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Systemic Therapy for Patients With Pancreatic Cancer: Current Approaches and Opportunities for Novel Avenues Toward Precision Medicine

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis with a 5-year overall survival of 11%. The disease is usually diagnosed at advanced stages, and systemic chemotherapy is the standard-of-care treatment for the majority of patients with PDAC. Although novel treatment options, such as targeted therapy and immunotherapy, have achieved substantial progress leading to practice-changing results, with FDA approvals for several solid tumors so far, the progress achieved for PDAC is relatively limited. Recent studies uncovered potential therapeutic targets for patients with PDAC, and potential therapeutic opportunities are currently being further examined. Herein, we review recent advances in systemic therapy regimens, including cytotoxic agents, targeted therapies, immunotherapy, and novel therapeutic options for managing patients with PDAC. We also elaborate on molecular profiling to guide treatment and existing therapeutic opportunities that may further advance the clinical care of patients with this devastating disease.

Keywords

Pancreatic adenocarcinoma; Immunotherapy; KRAS12C; Fusion genes; Targeted therapy

Introduction

The incidence of pancreatic cancer has been increasing significantly over the last decade with a concerning trend in mortality, particularly due to limited therapeutics for management.[1] With the current trend, pancreatic cancer is expected to be the second leading cause of cancer-related death in the US, driven by both the increasing incidence of cases and

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the aggressive biological nature of this disease.[2] Currently, the 5-year overall survival (OS) for advanced-stage pancreatic ductal adenocarcinoma (PDAC) is approximately 2.5% to 5%, indicating an unmet need for developing novel therapeutics to improve outcomes for patients with pancreatic cancer, particularly those with advanced-stage disease.[3]

The biology of pancreatic cancer carries unique characteristics. The molecular underpinning of pancreatic adenocarcinoma remains one of the key drivers of the aggressive biology of this cancer.[4] One of the key molecular features of pancreatic cancer is the high incidence of KRAS and TP53 mutations, leading to dysregulation in both oncogenic and tumor suppressor pathways.[5] Several other tumor suppressor genes, such as SMAD4 and CDKN2A (p16), are also frequently mutated in PDAC and are also considered to be founder alterations that contribute to the aggressive nature of PDAC and its resistance to chemotherapy.[6,7] Nonetheless, systemic combination chemotherapeutics remain the mainstay treatment of advanced-stage pancreatic cancer. Although novel targeted therapy or immunotherapy agents improve OS rates in certain cancer types (eg, NSCLC, renal cell carcinoma, and malignant melanoma), the majority of these drugs yielded limited clinical benefits in pancreatic cancer.[5,8] Therefore, these tumors represent an unmet clinical need.

Despite the challenges in drug development for PDAC, there has been promising progress in targeted therapeutics for pancreatic cancer, and research efforts continue to investigate immunotherapeutics to change the course of this aggressive disease. Herein, we discuss recent advances in treatments of patients with PDAC and future therapeutic opportunities for novel therapeutics.

Systemic Chemotherapy

Standard-of-care treatment for metastatic pancreatic cancer (mPDAC) has significantly evolved over the last decade. The study by the PRODIGE group investigated the role of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) for patients with mPDAC.[9] In this study, 342 patients with mPDAC with an ECOG status 0 to 1 were randomized to receive FOLFIRINOX or single-agent gemcitabine. The median progression-free survival (PFS) and OS for FOLFIRINOX and gemcitabine were 6.4 months versus 3.3 months (HR, 0.47 [95% CI, 0.37-0.59]; P <.001) and 11.1 months versus 6.8 months (HR, 0.57 [95% CI; 0.45-0.73]; P < .001), respectively. These findings are consistent with improved outcomes with the use triplet regimen over single-agent gemcitabine and resulted in practice change after a long period of time without significant progress. This study was followed by a clinical trial that investigated gemcitabine and albumin-bound paclitaxel (nab-paclitaxel) combination.[10] In this study, patients with a Karnofsky Performance Status Score of 70 or above (ECOG 0-1) were randomized to receive either gemcitabine (1000 mg/m^2) and nab-paclitaxel (125 mg/m^2) weekly for 3 weeks, followed by a week off or single-agent gemcitabine (1000 mg/m^2) weekly 7 out of 8 weeks, followed by days 1, 8, and 15 every 4 weeks. In this study, patients who received the combination therapy had a median PFS of 5.5 months and OS of 8.5 months, while patients who received gemcitabine single agent had a median PFS of 3.7 months and OS of 6.7 months (HR for PFS and OS [0.69 and 0.62]; P < .001 for PFS and OS). This study established gemcitabine and nab-paclitaxel as alternative first-line therapy for patients with mPDAC. Although a retrospective

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comparative study suggested improved OS and PFS rates with FOLFIRINOX as compared to gemcitabine and nab-paclitaxel, at this time, there is no prospective data to confirm the superior efficacy of FOLFIRINOX over the gemcitabine–nab-paclitaxel combination.[11] Given relatively better tolerance with the use of doublet regimens, for patients who are not eligible to receive modified FOLFIRINOX due to poor performance status, a gemcitabine-based regimen can be considered.[12] Biweekly dosing of gemcitabine and nab-paclitaxel is an effective alternative for patients with relatively poor performance status.[13] Importantly, patients with germline or sporadic *BRCA1, BRCA2*, and *PALB2* alterations should be considered for platinum-based chemotherapies as first-line treatment, including gemcitabine and cisplatin.[14,15]

Second-line chemotherapy for patients with PDAC and otherwise no actionable gene has been established in the NAPOLI trial. In this 3-arm randomized phase III trial, patients who previously had disease progression with gemcitabine-based first-line therapy received either nanoliposomal irinotecan alone or in combination with fluorouracil plus folinic acid or fluorouracil plus folinic acid alone.[16] Patients who received combination therapy with nanoliposomal irinotecan had significantly improved OS (6.1 months) compared to patients who received fluorouracil plus folinic acid alone (4.2 months) (HR, 0.67 [95% CI 0.49-0.92]; $P = .012$). Although the therapeutic value of nanoliposomal irinotecan is not well established for patients with prior irinotecan therapy (such as FOLFIRINOX), the benefit appears to be more pronounced for patients with no prior irinotecan-based therapy.[17] Other systemic chemotherapy options include FOLFOX[18] or gemcitabine-based combinations, depending on prior line of therapy.

Targeted Therapies

Next-generation sequencing (NGS) has revolutionized the care of patients with cancer. Aguirre et al demonstrated that up to 25% of patients with PDAC may have potentially targetable genomic alterations (Figure 1).[19] According to the Know Your Tumorinitiative, the median OS of patients with PDAC with actionable alterations on matched therapy is approximately 2.5 years when compared to 1.5 years among patients on unmatched therapies, indicating that targeting therapy for potentially actionable genes should be evaluated for all patients with advanced-stage pancreatic cancer.[20] Given that growing evidence suggests that survival benefit matched therapies, genome-driven clinical decisions should be implemented in routine patient care, which is discussed further in the following sections.

Homologous Recombination Deficiency

Genomic integrity is maintained by DNA-damage response and repair pathway. *BRCA1, BRCA2*, and *PALB2* are key genes that play a significant role in DNA-damage repair, which is triggered by DNA-damage response molecules, including *ATM* and *ATR*.[21] Homologous recombination is one of the most important and precise DNA-damage repairs in humans, and this pathway is orchestrated by *BRCA1, BRCA2*, and *PALB2* proteins. Patients whose tumors harbor homologous repair deficiency (HRD) due to loss of function alterations in their key genes are known to be more sensitive to platinum-based chemotherapy regimens.[22]

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Important to note that several cohort studies evaluating outcomes of patients with HRD consistently reported improved outcomes with the use of platinum-based chemotherapeutics as a first-line therapy.[23] A recent clinical trial investigated cisplatin-based chemotherapy with or without veliparib, which is a poly (ADP-ribose) polymerase inhibitor(PARPi).[24] In this study, although veliparib did not add any significant value to platinum therapy, cisplatin and gemcitabine combination resulted in an ORR of 74.1% and a median PFS of 10.1 months, creating this combination as an alternative standard of care to FOLFIRINOX, which also contains oxaliplatin. At this time, there is no comparative study of cisplatin-based doublet and FOLFIRINOX first line, and both combinations can be considered for patients with pancreatic cancer and HRD. Notably, there is also growing evidence irinotecan which also induces cytotoxic DNA damages, may have a clinical advantage for the treatment of patients with HRD.[25]

Olaparib, a PARPi, was investigated in patients with germline *BRCA1/2* alterations and as maintenance therapy. In this randomized phase III trial, patients received olaparib 300 mg twice daily or a placebo after induction platinum-based chemotherapy if their disease did have progression.[26] Although there was not any difference in OS, patients who received olaparib had improved median PFS (7.4 months vs. 3.8 months HR, [0.53]; $P = .004$). Based on this evidence, olaparib was approved by the FDA for the maintenance treatment of patients with pancreatic cancer with a germline *BRCA1/2* mutation in early 2020.[26] Moreover, rucaparib, a PARPi, has been demonstrated to be effective in patients whose tumors harbor either germline *PALB2* or somatic *BRCA2* mutations in a phase II trial.[27] In this single-arm study, a total of 46 patients were enrolled and received platinum-based chemotherapy for at least 16 weeks, and if no progression was noted, then they received rucaparib 600 mg twice daily. In this study, median PFS and OS were 13.1 and 23.5 months, respectively. Although the results of this study are promising, the lack of randomization limits our understanding of the true additive benefit of this therapy to platinum-based induction chemotherapy in the maintenance setting. Nonetheless, both agents are already included in NCCN guidelines as therapeutic approaches for patients with pancreatic cancer harboring HRD.[28] The progress on PARPi continues to evolve with novel approaches and combinations. A recent study investigated the combination of niraparib, a parp inhibitor, with nivolumab or ipilimumab, which are immune checkpoint inhibitors in a phase 1b/2 trial.[29] Interestingly, patients who received niraparib and ipilimumab achieved promising outcomes (6-month PFS rate of 59.6% 95% CI 44·3–74·9; $P = .045$) while patients who received niraparib with nivolumab had inferior outcomes (6-month PFS rate of 20·6% 95% CI 8·3-32·9; $P = .0002$). This biological dilemma warrants further translational studies to better define conflicting outcomes noted with 2 classes of immune checkpoint inhibitors. There is an ongoing NCI-sponsored phase II clinical trial assessing whether the addition of pembrolizumab to olaparib would be more beneficial in patients with metastatic PDAC with germline *BRCA1* or *BRCA2* mutations (NCT04548752).

KRAS Pathway

Although *KRAS* mutations are the most prevalent genetic alterations in patients with PDAC, attempts to target *KRAS* have failed thus far. Recently, sotorasib received FDA approval for $KRAS^{G12C}$ mutant NSCLC patients.[30] However, this *KRAS* mutation accounts for

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only 1% of patients with *KRAS* mutant PDAC (Table 1).[31,32] On the other hand, the vast majority of patients with *KRAS* mutant PDAC harbor $KRAS^{G12D}$ mutation, and inhibitors specific to this mutation are yet to be investigated in clinical trials for PDAC. At this time, growing $KRAS^{G12C}$ targeting approaches are being developed with highly promising outcomes for patients with PDAC.[12,33] Sotorasib, one of the first specific, irreversible *KRAS* G12C small-molecule inhibitors, has been investigated for patients with pancreatic cancer in the CodeBreak100 trial. In this phase I/II study, 38 patients with chemotherapy-refractory advanced pancreatic cancer with a tumor harboring a $KRAS^{G12C}$ mutation were enrolled and received sotorasib monotherapy.[34] The authors have reported an objective response rate (ORR) of 21% with no fatal treatment-related adverse event and a disease control rate of 84.2%, indicating a highly promising response with monotherapy. This agent is now being investigated in combination with chemotherapy as second-line therapy for patients with metastatic PDAC (NCT05251038). Most recently, adagrasib, an irreversible and selective $KRAS^{G12C}$ inhibitor, has been investigated in the KRYSTAL-1 trial (phase 1/2) for patients with solid tumors, including metastatic PDAC.[35] In one of the cohorts of this phase II study, 12 patients with metastatic PDAC received adagrasib 600 mg twice daily. Ten patients were evaluable, 5 patients (50%) achieved partial response, and the disease control rate was 100%, indicating there is highly promising antitumor activity of this agent for patients with $KRAS^{G12C}$ mutant PDAC. The median PFS was also promising and was noted to be 6.6 months. Although the numbers are relatively low in this study, early signals noted with both $KRAS^{G12C}$ inhibitors carry significant future therapeutic opportunities for patients with PDAC. Other novel $KRAS^{G12C}$ inhibitors are also being developed and investigated in solid tumors (NCT05009329).

Given that the vast majority of PDAC patients harbor *KRAS* mutations, pan-RAS inhibitors might be attractive candidates to lead durable responses. RMC-6236, a pan-RAS inhibitor against G12D, G12V, and G12R mutations, demonstrated durable complete responses in combination with anti–PD-1 treatment in preclinical PDAC models.[36] Another pan-RAS inhibitor, BI 1701963, that impairs KRAS and SOS protein interaction is currently being investigated in early phase clinical trials.[37] Other potent mutation-specific KRAS inhibitors, including KRAS G12D, demonstrated promising preclinical signals for further development.[38] Another approach for patients with *KRAS* mutations is cancer vaccine development by utilization of lipid nanoparticle mRNA-based vaccine strategies to target mutations such as *KRAS* G12D, G12V, and G13D could accelerate the development of effective treatment options for these undruggable targets. There is an ongoing phase I clinical trial to assess the safety of the mRNA-based vaccine against *KRAS* G12D, G12V, G13D, and G12C mutations in combination with pembrolizumab (NCT03948763) in patients with NSCLC, colorectal cancer, and pancreatic cancer. ELI-002 is a novel lymph node-targeted, AMP-modified therapeutic vaccine targeting KRAS-driven cancers currently being investigated in early phase clinical trials for patients who have minimal residual cancer.[39] Recently a proof of concept case study reported successful tumor regression for a patient whose T cells were engineered to express T cell receptors targeting KRAS 12D mutation.[40] This study suggests autologous T cell therapy may have the potential to generate clinically meaningful antitumor immunity. Further studies with expanded cohorts are warranted.

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The unmet need to target *KRAS* mutations led researchers to pursue inhibition of upstream activator proteins such as SHP2 or SOS1.[41] There are several SHP2 inhibitors utilized in clinical trials as a single or combinatorial agent in different cancer types. However, the majority of the SOS1 inhibitors are in the preclinical phase except for BI1701963 (NCT04975256).

Fusion Genes

The majority of patients with PDAC patients harbor *KRAS* mutations. However, *KRAS* wild-type ~10%) tumors have alternate fusion genes to drive tumor progression. To date, *BRAF, ROS, NTRK, ALK*, and *RAF1* fusion genes have been identified to drive oncogenic transformation.[42,43] In a study, patients with *RAS* wild-type disease were found to be enriched with fusion genes; *BRAF* (6.6%), Fibroblast growth factor receptor 2 (*FGFR2*) (5.2%), *ALK* (2.6%), *RET* (1.3%), and neuregulin 1 (*NRG1*) (1.3%).[43] Although fusion genes are relatively uncommon overall population, they are potentially actionable. For example, a patient with *MET* gene fusion received crizotinib, a multikinase inhibitor with potent activity against *MET*, and achieved a complete radiological response, and the duration of response was continuing at the time of report over 12 months.[44] *RAF1* fusion genes are common in pancreatic acinar cell carcinomas (14.3%-18.5%).[45] In a multicenter study, 4 out 5 patients with PDAC and with a *RAF* fusion gene achieved response top MEK inhibitor monotherapy (trametinib). Although there is a growing body of evidence demonstrating that *RAF1* gene rearrangements are sensitive to MEK inhibitors, it is context-dependent. Contrary to the aforementioned case with a remarkable response to trametinib, a patient with pancreatic acinar cell carcinoma whose tumor harbors the *GATM-RAF1* fusion gene did not show significant clinical improvement on trametinib (2 mg/day), indicating disease heterogeneity.[46]

Larotrectinib and entrectinib, both NTRK inhibitors, received accelerated approval by FDA in a tumor-agnostic manner in 2018 and 2019, respectively.[12, 47] *NTRK* fusions are also potentially actionable with these novel agents for patients with pancreatic adenocarcinoma. In a case series, patients with *NTRK* gene fusions who were treated with entrectinib and 2 out 3 patients achieved radiological response to therapy.[48] In another report, a patient with pancreatic acinar cell carcinoma achieved a deep and durable response with larotrectinib 100 mg twice daily, indicating *NTRK* fusions are highly actionable for patients with PDAC as well.

NRG1 fusions are also actionable genes for patients with cancer, and it has been demonstrated among patients with PDAC.[49] Pathogenic NRG fusion products function as a ligand for epidermal growth factor receptor 3 (HER3), resulting in heterodimerization of HER3 with HER2 receptor with aberrant epidermal growth factor receptor (*ERBB*) downstream activity. In a precision medicine study, 2 patients with *KRAS* wild-type PDAC were found to have *NRG1 gene fusion*.[49] Patients were treated with ERBB inhibitors (afatinib and erlotinib/pertuzumab), and they achieved radiological response.[49] Currently, several agents are being developed to target NRG1-driven oncogenesis, including seribantumab (HER3 blockade, NCT04790695) and zenocutuzumab[50] (bispecific HER2/

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HER3 blockade, NCT02912949). More prospective data are needed to further define the benefits of these agents and the actionability of this pathway for patients with PDAC.

Immune Checkpoint Inhibitors

It has been previously demonstrated that patients with microsatellite instability-high (MSI-H) tumors better respond to immune checkpoint inhibitors (ICIs). Currently, both pembrolizumab (humanized anti-programmed cell death protein 1 (PD-1) antibody), nivolumab (human IgG4 monoclonal antibody targeting PD-1), and dostarlimab (humanized anti-PD-1 antibody) have been approved for patients with metastatic MMR-D/MSI-H pancreatic cancer. However, MSI-H disease is seen in approximately 2% of patients with PDAC. Given the low prevalence of MSI pancreatic cancer, it is critical to determine which subgroup of patients should be screened for microsatellite instability. In a comparative study, Luchini et al demonstrated that patients with MSI PDAC show medullary and mucinous/colloid histology, *KRAS/TP53* wild-type background, and more common *JAK* mutations.[51]

While observed responses among patients with MSI-H PDAC are highly encouraging, anti–PD-1 and anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) monoclonal antibodies have not shown any signal for efficacy for patients with microsatellite stable (MSS) PDAC.[52] Durvalumab (anti-PD1 blockade) and tremelimumab (anti-CTLA4) have been investigated for patients with PDAC whose disease has progressed on first-line systemic therapy.[53] In this study, randomized phase II patients received either durvalumab and tremelimumab combination or durvalumab monotherapy, and unfortunately, the ORR was only 3.1%, while there was no objective response in the monotherapy arm, indicating a very poor response to ICI therapy. The authors reported a median PFS of 1.5 months for both arms, and the 6-month PFS rate was only 9.4%. ICIs have also been combined with chemotherapeutics to achieve a synergistic approach. The study by the Canadian Cancer Trials Group (PA.7) investigated the combination of durvalumab and tremelimumab doublet with gemcitabine and nab-paclitaxel for patients with metastatic PDAC.[54] In this randomized phase II trial, patients were randomized to receive durvalumab and tremelimumab in combination with gemcitabine and nab-paclitaxel or chemotherapy alone. The authors reported no significant improvement in median PFS (5.5 months vs. 5.4 months, HR = 0.98) or OS (9.8 vs. 8.8 months, HR = 0.94) and ORR (30.3% vs. 23.0%), suggesting a lack of synergistic effect with combination of chemotherapy and ICIs.

To sensitize patients with MSS pancreatic cancer to ICIs, ICIs were combined with stroma-modifying agents. In a randomized phase II trial, patients received atezolizumab in combination with PEGylated recombinant human hyaluronidase (PEGPH20), which is a stroma-depleting agent or standard-of-care of chemotherapy (the MORPHEUS trial).[55] In the interventional arm, the ORR was only 6.1%, and the median PFS was 1.5 months, consistent with the absence of a promising clinical signal with this approach. In another study, Parikh et al conducted a phase II clinical trial to assess the efficacy of radiotherapy along with immune checkpoint blockades (anti-PD1 and anti-CTLA4) for patients with MSS PDAC and colorectal cancer to convert their *immune cold* biology to an *immune hot* one.[56] This proof-of-concept study showed the feasibility and safety of combining immunotherapy and radiation therapy with modest activity, and the lack of randomization

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limits conclusions on the true additive benefit of immunotherapy to radiation therapy. In this study, the authors did not detect any change in tumor-mutation burden before and after therapy; however, notably, elevated levels of NK cells prior to treatments were found to be associated with improved response. Given that it was the first proof-of-concept study showing the effectiveness of ICIs in combination with radiotherapy in one of the hard-to-treat cancers such as PDAC, further studies are warranted to evaluate scheduling and sequence of treatment modalities to improve outcomes in patients with PDAC. Further studies are needed to change the immune cold nature of PDAC to make it more sensitive to immunotherapy.

Other Targeted Approaches and Novel Therapeutic Avenues

The unmet research need in pancreatic cancer has triggered several novel approaches to identify new therapeutic opportunities. Indoleamine 2,3-dioxygenase 1 (IDO), a key enzyme that catalyzes L-tryptophan, has been associated with immune evasion of cancer cells and has become an interest of cancer research as a therapeutic target (Table 2).[57] Based on preclinical data that supported the IDO1 inhibition to enhance anticancer immune response,[58,59] indoximod, an IDO1 inhibitor, was investigated in clinical trials. A single-arm phase II study of indoximod, in combination with gemcitabine and nab-paclitaxel, did not meet the predetermined primary goal of a 30% reduction in HR;[60] however, this combination provided a promising overall response rate of 46.2% and increased intratumoral CD8 T-cell density. Given that indoximod improved intratumoral CD8 density, particularly among responders, the addition of ICIs should be further considered as a therapeutic opportunity for a chemoimmunotherapy approach.

Targeting cancer stem cells and pathways associated with cancer-cell stemness has also been interrogated in PDAC. In a randomized phase II trial, tarextumab, a notch receptor inhibitor that targets cancer-cell stemness, has been investigated in combination with gemcitabine and nab-paclitaxel and compared to standard-of-care chemotherapy alone arm for patients with PDAC.[61] In this study, unfortunately, patients who received tarextumab had inferior survival outcomes compared to patients who received standard-of-care chemotherapy (median OS 6.4 months vs. 7.9 months), leading to disappointment.[61] Wnt signaling, which is also associated with cancer-cell stemness, was considered to be a therapeutic target. In a phase Ib trial, ipafricept (a Wnt inhibitor), in combination with gemcitabine and nab-paclitaxel, was investigated among patients with PDAC.[62] In this single-arm study, median PFS and OS were noted at 5.9 months and 9.7 months, respectively,[62] and they were relatively similar to historical controls.[10] In addition to oncogenic drivers, targeting the tumor microenvironment was an attractive strategy to improve the efficacy of mainstay treatments in PDAC. In particular, stromal cells and extracellular matrix comprise 90% of pancreatic cancer tissue.[63] Therefore, modifying stroma has been of interest as a therapeutic target for patients with PDAC. However, the results from clinical and preclinical studies are discouraging. Clinical studies assessing the efficacy of stroma-targeting agents in combination with chemotherapy have not resulted in significant improvement in clinical outcomes.[64] Sonic Hedgehog pathway, which has been shown to be involved in dense stroma formation and desmoplasia, has been targeted by the use of vismodegib[65] and saridegib[66] in combination with chemotherapies, which did not yield any significant clinical improvement.[65,66] PEGPH20

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was also used to target dense pancreatic stroma in combination with FOLFIRINOX[67] and gemcitabine and nab-paclitaxel combinations,[68] and neither approach resulted in clinical benefit and perhaps led to inferior outcomes when combined with FOLFIRINOX.[67] A recent translation study also showed better outcomes with dense stroma and more aggressive features with low-density stroma, which has been consistent with the findings of these clinical trials.[69] Therefore, at this time, targeting PDAC stroma has limited clinical offerings for future therapeutic approaches.

Future Perspective

Currently, the mainstay treatment for patients with advanced-stage PDAC remains to be systemic chemotherapy. Recent discoveries have further advanced potential druggable targets among subgroups of PDAC patients, particularly those with RAS wild-type disease, which includes HRD, MMR deficiency, and gene fusions and amplifications. Perhaps more exciting progress for patients with PDAC is the evolution of *KRAS* targeting, which is the most seen genetic alteration in PDAC. The development of *RAS* targeting will further open therapeutic pathways for this challenging disease and will play a locomotive role in drug development.

Although the role of immunotherapy is limited except for patients with MSI-H PDAC, the effective targeting of *RAS* will likely impact the horizons of immunotherapy in PDAC. *RAS* oncogenes are associated with the immune-exclusion process and recruitment of tumor-suppressive macrophages to the tumor micoenvironement.[70–73] Effective therapeutic-level RAS inhibition may at least partially reverse the *immune exclusion* process that renders a haven for cancer cells and enhances T-cell infiltration to the tumor microenvironment, which may create an opportunity for therapeutic synergy. This approach should be further investigated for patients with advanced-stage PDAC. Similarly, targeting other oncogenic drivers of the mitogen-activated protein kinase pathway may also derive additional therapeutic synergism for immunotherapy. Importantly, transforming growth factor beta (*TGF-β*) is another dysregulated pathway, particularly due to increased *SMAD4* alterations that result in upregulation of this pathway[74]. Notably, TGF-*β* signaling has also been associated with the immune-exclusion process,[75] and the role of immunotherapy with TGF-*β* targeting remains to be seen for patients with PDAC. Currently, a study is investigating TGF-*β* blockade in combination with chemotherapy with or without immune checkpoint blockade (NCT04390763) (Table 2). Combinations of PARPis and IOs are currently in progress (NCT04548752) in the maintenance setting, and if found to be significant, then further exploration can be considered in the other clinical scenarios, including for patients with chemotherapy-refractory diseases. The claudin 18.2, a tight junction protein that promotes carcinogenesis, is currently being targeted in clinical trials. A study investigating zolbetuximab, a monoclonal antibody directed to claudin 18.2 to provoke antibody-dependent cellular cytotoxicity, is currently being investigated in combination with gemcitabine and nab-paclitaxel (NCT03816163).[76] Collectively, these novel approaches may create more therapeutic opportunities and create new avenues for the management of patients with PDAC.

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Conclusion

The therapeutic evolution of PDAC has been evolving slowly, particularly the molecular underpinnings of PDAC. Unlike other solid tumors so far, targeted therapy and immunotherapy have major limitations, and they have been effective among relatively uncommon subgroups of patients with PDAC with wild-type *KRAS*. However, as *RAS* targeting evolves, therapeutic avenues of PDAC will likely speed up progress in the treatment paradigm of PDAC, including immunotherapy. Perhaps targeting other oncogenic-driver pathways that directly involve pancreatic carcinogenesis, such as *TGF-β*, may also provide further therapeutic progress. Identifying pancreas-specific neoantigens, such as claudin 18.2, may accelerate advances in managing PDAC, particularly for cellular-based therapies. Collectively, although the progress has been slow, more opportunities and scientifically promising approaches are being developed to change the course of this aggressive disease, and there is hope on the horizon.

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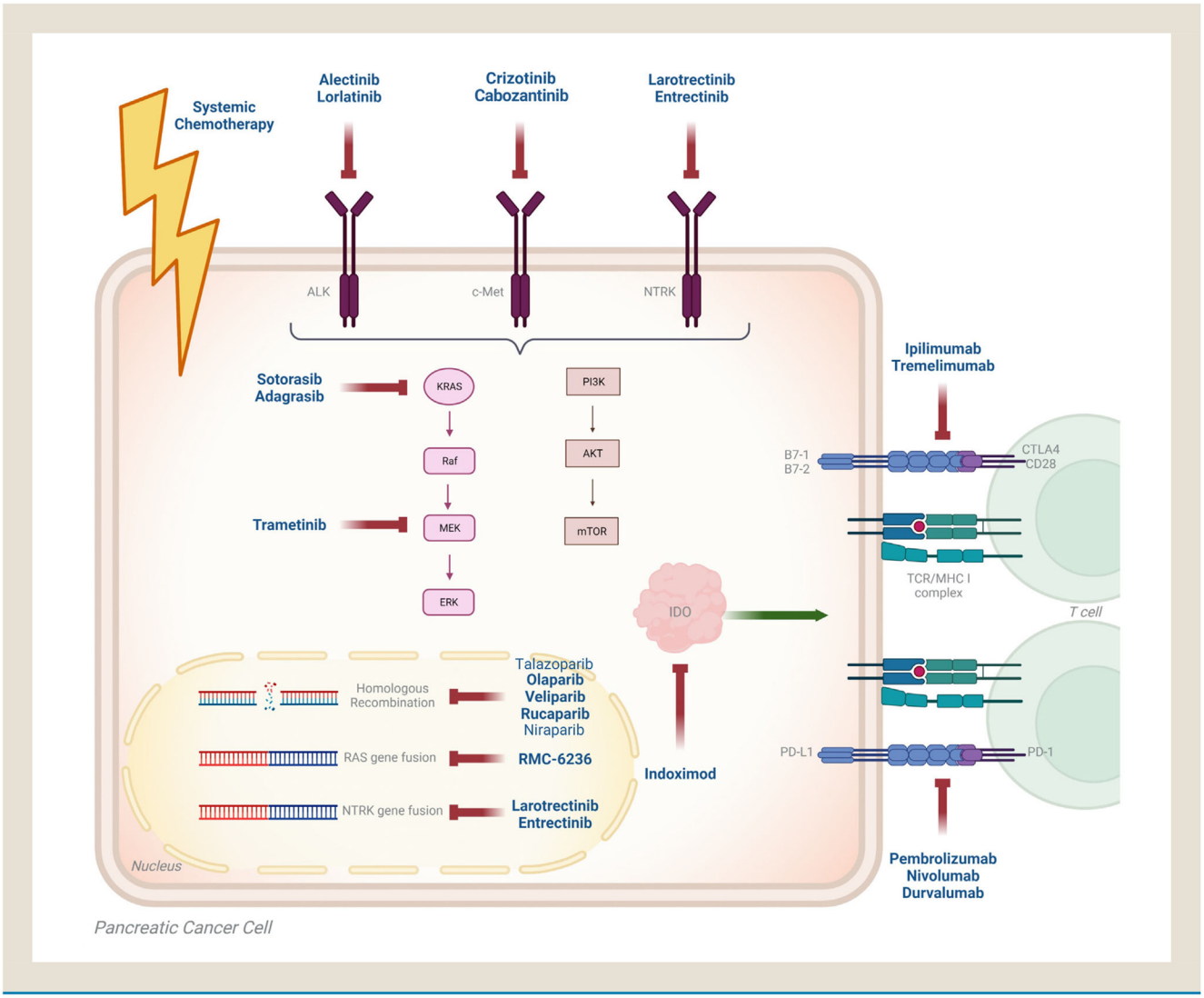

Figure 1.
Potentially actionable genetic alterations in pancreatic ductal adenocarcinoma

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Table 1

Selected Clinical Trials With Targeted Therapeutics for the Management of Metastatic Pancreatic Cancer

Drug	Target	Mechanism	Phase of Trial	Trial Design	Cancer Type	Primary Endpoint	Clinical Reference	Results	Adverse Events (Any Grade)	Current Status
Sotorasib	$KRAS^{G12C}$	Small molecule inhibitor of $KRAS^{G12C}$	I/II	Monotherapy or in combination with PD-1/PD-L1 inhibitors	Basket trial	Treatment-related adverse effects, objective response	NCT03600883 (CodeBreak 100)	8 PR 21.1% ORR 32% DCR Median PFS 3.98 months Median OS 6.87 months	Diarrhea (5.3%) Fatigue (5.3%) Abdominal pain (2.6%)	Recruiting
Adagrasib	$KRAS^{G12C}$	Small molecule inhibitor of $KRAS^{G12C}$	I/II	Monotherapy or in combination with PD-1 or EGFR inhibitors	Basket trial	Treatment-related adverse effects, objective response	NCT03785249 (KRYSTAL-1)	5 PR 100% DCR Median PFS 6.6 months	Nausea (48%) Diarrhea (43%) Vomiting (43%)	Recruiting
Olaparib	PARP	Small molecule inhibitor of PARP	III	Monotherapy or placebo	gBRCA mutated pancreatic cancer	Objective response	NCT02184195	Median PFS 7.4 months Median OS 18.9 months Hazard Ratio 0.53	Fatigue (60%) Nausea (45%) Anemia (27%)	Active, not recruiting
Rucaparib	PARP	Small molecule inhibitor of PARP	II	Monotherapy	BRCA1, BRCA2 or PALB2 mutated pancreatic cancer	Treatment-related adverse effects	NCT03140670	Median PFS 13.1 months Median OS 23.5 months 41.7% ORR 66.7% DCR	Anemia (74%) Nausea (48%) Increased ALT (47%)	Active, not recruiting
Niraparib	PARP	Small molecule inhibitor of PARP	Ib/II	In combination with Ipilimumab or Nivolumab	Platinum-sensitive advanced pancreatic cancer	Treatment-related adverse effects, objective response	NCT03404960	Niraparib + Nivolumab 6-month PFS 20.6% Niraparib + Ipilimumab 6-month PFS 59.6%	Niraparib + Nivolumab Hypertension (8%) Anemia (4%) Thrombocytopenia (4%) Niraparib + Ipilimumab Fatigue (14%) Anemia (11%)	Active, not recruiting
Entrectinib	TRK, ROS1 and ALK	Small molecule inhibitor of TRK, ROS1 and ALK	II	Monotherapy	Basket trial	Objective response	NCT02568267	2 PR 1 SD	Arthralgias Myalgias Fatigue	Recruiting
Zenocutuzumab	HER2 and HER3	IgG1 bispecific antibody	I/II	Monotherapy	Basket trial	Objective response	NCT02912949	ORR 39%	Asthenia, Diarrhea, Anemia Nausea	Recruiting

Clin Colorectal Cancer. Author manuscript; available in PMC 2024 July 03.

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Drug	Target	Mechanism	Phase of Trial	Trial Design	Cancer Type	Primary Endpoint	Clinical Reference	Results	Adverse Events (Any Grade)	Current Status
		targeting HER2 and HER3								
Durvalumab and Tremelimumab	PD-L1 and CTLA4	Monoclonal antibody against PD-L1 and CTLA4	II	Combination therapy or placebo (in combination with Gemcitabine and Nab-Paclitaxel)	Metastatic pancreatic cancer	Objective response	NCT02879318	Median OS 9.8 months Median PFS 5.5 months	Fatigue (20%) Thromboembolic event (15%) Sepsis (11%)	Active, not recruiting
Indoximod	IDO pathway	Small molecule inhibitor of IDO	I/II	In combination with Gemcitabine and Nab-Paclitaxel	Metastatic pancreatic cancer	Treatment-related adverse effects, objective response	NCT02077881	ORR 46.2% CR 1% PR 45.2% Median OS 10.9 months	Fatigue Nausea Anemia	Completed
Tarextumab	Notch Signaling	Monoclonal antibody against Notch receptor	Ib/II	Monotherapy or placebo (in combination with nab-paclitaxel and gemcitabine)	Previously untreated stage 4 pancreatic cancer	Treatment-related adverse effects, objective response	NCT01647828	Median OS 6.4 months Median PFS 3.7 months ORR 20.2%	Diarrhea (72%) Fatigue (52%) Thrombocytopenia (49%)	Completed
Vismodegib	Hedgehog Pathway	Small molecule inhibitor of PTCH and SMO	Ib/II	Monotherapy or placebo (in combination with gemcitabine)	Metastatic pancreatic cancer	Objective response	NCT01064622	Median PFS 4.0 months Median OS 6.9 months PR 8% SD 51%	Neutropenia (28%) Fatigue (13%) Anorexia (9%)	Completed
PEGPH20	Hyaluronic Acid	Recombinant form of human hyaluronidase	Ib/II	Monotherapy or placebo (in combination with FOLFIRINOX)	Metastatic pancreatic cancer	Treatment-related adverse effects, objective response	NCT01959139	Median OS 7.7 months Median PFS 4.3 months RR 33%	Nausea (25%) Diarrhea (24%) Vomiting (22%)	Active, not recruiting

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Table 2

Ongoing Selected Clinical Trials for Pancreatic Cancer

NCT	Phase	Treatment	Current Status	Study Group
NCT05251038	I/II	Sotorasib plus systemic chemotherapy	Not yet recruiting	KRAS G12C-mutant advanced pancreatic cancer with progression of disease after first line treatment
NCT05009329	I/II	JAB21822 monotherapy	Recruiting	KRAS G12C-mutant advanced solid tumors
NCT04975256	I/Ib	Adagrasib plus BI 1701963	Active, not recruiting	KRAS G12C-mutant advanced solid tumors
NCT04548752	II	Olaparib plus Pembrolizumab or Olaparib alone	Recruiting	Metastatic pancreatic cancer with germline BRCA1/2 mutations
NCT03948763	I	mRNA-5671/V941 plus Pembrolizumab or mRNA-5671/V941 alone	Active, not recruiting	KRAS mutant advanced or metastatic NSCLC, CRC or Pancreatic Adenocarcinoma
NCT02077881	I/II	Indoximod plus Gemcitabine and Nab-Paclitaxel	Completed	Metastatic pancreatic cancer
NCT04361162	II	Nivolumab plus Ipilimumab and Radiation	Recruiting	Microsatellite stable pancreatic cancer
NCT04543071	II	Cemiplimab and Motixafortide plus systemic chemotherapy	Recruiting	Metastatic treatment naïve pancreatic cancer
NCT02451982	II	Nivolumab, Urelumab, BMS-986253, GVAX and systemic chemotherapy	Recruiting	Surgically resectable pancreatic cancer
NCT03816163	II	Zolbetuximab plus nab-paclitaxel and gemcitabine	Recruiting	CLDN18.2 positive metastatic pancreatic cancer
NCT04111458	I	BI 1701963 plus Trametinib or BI 1701963 alone	Active, not recruiting	Basket trial
NCT03935893	II	Autologous Tumor Infiltrating Lymphocytes	Recruiting	Basket trial
NCT04853017	I	ELI-002; Therapeutic cancer vaccine targeting KRAS	Recruiting	Microsatellite stable pancreatic cancer
NCT03193190	Ib/II	Atezolizumab, Cobimetinib, PEGPH20, Motixafortide, Selicrelumab, Bevacizumab, Simlukafusp alfa, Etrumadenant, Tiragolumab, Tocilizumab and systemic chemotherapy	Recruiting	Metastatic pancreatic cancer

Clin Colorectal Cancer. Author manuscript; available in PMC 2024 July 03.