patients.

Macrophage infiltration—CCL2/CCR2

Although PDAC tumors contain few tumor-infiltrating lymphocytes, they contain bone marrow–derived myeloid cells, including TAMs, which play an important role in tumor propagation, including immune evasion, treatment resistance, and tumor spread (53). The CC-chemokine ligand 2 (CCL2) plays a pivotal role in recruiting CC-chemokine receptor 2 (CCR2) myeloid cells from the bone marrow into the peripheral blood and ultimately into the PDAC tumor where the cells differentiate into immune-suppressive macrophages. Both CCL2 and CCR2 are expressed in PDAC, making this an attractive axis to target (54). In resected human PDAC, CCL2 is highly expressed within the malignant ducts as well as the stroma, whereas CCR2+ macrophages represent a significant portion of tumor-infiltrating leukocytes (28%) compared with infiltrating CD8+ T cells (7%), as reported in one study (54). This is thought to be associated with the overall immune-restricted environment of PDAC (Fig. 2).

Indeed, low CCL2 expression within the tumor in combination with high CD8+ T-cell infiltration is associated with improved OS in PDAC patients (55). It is unclear to what extent CCL2 contributes to this favorable outcome, as other studies have also reported increased CD8+ T-cell infiltration to be a good prognostic marker (56). In a murine orthotopic model, inhibition of CCR2 by PF-04136309, a CCR2 kinase antagonist, resulted in decreased tumor growth, liver metastasis, and infiltration of TAMs. These preclinical findings led to an open-label phase Ib study in patients with borderline or locally advanced treatment-naive PDAC, in which patients received either FOLFIRINOX alone (n = 8) or FOLFIRINOX in combination with PF-04136309 (n = 39). Sixteen of 33 (49%) patients in the combination arm and none in the FOLFIRINOX group attained an objective tumor response (57). Note that the RR in the combination arm was higher than that reported in the seminal phase III study (31.6%) but was surprisingly poor (0%) in the control group, perhaps due to the small number of evaluable patients. Paired pretreatment and on-treatment biopsies from patients treated with the combination demonstrated decreased numbers of TAMs and Tregs while over a 2-fold increase in CD4+ and CD8+ T cells (57). However, no samples from the FOLFIRINOX-alone group were available for comparison, making any attribution for these findings to PF-04136309 premature.

Macrophage infiltration—colony-stimulating factor 1 receptor

Colony-stimulating factor 1 receptor (CSF1R) is a myeloid growth factor receptor that is critical for macrophage infiltration and differentiation, which allows tumor growth and promotes metastatic dissemination. Elevated tumor-infiltrating myeloid cells correlate with early relapse and lead to poor survival in PDAC (53). Human PDAC tumors express elevated levels of CSF1, whereas CSF1R was detected within the stroma with only 10% of tumor epithelium expressing the receptor (58). In an orthotopic model of PDAC, PLX3397, an inhibitor of CSF1R, resulted in tumor regressions and a decline in TAMs. Combination of a CSF1R inhibitor or a CSF1-neutralizing antibody with gemcitabine resulted in further tumor regressions. This effect was further enhanced by addition of immune checkpoint inhibitors (58). In another orthotopic mouse model of PDAC, addition of gemcitabine to a CSF1R inhibitor resulted in enhanced tumor growth inhibition compared with CSF1R inhibition alone. This effect was neutralized when combined with CD8-depleting antibodies, suggesting that the CSF1R inhibitor–mediated efficacy is largely dependent on CD8+ T lymphocytes (59). These results provide further evidence of cross-talk among immune cells within the TME. Combination of PLX3397 and inhibitors of CSF1R is also being pursued in combination therapy with IC8s in the clinic (Supplementary Table S1).

PDAC is heterogeneous and likely to have multiple pathways of immune resistance, with different levels of contribution of each pathway within the tumor. Biomarkers that identify the extent of involvement of these resistance pathways need to be identified for personalized treatment to yield better efficacy. Although a chemotherapy-free regimen would be of value in PDAC, there is no evidence to support such a strategy as yet. Various biomarker-driven studies, including targeting of CA19-9 (MVT-5873) and CEA (CEA-TCB) by modified antibodies, are currently underway and will hopefully change this paradigm (Fig. 2).

Gene therapy—TP53

The tumor suppressor TP53 is the most commonly mutated gene among all cancers, and 75% of PDAC tumors contain mutations in p53, which is implicated in its pathogenesis and may drive metastasis (60–62). Various approaches to target p53 have been attempted, some of which include restoring wild-type p53 conformation and transcriptional function, depletion of mutant p53, targeting mutant p53, and inhibition of downstream targets of mutant p53 (63). One such recent attempt is SGT-53, a gene delivery system that contains wild-type p53 plasmid DNA encapsulated within a cationic liposome that is co-administered with anti-transferrin receptor single-chain antibody fragment (64). In a mouse model of metastatic pancreatic cancer, treatment of mice with SGT-53 resulted in expression of wild-type P53 within hepatic tumors and resulted in a survival benefit. In a phase I study of SGT-53 in solid tumors, wild-type P53 expression was detected in metastatic tumor sites, and patients tolerated the therapy well, with a majority of patients demonstrating stable disease at 6 weeks (65). SGT-53 is currently being tested in the front-line metastatic setting in combination with gemcitabine and nab-paclitaxel (NCT02340117; Table 1).

PARP inhibitors

PARP inhibitors act by inactivating a key protein for the repair of single-stranded DNA breaks. These drugs are capable of inducing death in homologous recombination–deficient tumors, including those with breast cancer (BRCA) 1, BRCA2, and partner and localizer of BRCA2 (PALB2) mutations. This is because those tumors have a preexisting higher burden of double-stranded breaks due to deficiency in accurate natural repair mechanisms (66). A recent study of 306 Canadian patients suggested that the rate of BRCA mutations in pancreatic cancer is between 4% and 5%, whereas a New York study revealed a rate of approximately 10%, suggesting some variability in geographic distribution, perhaps relating to the prevalence of these mutations in Ashkenazi
Jews (67, 68). PALB2 mutations are significantly rarer, generally less than 2% (68, 69). Other mutations may confer a BRCA-like phenotype of responsiveness, although this is less well established in pancreatic cancer (70). BRCA mutation associates with a better response to platinum-based chemotherapy, anthracyclines, and radiotherapy in multiple malignancies, most likely due to the inability of the cell to recover from chemotherapy-induced DNA damage. PARP inhibitors are thus commonly given in combination with DNA-damaging agents in clinical studies. Furthermore, in pancreatic cancer specifically, platinum analogues have been shown to significantly improve survival in BRCA-mutated patients as compared with other therapeutic strategies (71). The
best data to support efficacy of PARP inhibitors are in ovarian cancer, where olaparib was approved and efficacy has been confirmed in phase III studies (72). In pancreatic cancer, PARP inhibitors have shown activity in preclinical models as monotherapy and in combination with platinum chemotherapy (73). A multi-histology trial of olaparib reported an RR of 50% in BRCA-mutated pancreatic cancer, and multiple clinical trials using PARP inhibitors are underway (ref. 74; Table 1). Rucaparib, another PARP inhibitor, resulted in an RR of 11% and a disease control rate (stable disease for at least 12 weeks) of 32% in advanced PDAC (75). These preliminary results offer enthusiasm to pursue PARP inhibitors in BRCA-mutated cancers. However, identification of a biomarker that identifies tumors with yet unknown mutations that affect DNA repair could broaden the utility of PARP inhibitors in pancreas cancer.

Conclusions

Current therapeutic options for PDAC involve combination cytotoxic chemotherapy, which affords a marginal survival benefit at the cost of significant toxicity. The many trials discussed in this review aim to change the trajectory of this outlook by targeting multiple pathways within the TME that are thought to be barriers to neoplastic cell death. Moreover, biomarker-driven trials that preselect patients who are likely to respond are a major step forward. Current ongoing trials targeting HA with PEGPH20 and CCR2 with PF-04136309 in early studies show promise. There are, however, major obstacles when treating patients with PDAC on investigational studies that need mentioning. First, PDAC is a rare malignancy for which disease-specific trials are not available at large, limiting treatment options for patients, particularly beyond first line. Second, compared with many of the other solid malignancies, the anatomical location and aggressiveness of PDAC is incompatible with any administrative delay in enrolling patients, particularly for biomarker-driven studies that require central testing of tissue specimens. These delays likely select for patients who either have low-burden disease or have a less aggressive biology. There needs to be an urgency when considering these patients, particularly within phase I groups where PDAC patients are referred beyond first line, as is done for some hematologic malignancies. Overall, the multitude of pathways that are being targeted and the results from early-stage studies for some of these studies show promise, with the hope that a breakthrough is on the horizon.

Disclosure of Potential Conflicts of Interest

G.A. Manji reports receiving commercial research grants from Plexxikon and is a consultant/advisory board member for Aderyk Inc. Y.M. Saenger reports receiving commercial research grants from Amgen and Intensity Therapeutics, and is a consultant/advisory board member for Amgen and Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

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