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Current Management and Future Directions in Metastatic Pancreatic Adenocarcinoma

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Abstract

Of the anticipated 50,000 individuals expected to be diagnosed with pancreatic cancer in 2016, the majority will have metastatic disease. Given the noncurative nature of advanced pancreatic adenocarcinoma, treatment is aimed at inducing disease regression, controlling symptom, and extending life. The last 5 years have been marked by advances in the treatment of metastatic pancreatic cancer, specifically the approval by the US Food and Drug Administration of 2 combination chemotherapy regimens and the widespread use of a third, which have reproducibly been shown to improve survival. Ongoing studies are building on these regimens along with targeted and immunotherapeutic agents. This article will review the current treatment standards and emerging targets for metastatic pancreatic cancer.

Keywords

chemotherapy; metastatic; pancreatic cancer; targets; treatment standards

INTRODUCTION

Pancreatic adenocarcinoma (PAC) is expected to be diagnosed in approximately 53,070 individuals in 2016 and is the 11th most common cause of cancer. However, this disease represents the third highest cause of cancer-related deaths, with 41,780 deaths estimated to occur in 2016.¹ This review will focus on standard therapy for patients with metastatic PAC and emerging directions.

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Anna M. Varghese: Conceptualization, writing-original draft, and writing-review and editing. **Maeve A. Lowery:** Writing-review and editing. **Kenneth H. Yu:** Writing-review and editing. **Eileen M. O'Reilly:** Conceptualization, writing-original draft, and writing-review and editing. **Anna M. Varghese** and **Eileen M. O'Reilly** are responsible for the overall content.

Chemotherapy in the Treatment of Metastatic Disease

Cytotoxic chemotherapy—In 1997, gemcitabine was determined to be the standard treatment for patients with metastatic PAC when it was identified as being superior to 5-fluorouracil (5-FU) in a randomized study of 125 patients. Patients receiving gemcitabine were found to have improved overall survival (OS) compared with those receiving 5-FU (median OS of 5.7 months for gemcitabine and 4.4 months for 5-FU [$P=.0025$]).² Many gemcitabine-based combinations have been evaluated to date, and the majority of trials have found no meaningful improvements when combining gemcitabine with cytotoxic agents (Table 1).^{3–20} Two meta-analyses of these trials did note improvements in OS and the response rate (RR) with gemcitabine-based combinations for those patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1.^{21,22}

In 2011, the PRODIGE 4/ACCORD 11 study (Partenariat de Recherche en Oncologie Digestive/Actions Concertées dans les Cancers Colo-Rectaux et Digestifs) was reported and evaluated a combination of 5-FU, leucovorin (LV), irinotecan, and oxaliplatin (FOLFIRINOX) compared with gemcitabine for patients with newly diagnosed metastatic PAC with a good PS (ECOG PS of 0–1).¹³ Patients receiving FOLFIRINOX experienced a median OS of 11.1 months with a 31.6% objective RR, compared with a median OS of 6.8 months (hazard ratio [HR], 0.57; 95% confidence interval [95% CI], 0.45–0.73) and an objective RR of 9.4% among patients receiving gemcitabine ($P<.001$).¹³ Significant increases in toxicity with FOLFIRINOX compared with gemcitabine were observed with regard to neutropenia (45.7% vs 21%; $P<.001$), diarrhea (12.7% vs 1.8%; $P<.001$), and neuropathy (9% vs 0%; $P<.001$). Although side effects were increased with this combination, fewer patients receiving FOLFIRINOX noted a degradation to their quality of life compared with patients receiving gemcitabine (31% vs 66%; HR, 0.47 [95% CI, 0.3–0.7]).²³ Those patients receiving FOLFIRINOX noted that time until deterioration was prolonged compared with that of patients receiving gemcitabine (HR, 4.7; 95% CI, 2.3–9.5).^{13,23} These findings suggest that improvement in symptoms outweighed the increased toxicities observed with FOLFIRINOX in patients with good PS.

Also in 2011, a phase 1/2 study of gemcitabine and nab-paclitaxel in 67 patients with an excellent PS demonstrated an RR of 48% with a median OS of 12.2 months.¹⁴ Due to these promising findings, the phase 3 Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) ensued, in which 861 patients (with an ECOG PS of 0–2 or a Karnofsky PS of 70%–100%) were randomized to receive gemcitabine and nab-paclitaxel or gemcitabine alone.¹⁵ This study reported an OS of 8.5 months and an RR of 23% for patients receiving gemcitabine and nab-paclitaxel compared with an OS of 6.7 months (HR, 0.72; 95% CI, 0.62–0.83) and an RR of 7% for patients receiving gemcitabine ($P<.0001$).¹⁵ It is interesting to note that the MPACT study included patients with an ECOG PS of 0 to 2, whereas the PRODIGE/ACCORD 11 study included only those patients with an ECOG PS of 0 to 1. Based on these data, the combination of gemcitabine and nab-paclitaxel is recommended as a first-line treatment of patients with metastatic PAC and either FOLFIRINOX or the combination of gemcitabine and nab-paclitaxel is an appropriate choice for the treatment of patients with untreated metastatic PAC.

Nanoliposomal irinotecan—Irinotecan has known activity in PAC as evidenced by its role in FOLFIRINOX and in multiple single-agent and combination studies.^{7,13,24–29} Nanoliposomal irinotecan includes the free base of irinotecan within a liposome barrier, which impairs irinotecan metabolism and allows for increased plasma and, potentially, intratumoral exposure of irinotecan and its active metabolite SN-38. In a single-arm phase 2 study in which patients previously treated with gemcitabine received nanoliposomal irinotecan, OS was measured at 5.2 months.³⁰ The phase 3 NAnoliPOsomal Irinotecan-1 (NAPOLI-1) study compared nanoliposomal irinotecan and 5-FU/LV among patients previously treated with gemcitabine.³¹ A total of 417 patients were randomized to treatment with nanoliposomal irinotecan plus 5-FU/LV, nanoliposomal irinotecan alone, or 5-FU/LV alone, with a median OS of 6.1 months, 4.9 months, and 4.2 months, respectively, reported. The combination of nanoliposomal irinotecan and 5-FU/LV compared with 5-FU/LV alone resulted in improvements in the median OS (6.1 months vs 4.2 months; HR, 0.67 [95% CI, 0.49–0.92]). The OS for patients receiving single-agent nanoliposomal irinotecan compared with 5-FU/LV alone was found to be similar (HR, 0.99; 95% CI, 0.77–1.28).³¹ As a result of these findings, the combination of 5-FU/LV and nanoliposomal irinotecan was approved by the US Food and Drug Administration for patients previously treated with gemcitabine-based therapy.

Targeted therapies in patients with metastatic PAC—Although targeted therapies have altered outcomes in several malignancies, their use has met with limited success in patients with PAC. One example is targeting epidermal growth factor receptor despite compelling preclinical rationale.^{16,17,32,33} In a randomized phase 3 study of gemcitabine compared with gemcitabine and erlotinib, the median OS was found to be significantly improved from 5.9 months to 6.2 months (HR, 0.82; 95% CI, 0.69–0.99).¹⁶ Although the combination of gemcitabine and erlotinib was approved as a treatment option in patients with metastatic PAC, the modest signal, toxicity, and more recent cytotoxic developments have resulted in low uptake of this regimen. Other studies evaluating gemcitabine in combination with targeted therapies such as the epidermal growth factor receptor-directed antibody cetuximab and antivascular agents have demonstrated no significant improvements (Table 1).^{1–20}

Treatment decision making in patients with metastatic PAC—In practice, the choice of which chemotherapeutic agents to use is determined by a patient's PS along with potential toxicities and patient preference. For fit patients, FOLFIRINOX, gemcitabine and nab-paclitaxel, or consideration of a clinical trial is recommended. For those patients with a lower PS (ECOG PS 2), single-agent gemcitabine, gemcitabine-based combinations along with supportive care, or supportive care alone is recommended.

To improve the tolerability of FOLFIRINOX, modifications to the regimen have been undertaken. Several single-institution, retrospective studies have reported elimination of the 5-FU bolus, using dose-reduced irinotecan, or using routine growth factor support.^{34,35} Similar OS and improved toxicity profiles have been reported in studies of full-dose and dose-adjusted FOLFIRINOX, suggesting that dose-adjusted FOLFIRINOX appears to be more tolerable than full-dose FOLFIRINOX with limited detrimental effects on efficacy.

Many questions remain regarding the use of these combinations for patients with untreated metastatic PAC. First, which regimen is superior: FOLFIRINOX or gemcitabine and nab-paclitaxel? Although these regimens have not been compared in the metastatic setting, insights into their comparative efficacy may come from the ongoing S1505 trial, a Southwest Oncology Cooperative Group study evaluating induction chemotherapy with FOLFIRINOX versus gemcitabine and nab-paclitaxel in patients with resectable PAC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02562716) identifier NCT02562716).

Second, what is the optimal sequencing of these regimens? In a retrospective study evaluating 57 patients receiving gemcitabine and nab-paclitaxel after experiencing disease progression while receiving FOLFIRINOX, patients received a median of 4 cycles of gemcitabine and nab-paclitaxel with a disease control rate of 58%, thereby suggesting that this combination can add significantly after first-line FOLFIRINOX. Notably, the median OS was 18 months from the time of first treatment with FOLFIRINOX.³⁶

Third, can we identify which patients are more likely to respond to gemcitabine-based or 5-FU-based regimens? Currently, there are no biomarkers with which to determine the likelihood of response. Yu et al have developed pharmacogenomic RNA-based expression arrays associated with sensitivity to cytotoxic treatments, including gemcitabine, nab-paclitaxel, FOLFIRINOX, and others.³⁷ These pharmacogenomic models were tested with circulating tumor cells from patients receiving treatment for metastatic PAC and were found to predict which patients were likely to respond to 5-FU-based therapies compared with gemcitabine-based therapies, thereby holding promise for a noninvasive, prospective method with which to match patients to a particular therapy.³⁷

Fourth, how does the combination of 5-FU/LV and nanoliposomal irinotecan fit into these regimens, and what is the optimal treatment after gemcitabine-based therapy? Data from the NAPOLI-1 trial add to several studies designed to answer this question. In Charite Okologie-003 (CONKO-003), a total of 160 patients previously treated with gemcitabine were randomized to treatment with either 5-FU/LV or 5-FU/LV and oxaliplatin.³⁸ The median OS in the 5-FU/LV and oxaliplatin arm was found to be significantly improved compared with that of patients treated with 5-FU/LV alone, at 5.9 months versus 3.3 months, respectively (HR, 0.66; 95% CI, 0.48–0.91).³⁸ However, conflicting findings were preliminarily reported in the PANCREOX study, in which 108 patients previously treated with gemcitabine were randomized to treatment with infusional and bolus 5-FU, LV, and oxaliplatin (FOLFOX) or 5-FU/LV, and the median OS was found to be inferior in patients receiving FOLFOX (6.1 months vs 9.9 months; $P=.02$).³⁹ Within the context of these differing results, the combination of 5-FU/LV and nanoliposomal irinotecan is an emerging standard after gemcitabine-based therapy.

Although many questions remain regarding the optimal sequencing of therapies in patients with advanced PAC, the advances in the last 5 years have unequivocally improved outcomes. Although the OS in patients with this disease is typically measured as <1 year, several retrospective and limited prospective studies cited above have noted an OS of 18 months in patients with good PS in this era of modern cytotoxic combination therapy.^{36,40–42}

Promising New Targets and Treatment Strategies in Patients With Metastatic PAC

Beyond cytotoxics, a major unmet need exists for new therapies. Historically, PAC has been characterized as a poorly immunogenic tumor harboring no clear actionable molecular alterations and hallmarked by a dense and inert stroma. Each of these features of PAC is being explored and, in some instances, debunked entirely. Preclinical work has demonstrated that there is a dynamic and inhibitory role of PACs and their associated stroma that may allow for evasion of the immune system. Exploiting this complex interplay among the tumor, immune system, and stroma is a focus of ongoing trials (Table 2) (Fig. 1).

Stromal targeting agents—The dense stroma associated with PAC provides a physical barrier to chemotherapy.^{43,44} Preclinical work from Hingorani et al have confirmed a changing interplay between the tumor and its stroma such that disease progression is associated with a robust desmoplastic reaction, thereby limiting delivery of therapeutic agents.^{45–47} The in vivo administration of PEGPH20, a pegylated recombinant hyaluronidase, alone and in combination with gemcitabine to mice models with PAC demonstrated degradation and depletion of hyaluronic acid, a component of the tumor stroma, with an improvement in RR and prolonged responses.⁴⁷ Ongoing trials are evaluating the combination of PEGPH20 with cytotoxic chemotherapy in patients with newly diagnosed PAC ([ClinicalTrials.gov](https://clinicaltrials.gov) identifiers NCT01839487, NCT01959139, and NCT02715804) (Table 2).

Heparin sulfate proteoglycans within the tumor stroma stimulate tumor growth, and necuparanib (M402) is a heparin sulfate mimetic that blocks these stimulatory activities. O'Reilly et al presented a phase 1 trial evaluating the combination of necuparanib, gemcitabine, and nab-paclitaxel, and a disease control rate of 88% was noted among the 16 patients who completed the first cycle of treatment.⁴⁸ This phase 2 study is currently ongoing ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT01621243) (Table 2).

Another dynamic component of the tumor stroma is mast cells, which are required for tumor progression and angiogenesis.⁴⁹ Preclinical models have suggested that ibrutinib, an inhibitor of mast cells, results in antitumor effect, and a trial currently is underway to evaluate its safety and efficacy in combination with chemotherapy ([ClinicalTrials.gov](https://clinicaltrials.gov) identifiers NCT02436668 and NCT02562898) (Table 2).⁵⁰

Application and investigation of immunotherapy treatments and strategies in PAC

—Some have argued that PAC is a poorly immunogenic tumor given that it lacks tumor-infiltrating lymphocytes and high numbers of somatic mutations, features that have been linked to diseases with responses to immune checkpoint inhibition with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or anti-programmed cell death protein 1 (PD-1) antibodies.^{43,51–58} In a trial of 27 unselected patients with PAC, single-agent checkpoint inhibitors demonstrated a modest signal of activity.⁵⁹ No patients experienced an objective initial response, although one patient did experience a delayed response.⁵⁹ These findings are consistent with molecular analysis of PACs, which has found that a subset of PACs may be more immunogenic than others, suggesting that immunotherapy may be helpful in a selected patient population.⁶⁰ In addition, preliminary reports of single-agent

check-point inhibition in patients with mismatch repair (MMR)-deficient pancreatic cancer are promising, with stable disease noted among 3 of 4 patients with MMR-deficient pancreatic cancer and 1 of 4 patients experiencing a partial response, thereby expanding on responses observed with checkpoint inhibition for patients with MMR-deficient colorectal cancers ([ClinicalTrials.gov](#) identifier NCT01876511).^{51,61} Given the synergistic effect of multiple agents targeting checkpoint blockade with anti-PD-1 and anti-CTLA-4 antibodies in melanoma, combination strategies are ongoing in PAC ([ClinicalTrials.gov](#) identifier NCT02558894) (Table 2).⁵⁴

The tumor stroma also contributes to immune system evasion. Fibroblasts within the stroma produce chemokine (C-X-C motif) ligand 1/2 (CXCL1/2), a cytokine that inhibits T-cell recruitment. CXCL1/2 inhibition was reported to work synergistically with checkpoint blockade to cause tumor regression in preclinical models.⁶² This combination strategy currently is being evaluated in a trial of ulocuplumab (antibody to C-X-C motif chemokine receptor 4 [CXCR4], a receptor for CXCL1/2) with nivolumab ([ClinicalTrials.gov](#) identifier NCT02472977) (Table 2).

The chemokine (C-C motif) ligand 2 (CCL2)/C-C chemokine receptor type 2 (CCR2) axis likely plays an important role in disease progression as well. CCL2 and its receptor CCR2 mobilize inflammatory monocytes to the tumor-stroma microenvironment to promote metastatic disease. Using in vivo PAC models, CCR2 inhibition was found to result in decreased tumor growth.⁶³ A phase 1 study found that the CCR2 inhibitor CCX872-B was tolerable as a single agent, and a phase 1B study currently is ongoing with CCX872-B combined with FOLFIRINOX ([ClinicalTrials.gov](#) identifier NCT02345408) (Table 2).⁶⁴

Immunotherapy using the GVAX and CRS-207 vaccines also has been studied in patients with PAC. GVAX induces T-cell response against PAC-associated antigens, including mesothelin. CRS-207 secretes mesothelin into antigen-presenting cells. The combination of CRS-207 and GVAX is believed to stimulate an autoimmune response to mesothelin-expressing PAC cells. Although preliminary reports evaluating the combination of these agents suggested a tolerable side effect profile and promising efficacy, an interim analysis from the phase 2b ECLIPSE (Safety and Efficacy of Combination *Listeria*/GVAX Pancreas Vaccine in the Pancreatic Cancer Setting) trial demonstrated no significant difference in OS for patients receiving CRS-207 with and without GVAX (3.8 months vs 5.4 months).^{65,66} However, treatment with CRS-207 alone did demonstrate outcomes similar to those of patients receiving chemotherapy (4.6 months), thereby suggesting some benefit to CRS-207.⁶⁶

The combination of checkpoint inhibitors and vaccines provides another therapeutic avenue. The STELLAR trial (Safety and Therapeutic Efficacy of Live-attenuated *Listeria*/GVAX with Anti-PD1 Regimen) currently is evaluating the activity of this regimen ([ClinicalTrials.gov](#) identifier NCT02243371) (Table 2). In this randomized phase 2 trial, patients receive CRS-207/GVAX with and without nivolumab with OS as the primary endpoint. Another recently completed but not yet reported randomized phase 2 trial study evaluated the role of ipilimumab with and without the PAC vaccine GVAX in the second-line setting

(Table 2). Further trials investigating novel combinations of immunotherapy, chemotherapy, and vaccines currently are ongoing, a selection of which are described in Table 2.

Deficiencies in homologous recombination and DNA repair as a biomarker for novel treatments in patients with PAC

Up to 10% to 15% of patients with PAC harbor an increased susceptibility to cancer due to an inherited cancer predisposition syndrome. The most common germline alterations are observed in the genes *BRCA1*, *BRCA2*, and *PALB2* (Partner And Localizer of BRCA2). As described by Salo-Mullen et al, approximately 15.1% (95% CI, 9.5%–20.7%) of patients who underwent genetic testing in a clinical genetics service at a tertiary care cancer hospital were found to have germline pathogenic mutations. Alterations were observed most often in the genes listed above and genes in the MMR pathway suggestive of Lynch syndrome. *BRCA1/2* and *PALB2* play critical roles in the homologous recombination and repair of DNA double-stranded breaks, and these impaired DNA repair pathways represent another therapeutic target with platinum agents and inhibitors of poly(ADP-ribose) polymerase (PARP).

Platinum agents cause interstrand crosslinks that ultimately lead to DNA double-strand breaks. In the setting of deficient homologous repair such as in *BRCA*-deficient tumors, platinum agents can exploit this weakness and have been shown to be effective.^{68,69} Lowery et al reported that 5 of 6 patients with PAC and germline *BRCA1/2* alterations achieved a partial response to platinum-containing regimens, and another retrospective review of 71 patients with *BRCA*-associated PAC noted an improvement in OS with platinum-containing regimens compared with those who did not receive platinum therapies (22 months vs 9 months; $P=.039$).^{68,69} Likewise, single-strand DNA breaks require repair and modification by PARP. PARP inhibition can further limit the ability to repair these single-strand DNA breaks, resulting in DNA double-strand breaks and cell death within the setting of impaired homologous recombination. In a phase 2 trial of 23 patients with a germline *BRCA1/2* alteration and PAC who received the PARP inhibitor olaparib, 22% achieved a complete or partial response and 35% achieved stable disease, a finding that is consistent with those reported in other *BRCA*-related tumors.⁷⁰ Given that PARP activity is increased within the setting of DNA damage, PARP inhibitors administered with platinum agents may have a synergistic effect that can be used to therapeutic benefit in patients with PACs with deficient homologous repair mechanisms.

Studies currently are ongoing to evaluate the role of platinum and PARP inhibitors in patients with *BRCA*-related PAC. Preliminary results from a phase 1B study in which patients with *BRCA1/2* or *PALB2* germline alterations received cisplatin, gemcitabine, and veliparib noted that 9 of 9 patients achieved disease control, with 5 of 9 patients achieving a partial response and 4 of 9 having stable disease.⁷¹ These findings suggest that deficient homologous recombination as identified by germline *BRCA1/2* or *PALB2* alterations is a biomarker for treatment with PARP inhibitors and platinum therapy. Several phase 2 studies evaluating platinum-based chemotherapy with and without PARP inhibitors currently are ongoing ([ClinicalTrials.gov](https://clinicaltrials.gov) identifiers NCT01585805 and NCT01489865) (Table 2). A phase 3 study is ongoing among patients with metastatic PAC and germline *BRCA*

alterations in which they receive maintenance therapy with a PARP inhibitor after disease stability is achieved on first-line platinum-based chemotherapy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02184195) identifier NCT02184195) (Table 2).

Several phase 3 trials also recently have been reported that have demonstrated no significant benefits after promising phase 1 and 2 studies, thereby highlighting the need for the proper selection of patients in phase 1 and 2 studies as well as the more efficient use of patient time and resources with randomized phase 2 studies (Table 3).^{72–75}

With respect to molecular understanding of PAC, the vast majority of cases harbor molecular alterations in 1 of the genes *KRAS*, *TP53*, *CDKN2*, and *SMAD4*, genes that have been challenging to target successfully using precision medicine approaches at this time. Bailey et al published a genomic analysis of 456 patients with PAC and identified that the most commonly mutated genes clustered around 10 pathways, including *KRAS* transforming growth factor- β , *WNT*, *NOTCH*, DNA repair, and others, many of which do provide promising therapeutic opportunities (a selection of which are described in Table 2).⁶⁰ In addition, many clinicians and patients are seeking next-generation sequencing approaches with which to search for targetable alterations in tumors. Given the growing number of “basket studies” with targeted therapies in which patients are selected based on a molecular alteration rather than a cancer’s site of origin, this presents another opportunity for investigational treatment.

Conclusions—The treatment of patients with metastatic PAC has evolved significantly, with several new active cytotoxic regimens (FOLFIRINOX, gemcitabine/nab-paclitaxel, and nanoliposomal irinotecan/5-FU), all of which currently are in common use and have collectively improved survival. The interplay of the immune system and stromal targeting as well as enhanced understanding of molecular genomics, the identification of biomarkers and selected treatments for certain patient subgroups (homologous repair deficiency), and the emerging ability to classify subsets of patients with this disease collectively contribute to the optimism that meaningful improvements in patient outcomes for this cancer are on the horizon.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016; 66:7–30. [PubMed: 26742998]
2. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997; 15:2403–2413. [PubMed: 9196156]
3. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol*. 2002; 20:3270–3275. [PubMed: 12149301]

4. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol.* 2004; 22:3776–3783. [PubMed: 15365074]
5. Louvet C, Labianca R, Hammel P, et al. GERCOR; GISCAD. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol.* 2005; 23:3509–3516. [PubMed: 15908661]
6. Reni M, Cordio S, Milandri C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol.* 2005; 6:369–376. [PubMed: 15925814]
7. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer.* 2006; 95:587–592. [PubMed: 16909140]
8. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol.* 2006; 24:3946–3952. [PubMed: 16921047]
9. Herrmann R, Godsky G, Ruhstaller T, et al. Gemcitabine Plus Capecitabine Compared With Gemcitabine Alone in Advanced Pancreatic Cancer: A Randomized, Multicenter, Phase III Trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol.* 2007; 25:2212–2217. [PubMed: 17538165]
10. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2009; 27:3778–3785. [PubMed: 19581537]
11. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 2009; 27:5513–5518. [PubMed: 19858379]
12. Colucci G, Labianca R, Di Costanzo F, et al. Gruppo Oncologico Italia Meridionale (GOIM); Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD); Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol.* 2010; 28:1645–1651. [PubMed: 20194854]
13. Conroy T, Desseigne F, Ychou M, et al. Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011; 364:1817–1825. [PubMed: 21561347]
14. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol.* 2011; 29:4548–4554. [PubMed: 21969517]
15. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013; 369:1691–1703. [PubMed: 24131140]
16. Moore MJ, Goldstein D, Hamm J, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007; 25:1960–1966. [PubMed: 17452677]
17. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol.* 2010; 28:3605–3610. [PubMed: 20606093]
18. Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol.* 2011; 12:256–262. [PubMed: 21306953]
19. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer

- and Leukemia Group B (CALGB 80303). *J Clin Oncol*. 2010; 28:3617–3622. [PubMed: 20606091]
20. Rougier P, Riess H, Manges R, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. *Eur J Cancer*. 2013; 49:2633–2642. [PubMed: 23642329]
 21. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol*. 2007; 25:2607–2615. [PubMed: 17577041]
 22. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer*. 2008; 8:82. [PubMed: 18373843]
 23. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol*. 2013; 31:23–29.
 24. Yi SY, Park YS, Kim HS, et al. Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2009; 63:1141–1145. [PubMed: 18839175]
 25. Cereda S, Reni M, Rognone A, et al. XELIRI or FOLFIRI as salvage therapy in advanced pancreatic cancer. *Anticancer Res*. 2010; 30:4785–4790. [PubMed: 21115942]
 26. Gebbia V, Maiello E, Giuliani F, Borsellino N, Arcara C, Colucci G. Irinotecan plus bolus/infusional 5-fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: a multicenter experience of the Gruppo Oncologico Italia Meridionale. *Am J Clin Oncol*. 2010; 33:461–464. [PubMed: 20142727]
 27. Neuzillet C, Hentic O, Rousseau B, et al. FOLFIRI regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and platinum-salts. *World J Gastroenterol*. 2012; 18:4533–4541. [PubMed: 22969226]
 28. Yoo C, Hwang JY, Kim JE, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer*. 2009; 101:1658–1663. [PubMed: 19826418]
 29. Zaniboni A, Aitini E, Barni S, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. *Cancer Chemother Pharmacol*. 2012; 69:1641–1645. [PubMed: 22576338]
 30. Ko AH, Tempero MA, Shan YS, et al. A multinational phase 2 study of nanoliposomal irinotecan sucrosfate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. *Br J Cancer*. 2013; 109:920–925. [PubMed: 23880820]
 31. Wang-Gillam A, Li CP, Bodoky G, et al. NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet*. 2016; 387:545–557. [PubMed: 26615328]
 32. Fjallskog ML, Lejonklou MH, Oberg KE, Eriksson BK, Janson ET. Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors. *Clin Cancer Res*. 2003; 9:1469–1473. [PubMed: 12684421]
 33. Tobita K, Kijima H, Dowaki S, et al. Epidermal growth factor receptor expression in human pancreatic cancer: significance for liver metastasis. *Int J Mol Med*. 2003; 11:305–309. [PubMed: 12579331]
 34. Mahaseth H, Brucher E, Kauh J, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas*. 2013; 42:1311–1315. [PubMed: 24152956]
 35. Ghorani E, Wong HH, Hewitt C, Calder J, Corrie P, Basu B. Safety and efficacy of modified FOLFIRINOX for advanced pancreatic adenocarcinoma: a UK single-centre experience. *Oncology*. 2015; 89:281–287. [PubMed: 26372905]
 36. Portal A, Pernot S, Arbaud C, et al. Nab paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after failure of FOLFIRINOX: results of an AGEO multicenter prospective cohort [abstract]. *J Clin Oncol*. 2015; 33 Pages. Abstract 4123.

37. Yu KH, Ricigliano M, Hidalgo M, et al. Pharmacogenomic modeling of circulating tumor and invasive cells for prediction of chemotherapy response and resistance in pancreatic cancer. *Clin Cancer Res.* 2014; 20:5281–5289. [PubMed: 25107917]
38. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol.* 2014; 32:2423–2429. [PubMed: 24982456]
39. Gill S, Ko Y, Cripps M, et al. PANCREOX: a randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT) [abstract]. *J Clin Oncol.* 2014; 32 Pages. Abstract 4022.
40. Portal A, Pernot S, Tougeron D, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after FOLFIRINOX failure: an AGEO prospective multicentre cohort. *Br J Cancer.* 2015; 113:989–995. [PubMed: 26372701]
41. Ramanathan RK, Lee P, Seng JE, et al. Phase II study of induction therapy with gemcitabine and nab-paclitaxel followed by consolidation with mFOLFIRINOX in patients with metastatic pancreatic cancer. *J Clin Oncol.* 2014; 32(suppl 3) abstr 224.
42. Goldstein D, Chiorean EG, Tabernero J, et al. Outcome of second-line treatment following nab-paclitaxel + gemcitabine or gemcitabine alone for metastatic pancreatic cancer. *J Clin Onc.* 2016; 34(supple 4S) abstr 333.
43. Ko AH. Progress in the treatment of metastatic pancreatic cancer and the search for next opportunities. *J Clin Oncol.* 2015; 33:1779–1786. [PubMed: 25918299]
44. Chu GC, Kimmelman AC, Hezel AF, DePinho RA. Stromal biology of pancreatic cancer. *J Cell Biochem.* 2007; 101:887–907. [PubMed: 17266048]
45. Hingorani SR. Cellular and molecular conspirators in pancreas cancer. *Carcinogenesis.* 2014; 35:1435. [PubMed: 24987024]
46. Stromnes IM, DelGiorno KE, Greenberg PD, Hingorani SR. Stromal reengineering to treat pancreas cancer. *Carcinogenesis.* 2014; 35:1451–1460. [PubMed: 24908682]
47. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell.* 2012; 21:418–429. [PubMed: 22439937]
48. O'Reilly E, Mahalingam D, Roach J, et al. Safety, pharmacokinetics, pharmacodynamics, and antitumor activity of necuparanib combined with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer: phase 1 results [abstract]. *J Clin Oncol.* 2015; 33 Pages. Abstract 4114.
49. Soucek L, Lawlor ER, Soto D, Shchors K, Swigart LB, Evan GI. Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors. *Nat Med.* 2007; 13:1211–1218. [PubMed: 17906636]
50. Masso-Valles D, Jauset T, Serrano E, et al. Ibrutinib exerts potent antifibrotic and antitumor activities in mouse models of pancreatic adenocarcinoma. *Cancer Res.* 2015; 75:1675–1681. [PubMed: 25878147]
51. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015; 372:2509–2520. [PubMed: 26028255]
52. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med.* 2014; 371:2189–2199. [PubMed: 25409260]
53. Clark CE, Beatty GL, Vonderheide RH. Immunosurveillance of pancreatic adenocarcinoma: insights from genetically engineered mouse models of cancer. *Cancer Lett.* 2009; 279:1–7. [PubMed: 19013709]
54. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med.* 2015; 372:2006–2017. [PubMed: 25891304]
55. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015; 373:1627–1639. [PubMed: 26412456]
56. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med.* 2015; 373:123–135. [PubMed: 26028407]

57. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012; 366:2455–2465. [PubMed: 22658128]
58. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010; 363:711–723. [PubMed: 20525992]
59. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother*. 2010; 33:828–833. [PubMed: 20842054]
60. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature*. 2016; 531:47–52. [PubMed: 26909576]
61. Le DT, Uram JN, Wang H, et al. PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers [abstract]. *J Clin Oncol*. 2016; 34(suppl 4S) Pages. Abstract 195.
62. Feig C, Jones JO, Kraman M, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc Natl Acad Sci U S A*. 2013; 110:20212–20217. [PubMed: 24277834]
63. Sanford DE, Belt BA, Panni RZ, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. *Clin Cancer Res*. 2013; 19:3404–3415. [PubMed: 23653148]
64. Hezel A, Eskens F, Sleijfer S, et al. Abstract B24: pharmacokinetic and pharmacodynamic profile of the novel, oral and selective CCR2 inhibitor CCX872-B in a Phase 1B pancreatic cancer trial. *Mol Cancer Ther*. 2015; 14(12 suppl 2):B24.
65. Le DT, Wang-Gillam A, Picozzi V, et al. Safety and survival with GVAX pancreas prime and Listeria Monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *J Clin Oncol*. 2015; 33:1325–1333. [PubMed: 25584002]
66. Aduro Biotech. Aduro Biotech announces phase 2b ECLIPSE trial misses primary endpoint in heavily pretreated metastatic pancreatic cancer. [press release] <http://investors.aduro.com/phoenix.zhtml?c=242043&p=irol-newsArticle&ID=2168543>. Accessed May 20, 2016
67. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al. Identification of germline genetic mutations in patients with pancreatic cancer. *Cancer*. 2015; 121:4382–4388. [PubMed: 26440929]
68. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. *Br J Cancer*. 2014; 111:1132–1138. [PubMed: 25072261]
69. Lowery MA, Kelsen DP, Stadler ZK, et al. An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions. *Oncologist*. 2011; 16:1397–1402. [PubMed: 21934105]
70. Kaufman B, Shapira-Frommer R, Schmutzler R, et al. Olaparib monotherapy in patients with advanced cancer and a germ-line BRCA1/2 mutation: an open-label phase II study [abstract]. *J Clin Oncol*. 2013; 31 Pages. Abstract 11024.
71. O'Reilly E, Lowery M, Segal M, et al. Phase IB trial of cisplatin (C), gemcitabine (G), and veliparib (V) in patients with known or potential BRCA or ALB2-mutated pancreas adenocarcinoma (PC) [abstract]. *J Clin Oncol*. 2014; 32 Pages. Abstract 4023.
72. OncoMed Provides Update on Tarextumab Phase 2 Pancreatic Cancer ALPINE Trial. 2016. [press release] <http://investor.shareholder.com/oncomed/releasedetail.cfm?ReleaseID=951460>. Accessed June 27, 2016
73. Van Cutsem E, Lenz H, Furuse J, et al. Evofosfamide (TH-302) in combination with gemcitabine in previously untreated patients with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma: primary analysis of the randomized, double-blind phase III MAESTRO study [abstract]. *J Clin Oncol*. 2016; 34(suppl 4S) Abstract 193.
74. Incyte announces decision to discontinue JANUS studies of ruxolitinib plus capecitabine in patients with advanced or metastatic pancreatic cancer. [press release]. <http://www.incyte.com/ir/press-releases.aspx>. Accessed June 27, 2016
75. Immunomedics provides update on phase 3 PANCRT-1 trial of clivatuzumab tetraxetan in patients with advanced pancreatic cancer. [press release]. <http://www.immunomedics.com/pdfs/news/2016/pr03142016.pdf>. Accessed June 27, 2016

Figure 1.

Selected investigational agents and targets in metastatic pancreatic cancer. ALK, anaplastic lymphoma kinase; CCL2, chemokine (C-C motif) ligand 2; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCL1/2, chemokine (C-X-C motif) ligand 1/2 (CXCL1/2); EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; HER3, human epidermal growth factor receptor 3; mTOR, mammalian target of rapamycin; MUC5AC, mucin 5AC, oligomeric mucus/gel-forming; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase.

TABLE 1**Clinical Trials Comparing Single-Agent Gemcitabine With Combination Chemotherapy**

Study	Therapy	No.	Overall Survival, Months	Response Rate
E2297 Berlin 2002 ³	Gemcitabine/5-FU	322	5.4 vs 6.7	5.6% vs 6.9%
Rocha Lima 2004 ⁴	Gemcitabine/irinotecan	342	6.6 vs 6.3	4.4% vs 16.1%
Louvet 2005 ⁵	Gemcitabine/oxaliplatin	313	7.1 vs 9	17.3% vs 26.8%
Reni 2005 ⁶	Cisplatin/epirubicin/5-FU/gemcitabine	99	Not reported	8.5% vs 38.5%
Stathopoulos 2006 ⁷	Gemcitabine/irinotecan	145	6.5 vs 6.4	10% vs 15%
Heinemann 2006 ⁸	Gemcitabine/cisplatin	195	6 vs 7.5	8.2% vs 10.2%
Herrmann 2007 ⁹	Gemcitabine/capecitabine	319	7.2 vs 8.4	7.8% vs 10%
E6201 Poplin 2009 ¹⁰	Gemcitabine/oxaliplatin	832	4.9 vs 5.7	6% vs 9%
Cunningham 2009 ¹¹	Gemcitabine/capecitabine	533	6.2 vs 7.1	12.4% vs 19.1%
GIP-1 Colucci 2010 ¹²	Gemcitabine/cisplatin	400	8.3 vs 7.2	10.1% vs 12.9%
PRODIGE Conroy 2011 ¹³	FOLFIRINOX	342	6.8 vs 11.1	9.4% vs 31.6%
Von Hoff 2011 ¹⁴	Gemcitabine/nab-paclitaxel	67	12.2 ^a	48% ^a
MPACT Von Hoff 2013 ¹⁵	Gemcitabine/nab-paclitaxel	861	6.7 vs 8.5	7% vs 23%
PA.3 Moore 2007 ¹⁶	Gemcitabine/erlotinib	569	5.9 vs 6.2	8% vs 8.6%
S0205 Philip 2010 ¹⁷	Gemcitabine/cetuximab	745	5.9 vs 6.3	8% vs 7%
Kindler 2011 ¹⁸	Gemcitabine/axitinib	623	8.3 vs 8.5	2% vs 5%
CALGB 80303 Kindler 2010 ¹⁹	Gemcitabine/bevacizumab	535	5.9 vs 5.8	10% vs 13%
Rougier 2013 ²⁰	Gemcitabine/aflibercept	427	7.8 vs 6.5	Not reported

Abbreviations: 5-FU, 5-fluorouracil; CALGB, Cancer and Leukemia Group B; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; GIP-1, Gruppo Italiano Pancreas 1; PRODIGE, Partenariat de Recherche en Oncologie Digestive.

^aSingle-arm study of gemcitabine and nab-paclitaxel only.

TABLE 2

Selected Ongoing Clinical Trials for Patients With Metastatic Pancreatic Cancer

Categories	ClinicalTrials.gov Trial No.	Phase	Drugs	Mechanism of Action	Key Endpoint(s)
Stromal targeting	NCT01621243	1, 2	Phase 1: GN and necuparanib Phase 2: GN ± necuparanib	Necuparanib (M402); heparin sulfate mimetic	Phase 1: DLTs Phase 2: OS
	NCT01839487	2	GN ± PEGPH20	PEGPH20; pegylated recombinant hyaluronidase	PFS
	NCT01959139	1, 2	Phase 1: FOLFIRINOX and PEGPH20 Phase 2: FOLFIRINOX ± PEGPH20	PEGPH20; pegylated recombinant hyaluronidase	Phase 1: DLT Phase 2: OS
	NCT02715804	3	GN ± PEGPH20	PEGPH20; pegylated recombinant hyaluronidase	PFS, OS
Immunotherapy	NCT02345408	1	FOLFIRINOX, CCX872-B	CCX872-B; CCR2 inhibitor	PFS
	NCT02436668	2, 3	GN ± ibrutinib	Ibrutinib; Bruton tyrosine kinase inhibitor	PFS
	NCT02562898	1, 2	GN and ibrutinib	Ibrutinib; Bruton tyrosine kinase inhibitor	DLT
	NCT01876511	2	MK-3475	MK-3475 (pembrolizumab); anti-PD-1 antibody	PFS
	NCT01896869	2	Arm A: ipilimumab and GVAX Arm B: FOLFIRINOX	GVAX: vaccine against mesothelin-expressing cancer cells Ipilimumab; anti-CTLA-4 antibody	OS
	NCT02243371	2	CY, GVAX, and CRS-207 ± nivolumab	GVAX: vaccine against mesothelin-expressing cancer cells CRS-207: modified <i>Listeria</i> that promotes mesothelin expression Nivolumab; anti-PD-1 antibody	OS
	NCT02472977	1, 2	Phase 1: ulocuplumab and nivolumab Phase 2: Arm A: ulocuplumab and nivolumab Arm B: investigator's choice	Ulocuplumab; CXCR4 antibody	MTD, ORR, OS
	NCT02558894	2	MEDI4736 ± tremelimumab	MEDI4736; anti-PD-L1 antibody Tremelimumab; anti-CTLA-4 antibody	ORR
	NCT02620423	1	Pembrolizumab, pelareorep, and chemotherapy (gemcitabine, irinotecan, or 5-FU/LV)	Pelareorep; oncolytic virus targeting RAS-mutant cells	DLT
	NCT02548169	1	Dendritic cell vaccine and chemotherapy (FOLFIRINOX or GN)		DLT
DNA damage response	NCT02268825	1, 2	MK-3475, FOLFOX	MK-3475 (pembrolizumab); anti-PD-1 antibody	DLT
	NCT02672917	1	MVT-5873 ± chemotherapy	MVT-5873; monoclonal antibody targeting CA 19-9	MTD
	NCT01489865	1, 2	5-FU/LV, oxaliplatin, ABT-888	ABT-888 (veliparib); PARPi	DLT
	NCT01585805	2	Part 1: veliparib, gemcitabine, and cisplatin Arm B: gemcitabine and cisplatin Part 2: veliparib	Veliparib; PARPi	Part 1: DLT Part 2: ORR
Novel cytotoxic agents and combinations	NCT02184195	3	Arm A: olaparib Arm B: placebo	Olaparib; PARPi	PFS
	NCT02581501	1	GN and capecitabine		DLT

Categories	ClinicalTrials.gov Trial No.	Phase	Drugs	Mechanism of Action	Key Endpoint(s)
Cancer stem cell targeting	NCT02324543	1, 2	Gemcitabine, docetaxel, capecitabine, cisplatin, and irinotecan		DLT, OS
	NCT02333188	1, 2	5-FU/LV, irinotecan, and nab-paclitaxel		DLT
	NCT01893801	1, 2	Nab-paclitaxel, cisplatin, and gemcitabine		ORR
	NCT01954992	3	Arm A: glufosfamide Arm B: 5-FU	Glufosfamide: novel alkylating agent	OS
	NCT02620800	1, 2	5-FU/LV, nab-paclitaxel, bevacizumab, and oxaliplatin		Phase 1: DLT Phase 2: 1-y OS
	NCT02551991	2	Arm A: nanoliposomal irinotecan, 5-FU/LV, and oxaliplatin Arm B: nanoliposomal irinotecan, 5-FU/LV Arm C: nab-paclitaxel and gemcitabine		PFS
	NCT02080221	2	FOLFOX and nab-paclitaxel		OS
	NCT02651727	1	GN and VS-4718	VS-4718: focal adhesion kinase inhibitor	DLT
	NCT02289898	2	GN ± demcizumab	Demcizumab: delta-like ligand 4 antibody	PFS
	NCT02671890	1	Gemcitabine ± disulfiram	Disulfiram: acetaldehyde dehydrogenase inhibitor	DLT
Targeted therapies and others	NCT02546531	1	Gemcitabine, pembrolizumab, and defactinib	Defactinib: focal adhesion kinase inhibitor	DLT
	NCT02231723	1	Arm A: GN and BBI608 Arm B: FOLFIRINOX and BBI608 Arm C: FOLFIRI and BBI608 Arm D: 5-FU/LV, BBI608, and MM-398	BBI608: STAT, stem cell inhibitor	DLT
	NCT02050178	1	GN and OMP54F28	OMP54F28: WNT pathway antagonist	DLT
	NCT02005315	1	GN and vantiectumab	Vantiectumab: WNT signaling inhibitor	DLT
	NCT02077881	1, 2	GN and indoximod	Indoximod: IDO pathway inhibitor	Phase 1: DLT Phase 2: OS
	NCT02352831	1, 2	Tosedostat	Tosedostat: aminopeptidase inhibitor	Phase 1: DLT Phase 2: PFS
	NCT02574663	1	Arm A: TGR-1202 Arm B: GN and TGR-1202 Arm C: FOLFOX and TGR-1202 Arm D: FOLFOX, bevacizumab, and TGR-1202	TGR-1202: PI3K delta inhibitor	DLT
	NCT02501902	1	Nab-paclitaxel and palbociclib	Palbociclib: CDK4/6 inhibitor	DLT
	NCT02514031	1	GN and beta-lapachone	Beta-lapachone: novel 1,2-naphthoquinone	DLT
	NCT02468557	1	Arm A: Idelalisib Arm B: Nab-paclitaxel and idelalisib Arm C: FOLFOX and idelalisib	Idelalisib: PI3K delta inhibitor	DLT
	NCT02451553		Afatinib and capecitabine	Afatinib: EGFR/HER2 inhibitor	DLT
	NCT02178436	1, 2	GN and KPT-330	KPT-330: selective inhibitor of nuclear export inhibitor	Phase 1: DLT Phase 2: OS

Categories	ClinicalTrials.gov Trial No.	Phase	Drugs	Mechanism of Action	Key Endpoint(s)
	NCT02227940	1	Arm A: Certinib and gemcitabine Arm B: Certinib and GN Arm C: Certinib, gemcitabine, and cisplatin	Certinib: ALK inhibitor	DLT
	NCT02155088	1	GN and BYL719	BYL719: PI3K alpha inhibitor	DLT
	NCT02146313	1	DMUC4064A	Antibody-drug conjugate to MUC16	DLT
	NCT02154737	1	Gencitabine and erlotinib		DLT
	NCT02138383	1	GN and enzalutamide	Enzalutamide: nonsteroidal antiandrogen	MTD
	NCT01783171	1	Dinaciclub and MK-2206	Dinaciclub: CDK4 inhibitor MK-2206: AKT inhibitor	DLT
	NCT01924260	1	Gencitabine and alisertib	Alisertib: aurora kinase A inhibitor	DLT
	NCT01506973	1, 2	Hydroxychloroquine, gemcitabine, and nab-paclitaxel	Hydroxychloroquine: antimalarial drug, inhibits autophagy	OS
	NCT02048384	1, 2	Metformin ± rapamycin	Rapamycin: mTOR inhibitor	Safety and feasibility
	NCT02650804	2	BPM31510 and gemcitabine	BPM31510: small molecule targeting cancer metabolism	ORR
	NCT02570711	2	GN ± ACP-196	ACP-196: Bruton tyrosine kinase inhibitor	ORR
	NCT02329717	2	PBI-05204	PBI-05204: Oleander derivative, inhibitor of AKT, FGF-2, NF-Kb, and p70S6K	OS
	NCT02340117	2	SGT-53 and GN	SGT-53: nanoliposomal delivery method targeting p53	PFS
	NCT02399137	2	GN ± MM-141	MM-141: IGF-1R and ErbB3 bispecific antibody	PFS
	NCT02080260	2	Regorafenib	Regorafenib: oral multityrosine kinase inhibitor	PFS
	NCT01905150	2	Gemcitabine, 5-FU/LV, irinotecan, and oxaliplatin ± vitamin C		1-y OS
	NCT01834235	1, 2	GN ± NPC-1C	NPC-1C: monoclonal antibody targeting colon and pancreatic cancer cells	OS
	NCT01666730	2	FOLFOX and metformin		OS
	NCT01652976	2	FOLFOX and dasatinib	Dasatinib: oral multi-tyrosine kinase inhibitor	PFS
	NCT02244489	1	Capecitabine, oxaliplatin, and momelotinib	Momelotinib: JAK1/2 inhibitor	DLT
	NCT02101021	3	GN ± momelotinib	Momelotinib: JAK1/2 inhibitor	OS

Abbreviations: 5-FU/LV, 5-fluorouracil/leucovorin; ALK, anaplastic lymphoma kinase; CCR2, C-C chemokine receptor type 2 (CCR2) antagonist; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCR4, C-X-C motif chemokine receptor 4; DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; FGF-2, fibroblast growth factor 2; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; GN, gemcitabine and nab-paclitaxel; HER2, human epidermal growth factor receptor 2; IDO, indoleamine 2,3-dioxygenase; IGF-1R, insulin-like growth factor receptor 1; JAK1/2, Janus kinase 1/2; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor kB; ORR, objective response rate; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1 PFS, progression-free survival; PI3K, phosphoinositide 3-kinase.

TABLE 3

Recently Reported Negative Trials in Patients With Metastatic Pancreatic Cancer

Study	ClinicalTrials.gov Trial No.	Therapy	No.	Overall Survival, Months	Response Rate
ALPINE 2016 ⁷²	NCT01647828	GN ± OMP-59R5	177	OMP-59R5: notch 2/3 inhibitor	
MAESTRO 2016 ⁷³	NCT01746979	Gemcitabine ± evofosfamide	693	Evofosfamide	7.6 vs 8.7 (<i>P</i> =.0589)
JANUS 1 and JANUS 2 2016 ⁷⁴	JANUS 1: NCT02117479 JANUS 2: NCT02119663	JANUS 1: ruxolitinib plus capecitabine JANUS 2: capecitabine ± ruxolitinib		Ruxolitinib: JAK 1/2 inhibitor	15% vs 19% (<i>P</i> =.18)
PANCRIPT-1 trial 2016 ⁵	NCT01956812	Gemcitabine ± yttrium-90-labeled clivatuzumab tetraxetan		Yttrium-90-labeled clivatuzumab: monoclonal antibody targeting mucin conjugated with localized radiation	

Abbreviations: GN, gemcitabine and nab-paclitaxel; JAK1/2, Janus kinase 1/2.