Advances in Systemic Therapy in Pancreatic Cancer

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KEYWORDS

- Pancreatic adenocarcinoma • DNA damage repair • Mismatch repair
- Kirsten rat sarcoma viral oncogene homolog (*KRAS*) • Immunotherapy
- poly(adenosine diphosphate-ribose) polymerase (PARP)

KEY POINTS

- New cytotoxic chemotherapy regimens have changed the landscape for the treatment of pancreatic adenocarcinoma (PDAC).
- Next-generation sequencing identifies patients responsive to targeted and immune-based therapies.
- Experimental targeted and immune-based approaches may impact treatment paradigms in the future.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the 3rd leading cause of cancer mortality in the US, with an estimated 60,050 new cases diagnosed and 50,550 deaths in 2023.[1] Due to increasing incidence and a persistently high mortality, and improving outcomes in other malignancies, it is estimated that PDAC will surpass colorectal cancer as the 2nd leading cause of cancer mortality by 2025.[2] The risk of PDAC increases with increasing age. However, recent trends show a worrisome and significant increase in the incidence of PDAC, together with several other obesity-associated malignancies, in young adults aged 25 to 49 years, with steeper rises in successively younger generations.[3] Additionally, racial disparities in this disease are becoming increasingly appreciated. Black versus white individuals have been found to have a higher incidence, a later stage at diagnosis and lower likelihood of surgical resection even when diagnosed at an early stage; these and other factors have resulted in shorter overall survival for black and Hispanic patients.[4] These trends and findings are the focus of much ongoing research, and highlight the need for an improved the understanding of disease biology and more effective therapies. The focus of this article will be on new and innovative treatments that have been and are currently in

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Hematol Oncol Clin N Am 38 (2024) 617–627
https://doi.org/10.1016/j.hoc.2024.03.002
hemonc.theclinics.com

development, with a particular focus on biomarkers and genomically targeted therapeutics.

Ductal adenocarcinoma is the most common malignancy arising from the pancreas. PDAC tumors are thought to arise from one of the 2 precursor lesions. Most commonly, in 85% to 90% of tumors, the precursor lesion is defined as a pancreatic intraepithelial neoplasia (PanIN). Less commonly, tumors arise from precursor cystic lesions such as intraductal papillary mucinous neoplasms (IPMNs). The progression of normal ductal epithelium through PanIN or IPMN to invasive PDAC has been well defined at the molecular level. The initiating, oncogenic mutation is thought to occur in Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*). Activating mutations have been found in the earliest PanIN lesions, and are present in greater than 90% of PDAC tumors. Stepwise inactivation of tumor suppressors follows, most commonly in *TP53*, *SMAD4,* and *CDKN2A*. Looking at global patterns of gene expression, a number of efforts have been undertaken to classify PDAC tumors. A number of these studies have identified 2 overarching subtypes termed classical and basal.[5–7] The therapeutic and prognostic implications of tumor subtypes remains uncertain and an area of active investigation.[8,9] Mutation rate of cells present in human PDAC suggests a time interval of, on average, 11.7 years between the occurrence of the initiating mutation and the birth of the parental, nonmetastatic founder cell. On average, 6.8 more years are required for the acquisition of mutations conferring metastatic ability, suggesting an opportunity to intervene early in this disease.[10]

A substantial minority of patients with PDAC harbor a pathogenic germline gene variant associated with increased cancer risk, with estimates ranging from 3.8% to 9.7%. These variants occur most commonly in genes responsive to DNA damage repair, specifically *BRCA2*, *BRCA1,* and *ATM*.[11–13] Less commonly, germline variants in the mismatch repair genes *MLH1*, *MSH2*, *MSH6,* and *PMS2*, associated with Lynch syndrome, are present. While only 1% of patients with PDAC harbor a germline variant in mismatch repair genes, this can have important therapeutic implications.[14] Consequently, current National Comprehensive Cancer Network guidelines recommend the germline testing of all patients with newly diagnosed PDAC using a gene panel that includes *BRCA1*, *BRCA2*, *ATM*, *MLH1*, *MSH2*, *MSH6,* and *PMS2*.[15]

DISEASE STAGING

Traditionally, tumor staging has and continues to dictate the treatment modalities used for treating PDAC. In the absence of screening tools or symptoms capable of detecting tumors at an early stage, only 10% to 20% of tumors are detected early enough that surgical resection is possible. Localized tumors, without evident metastases, are deemed resectable based on the absence of vascular involvement. A combination of surgery and chemotherapy are typically used to treat these patients. PDAC is considered locally advanced and unresectable in the absence of distant metastasis and in the presence of vascular encasement, usually involving the superior mesenteric artery (SMA), superior mesenteric vein (SMV), celiac axis (CA) and/or portal vein. Chemotherapy and increasingly radiation therapy are typically used to treat these patients. In patients who experience a dramatic treatment response, surgery can be considered, however, this can only be achieved in a minority of patients. Of increased research interest are patients with borderline resectable PDAC. These tumors have a lesser degree of vascular involvement, typically defined as $\leq 180^{\circ}$ involvement of key vascular structures such as the SMA, SMV, CA or PV.[16] Strategies combining chemotherapy and radiation therapy have been and continue to be studied, with a goal of rendering tumors eligible for surgical resection.

ADVANCES IN STANDARDS OF CARE: METASTASTIC DISEASE

The standard of care for treating all stages of PDAC has evolved dramatically since 2010, with major progress occurring by way of new developments in and innovative combinations of cytotoxic chemotherapeutic agents (**Table 1**). The PRODIGE 4/ACCORD 11 trial demonstrated superior progression-free survival (PFS) and overall survival (OS) of a regimen consisting of 5-fluorouracil (5-FU), leucovorin (LV), oxaliplatin and irinotecan (FOLFIRINOX) compared with gemcitabine in patients with untreated, metastatic PDAC.[17] This 342 patient, randomized phase III trial found a median PFS of 6.4 months versus 3.3 months (hazard ratio (HR) 0.47; 95% confidence interval (CI), 0.37–0.59; $P < .001$) and median OS of 11.1 months versus 6.8 months (HR 0.57; 95% CI, 0.45–0.73; $P < .001$) for the FOLFIRINOX versus gemcitabine cohorts, respectively. Subsequently, the Metastatic Pancreatic Cancer Trial (MPACT) showed that the addition of albumin-bound (nab) paclitaxel to gemcitabine also improved median PFS and OS compared with gemcitabine alone in patients with untreated, metastatic PDAC.[18] This 861 patient, randomized phase III trial, found a median PFS of 5.5 months versus 3.7 months (HR 0.69; 95% CI, 0.58–0.82; $P < .001$) and

Table 1
Key endpoint from randomized clinical trials discussed

Experimental arm	Control arm	PFS	OS	Reference
Metastatic				
Frontline				
FOLFIRINOX	gemctabine	6.4 v 3.3 mo	11.1 v 6.8 mo	Conroy et al,[17] 2018
gemcitabine/nab-paclitaxel	gemctabine	5.5 v 3.7 mo	8.5 v 6.7 mo	Von Hoff et al,[18] 2013
NALIRIFOX	gemcitabine/nab-paclitaxel	7.4 v 5.6 mo	11.1 v 9.2 mo	Wainberg et al,[19] 2023
2nd line and beyond				
5-FU/LV/Nal-IRI	5-FU/LV	3.1 v 1.5 mo	6.1 v 4.2 mo	Wang-Gillam et al,[20] 2016
Maintenance, *BRCA* mutated				
Olaparib	placebo	7.4 v 3.8 mo	18.9 v 18.1 mo[a]	Golan et al,[25] 2014
Perioperative				
perioperative gemcitabine + radiation	adjuvant gemcitabine	8.1 v 7.7 mo	16.0 v 14.3 mo[a]	Versteijne et al,[36] 2020
mFOLFIRINOX	gemcitabine/nab-paclitaxel	10.9 v 14.2 mo[a]	23.2 v 23.6 mo[a]	Ahmad et al,[37] 2020
Adjuvant				
FOLFIRINOX	gemcitabine	21.6 v 12.8 mo	54.4 v 35.0 mo	Conroy et al,[33] 2018
gemcitabine/nab-paclitaxel	gemctabine	19.4 v 18.8 mo[a]	40.5 v 36.2 mo[a]	Tempero et al,[34] 2023
gemcitabine/capecitabine	gemcitabine	13.9 v 13.1 mo[a]	28 v 25.5 mo	Neoptolemos et al,[35] 2017

[a] Difference is not statistically significant.

median OS of 8.5 months versus 6.7 months (HR 0.72; 95% confidence interval [CI], 0.62–0.83; $P < .001$) for the gemcitabine/nab-paclitaxel versus gemcitabine cohorts, respectively. Most recently, the NAPOLI-3 trial compared a novel, nanoliposomal formulation of irinotecan (Nal-IRI), combined with 5-FU, LV, irinotecan and oxaliplatin (NALIRIFOX) to gemcitabine/nab-paclitaxel in patients with untreated, metastatic PDAC. This 770 patient randomized phase III trial found a median PFS of 7.4 months versus 5.6 months (HR 0.69; 95% CI, 0.58–0.83; $P < .0001$) and median OS of 11.1 months versus 9.2 months (HR 0.83; 95% confidence interval [CI], 0.70–0.99; $P = .036$) for the NALIRIFOX versus gemcitabine/nab-paclitaxel cohorts, respectively.[19] These trials suggest superior survival for treatment with a triplet regimen combining infusional 5-FU, oxaliplatin and either irinotecan or Nal-IRI.

Beyond frontline treatment, the NAPOLI-1 trial demonstrated that Nal-IRI, together with 5-FU and LV, improved median PFS and OS compared with 5-FU/LV alone, in patients with metastatic PDAC after disease progression on gemcitabine-based treatment. This 417 patient, randomized phase III trial found a median PFS of 3.1 months versus 1.5 months (HR 0.57; 95% CI, 0.43–0.76; $P < .0001$) and a median OS of 6.1 months versus 4.2 months (HR 0.67; 95% CI, 0.49–0.92; $P = .012$) for the 5-FU/LV/Nal-IRI versus 5-FU/LV cohorts, respectively.[20]

Our group and others are actively studying biomarkers for selecting the optimal chemotherapy selection for individual patients. O'Kane and colleagues identified tumor GATA6 expression as a biomarker of PDAC subtyping, either basal (GATA6 low) or classical (GATA6 high), and intriguingly, this was associated with chemotherapy response.[8] GATA6 low and basal subtype tumors experienced significantly worse median OS compared with GATA6 high and classical subtype tumors when treated with FOLFIRINOX chemotherapy, but not gemcitabine/nab-paclitaxel. We participated in a large collaborative effort to develop and characterize patient-derived organoids (PDOs) as a model system for studying PDAC biology and therapeutics.[21] PDOs can be derived reliably from individual patients and grown in three-dimensional tissue culture indefinitely. Tiriac and colleagues found that the drug responses of PDOs paralleled patient outcomes. Furthermore, gene-expression signatures could be derived that correlated well with treatment response to gemcitabine and oxaliplatin.[22] Our group has also pioneered work profiling circulating tumor cells to predict chemotherapy response.[23] We have developed an innovative invasion assay to isolate circulating tumor and invasive cells from peripheral blood and perform expression profiling in these cells to predict treatment response to individual chemotherapeutic agents. Our most recent study enrolled 70 patients with newly diagnosed advanced PDAC prior to receiving either FOLFIRINOX or gemcitabine/nab-paclitaxel at a 1:1 ratio. Our drug profiling classified patients as "sensitive" if patients were treated with the regimen, either FOLFIRINOX or gemcitabine/nab-paclitaxel, containing the single, highest scoring drug, otherwise samples were classified as "resistant." Patients classified as sensitive experienced longer PFS (7.8 months vs 4.2 months; $P = .0002$) and OS (21.0 months vs 9.7 months; $P = .002$) compared with those who were resistant. There was no significant difference in survival based solely on the regimen received, and the Assay predicted survival regardless of the regimen administered. These and other predictive tools are being actively validated presently in an ongoing clinical trial.[9]

Developing targeted therapies effective for treatment PDAC has been challenging. Although the EGFR inhibitor erlotinib was shown by Moore and colleagues in 2007 to have modest efficacy in advanced PDAC, the benefit was not clinically meaningful, and was outweighed by associated toxicities.[24] Patients harboring pathogenic alterations in DNA damage repair genes such as *BRCA1* and *BRCA2* have been shown

to have increased sensitivity to platinum-based chemotherapy[25] and the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib.[26] The POLO trial enrolled patients with pathogenic germline *BRCA* mutations whose disease had not progressed after $\geq$ 16 weeks of frontline platinum-based chemotherapy. Patients were randomized to either olaparib or placebo. Patients in the olaparib arm experienced significantly longer time to progression compared with placebo (HR, 0.44; 95% CI, 0.30–0.66; $P < .0001$); however, median OS was not significantly different. Expanding these findings to patients with other DNA damage repair deficiencies, and developing more effective therapies, are currently under active investigation.

While therapies designed to stimulate the immune system have improved outcomes in many cancer types, the same cannot be said in PDAC. Several trials testing immune checkpoint inhibitors targeting programmed cell death protein 1 ligand (PD-L1)[27] and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)[28] have shown these approaches to be entirely ineffective for the treatment of PDAC. A small subset of patients with PDAC (~1%) harbor pathogenic alterations in mismatch repair (MMR) genes, such as *MLH1*, *MSH2*, *PMS2,* and *MSH6*. The KEYNOTE-158 phase II trial treated patients with advanced PDAC, MSI-high/dMMR after progression on chemotherapy with the PD-1 inhibitor pembrolizumab.[14] Twenty-two patients were enrolled with an overall response rate (ORR) of 18.2% and a median duration of response of 13.4 months.

ADVANCES IN STANDARDS OF CARE: LOCALLY ADVANCED AND EARLY-STAGE DISEASE

Developments in the metastatic setting have informed studies and progress for treating locally advanced, unresectable, and borderline resectable disease. A number of studies have shown encouraging results from the administration of combination chemotherapy, particularly FOLFIRINOX, yielding high rates of surgical resection and survival.[29,30] Results from trials studying the role of radiation therapy have been disappointing, as typified by the LAP07 trial, a randomized phase III trial that did not show a benefit of standard dose and fraction chemoradiation after gemcitabine compared with gemcitabine alone in patients with locally advanced PDAC.[31] This study also included a randomization for erlotinib, which also did not show any benefit. Advancements in both chemotherapy and radiation have spurred interest in revisiting this approach. Our group has pioneered a hypofractionated ablative radiation approach, with promising results, both with regards to efficacy and safety.[32] These results stand in contrast to results from the multicenter AO21501 phase II trial, which did not show a benefit of adding stereotactic body radiotherapy to FOLFIRINOX chemotherapy in patients with borderline resectable PDAC. Further work to optimize the timing and dosing of chemotherapy and radiation are needed and are areas of active study.

Advancements in chemotherapy regimens have also translated to the adjuvant and perioperative setting. The pivotal randomized phase III trial conducted by the Canadian Cancer Trials and Unicancer-GI–PRODIGE Groups randomized 493 patients with resected PDAC to 24 weeks of either modified (m)FOLFIRINOX or gemcitabine adjuvant chemotherapy.[33] A significant benefit was seen in the mFOLFIRINOX cohort, with a median disease-free survival (mDFS) of 21.6 months versus 12.8 months (HR 0.58; 95% CI, 0.46–0.73; $P < .001$) and mOS of 54.4 months versus 35.0 months (HR0.64; 95% CI, 0.48–0.86; $P = .003$) in the gemcitabine cohort. A similar clinical benefit was not seen for gemcitabine/nab-paclitaxel in the adjuvant setting when compared with gemcitabine.[34] Not all patients are good candidates for mFOLFIRINOX

chemotherapy in the adjuvant setting. The ESPAC-4[35] trial randomized 732 patients to a combination of gemcitabine and capecitabine compared with gemcitabine alone for 24 weeks after surgical resection. The mOS was 28.0 months compared with 25.5 months (HR 0.82; 95% CI, 0.68–0.98; $P = .032$) in the gemcitabine/capecitabine and gemcitabine alone cohorts, respectively.

There remains great interest in the utilization of chemotherapy in the perioperative and neoadjuvant settings for treating patients with resectable PDAC. The PREOPANC trial provided intriguing support for this approach.[36] This phase III trial randomized 246 patients to either gemcitabine-based preoperative chemoradiotherapy followed by surgical resection and adjuvant gemcitabine chemotherapy, or upfront surgery followed by adjuvant gemcitabine. The R0 resection rate was higher (71% vs 40%) in the preoperative chemoradiotherapy group compared with the adjuvant chemotherapy group. The mOS was favorable (16.0 months vs 14.3 months (HR 0.78; 95% CI, 0.58–1.05; $P = .096$) but not significantly improved in the preoperative compared with the adjuvant treatment group. Interestingly, in a subset of patients who ultimately underwent surgical resection, mOS was improved in the preoperative treatment group (35.2 months vs 19.8 months; HR, 0.58; 95% CI, 0.35–0.95; $P = .029$). The SWOG S1505 trial compared perioperative chemotherapy with mFOLFIRINOX to gemcitabine/nab-paclitaxel.[37] This randomized phase II trial enrolled 147 patients with resectable PDAC to one of these regimens administered more than 12 weeks before and 12 weeks after surgical resection. No significant difference was seen between the 2 cohorts with regards to mOS or mDFS. Further work is needed and is ongoing to determine the optimal treatment regimen and timing.

ADVANCES IN EXPERIMENTAL THERAPEUTICS

Although significant progress has focused on innovative combinations and formulations of cytotoxic chemotherapeutic agents, progress with regards to targeted agents and immune therapies have been more challenging. A number of promising approaches are currently being tested; selected examples are discussed.

TARGETING KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG

No target has held the promise and challenge of KRAS, due to the oncogenic role and near-universal presence in PDAC. Mutated *KRAS* has until recently proven difficult to drug due in part to its smooth protein surface, strong grip of the GTP-binding pocket to its substrate and complexity of both upstream and downstream signaling pathways.[38] Elegant medical chemistry has finally led to initial breakthroughs. The G12 C variant of *KRAS* was the first to be successfully targeted. AMG510 (sotorasib) and MRTX849 (adagrasib) were 2 of the lead candidates to enter clinical trial testing. AMG510 is a small molecule inhibitor that specifically inhibits *KRAS* G12 C by binding and locking KRAS in the inactive GDP binding state.[39,40] The G12 C variant is much more common in nonsmall-cell lung cancer (13%) and less common in colorectal cancer (1%–3%) PDAC (1%–2%). The phase I trial of sotorasib showed promising safety and efficacy results.[41] This study was enriched for patients with lung and colorectal cancer, all heavily pretreated and harboring a *KRAS* G12 C mutation. Notably, 32.2% of patients with lung cancer had an objective response, 88.1% with disease control and their mPFS was 6.3 months. Responses were also seen in patients with PDAC enrolled. A follow-up phase I/II study was conducted, enrolling 38 patients with metastatic and pretreated PDAC harboring *KRAS* G12 C mutation.[42] Promising objective response rate of 21%, an mPFS of 4.0 months, and an mOS of 6.9 months were seen, and treatment was generally safe. Adagrasib, similarly, shows promising early

clinical results. In the phase II KRYSTAL-1 trial, 64 patients were accrued, including 21 with *KRAS* G12 C mutated PDAC. Adagrasib was found to be well tolerated and active, with a 33.3% objective response rate, mPFS of 5.4 months, and mOS of 8.0 in the PDAC cohort.

The development of inhibitors targeting the common pathogenic *KRAS* variants present in PDAC is perhaps an even more important recent advance. Medicinal chemistry was used to modify MRTX849 to specifically inhibit *KRAS* G12D, the most common PDAC variant.[43] The most promising compound, MRTX1133, is currently in clinical trial testing (ClinicalTrials.gov ID NCT05737706). Several other *KRAS* G12D inhibitors with high specificity and preclinical activity are currently in developments, including TH-Z827 and TH-Z835.[44] The tricomplex inhibitor, RMC-9805, binds covalently and specifically to KRAS G12D in the GTP-bound state, has promising preclinical activity, and is currently in early-phase clinical trial testing (ClinicalTrials.gov ID NCT06040541).[45] A number of other promising approaches to target *KRAS* are in clinical trial testing. One example involves the selective ubiquitination of target proteins, leading increased proteasome trafficking and degradation. ASP3082 selectively binds and induces the ubiquitination of KRAS G12D and is currently in early-phase clinical trial testing (ClinicalTrials.gov ID NCT05382559).

Effective strategies to target *KRAS* represent a major advance in treating PDAC. Despite promising early results, it is clear that these first generation of *KRAS* inhibitors are not capable of inducing cures or long-term remissions in the majority of patients treated. Further work to develop more effective inhibitors, as well as complimentary and synergistic approaches are underway and greatly needed.

IMMUNE THERAPY

The difficulty in leveraging the immune system to fight PDAC has been attributed to numerous factors, particularly an immunosuppressive tumor microenvironment and low mutation burden. Several promising efforts to overcome these obstacles are discussed.

As mentioned earlier, proof of principle has been established that for selected patients with DNA mismatch repair deficiency (dMMR) leading to microsatellite instability (MSI-H), checkpoint inhibition can be effective in PDAC.[14] Beyond the small cohort of patients with PDAC with these features (~1%), there is great interest in identifying other patients likely to benefit from immune therapy. Reiss and colleagues conducted a phase Ib/II study, using ongoing platinum chemotherapy response to select and randomize patients to treatment with a combination of the PARP inhibitor niraparib and either the CTLA-4 inhibitor ipilimumab or the PD-1 inhibitor nivolumab.[46] 91 patients were enrolled; interestingly, patients in the niraparib and ipilimumab cohort experienced a 6-month PFS of 59.6%, compared with 20.6% in the niraparib and nivolumab cohort. Validation of this study could yield a promising maintenance approach for patients following induction FOLFIRINOX chemotherapy. An ongoing study to further tease out genomic profiles and response to the PARP inhibitor olaparib with the PD-1 inhibitor pembrolizumab could help to validate and help select patients likely to benefit from this approach.[47]

While chimeric antigen receptor (CAR) T-cell therapy approaches have revolutionized the treatment of liquid tumors, translating these approaches to solid tumors, including PDAC, has been largely unsuccessful. Two small series show proof of principle. The first was a report on 2 patients with HLA-C*08:02 and *KRAS* G12D PDAC. Autologous T cells were engineered to target *KRAS* G12D and administered.[48] In one patient, metastatic lung lesions regressed, a partial response was achieved and was

durable at 6 months of follow-up, with engineered T cells representing > 2% of circulating T cells. A second treated patient experienced significant cytokine release syndrome and only a transient tumor response. This approach is limited to patients with HLA-C*08:02, which is relatively rare, however, preliminary results are promising. Separately, scientists at the National Cancer Institute have identified KRAS neoantigens presented by HLA-A*11:01, an phase I/II clinical trial in ongoing (ClinicalTrials.gov ID NCT03745326).[49] A second proof of principle approach used CART cells engineered to target the Claudin18.2 tight junction isoform, often overexpressed in gastric cancer and PDAC. This CAR-CLDN18.2 product demonstrated activity in preclinical models and was tested in a phase I pilot study in 12 patients, 7 with advanced gastric cancer and 5 with advanced PDAC.[50] Treatment was well-tolerated and 1 PDAC patient had a partial response. Overall, the ORR was 33.3%, mPFS was 130 days.

Vaccine-based approaches have long been studied for treating PDAC with limited efficacy. One of the earliest and most promising vaccines developed was the GVAX vaccine, formulated from irradiated, granulocyte-macrophage colony-stimulating factor secreting allogeneic PDAC cell lines.[51] Initial promising results, however, were not validated in later phase clinical testing, even when combined with chemotherapy and other immune-stimulating agents.[52] More recently, the development of mRNA vaccine technology has allowed for the development of vaccines targeting patient-specific neoantigens. Balachandran and colleagues performed the DNA sequencing of resected tumors from 16 patients with early stage PDAC.[53] Neoantigens were computed, and individualized mRNA vaccines were manufactured for each patient. The autogene cevumeran vaccine was well-tolerated. Half of vaccinated patients (8/16) mounted a neoantigen-specific T cell response. Incredibly, median RFS was not reached in the 8 responders, compared with 13.4 months in the 8 nonresponders (HR 0.08; 95% CI, 0.01–0.4; $P = .003$). A randomized phase II trial to validate these promising results is currently underway (ClinicalTrials.gov ID NCT05968326).

SUMMARY

Significant progress has been made toward developing innovative therapies for PDAC. New and innovative combinations of cytotoxic chemotherapies have improved survival in perioperative and metastatic settings. Targeted and immune therapies have improved survival in the subset of patients with DDR deficiency and MSI-high/dMMR. New and innovative approaches targeting *KRAS* and immune therapies aim to have broad applicability.

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