

Molecular targeted therapy for pancreatic adenocarcinoma: A review of completed and ongoing late phase clinical trials

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Molecular targeted therapy is widely utilized and effective in a number of solid tumors. In pancreatic adenocarcinoma, targeted therapy has been extensively evaluated; however, survival improvement of this aggressive disease using a targeted strategy has been minimal. The purpose of this study is to review therapeutic molecular targets in completed and ongoing later phase (II and III) clinical trials to have a better understanding of the rationale and progress towards targeted molecular therapies for pancreatic cancer. The PubMed database and the NCDI clinical trial website (www.clinicaltrials.gov) were queried to identify phase II and III completed and published (PubMed) and ongoing (clinicaltrials.gov) trials using the keywords: pancreatic cancer and molecular targeted therapy. The search engines were further limited by adding Phase II or III, active enrollment and North American. A total of 14 completed and published phase II/III clinical trials and 17 ongoing trials were identified. Evaluated strategies included inhibition of growth factor receptors (EGFR, PDGFR, VEGFR, IGF-1R), tyrosine kinase inhibitors, MEK1/2, mTOR blockade and PI3K and HER2-neu pathway inhibitors. Only one trial conducted by the National Cancer Institute of Canada and the PANTAR trial have demonstrated a survival improvement from EGFR inhibition using erlotinib. These trials ultimately led to FDA approval of erlotinib/Tarceva in advanced stage disease. It remains unclear whether new combinations of cytotoxic chemotherapy or immunotherapy plus molecular targeted therapy will be beneficial in management of pancreatic adenocarcinoma. Despite a number of phase II and III trials, to date, only erlotinib has emerged as an approved targeted therapy in pancreatic adenocarcinoma. There are several ongoing late phase trials evaluating a number of targets, the results of which will become available over the next 1 to 2 years.

Keywords Molecular targets, pancreatic cancer, clinical trials, phase II and III

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Introduction

Pancreatic adenocarcinoma is a challenging disease believed to arise from multiple genetic mutations. It has a concerning increasing incidence (1). It currently represents the fourth leading cause of cancer related death in the U.S, and it is projected to become the second by 2030 (2–4). Surgical resection has been shown to provide survival improvement and is the only potential curative treatment for this generally treatment refractory disease (5–7). Most patients, however,

are diagnosed at an unresectable stage thus underscoring the need to pursue novel alternatives or adjuncts to traditional cytotoxic chemotherapy regimens such as targeted therapy (8,9).

Molecular targets in cancer therapy were first approved in the U.S. by the Food and Drug Administration in February 2002 with the approval of imatinib mesylate (Gleevec) for the treatment of malignant metastatic and/or unresectable gastrointestinal stromal tumors (GIST). This Bcr-Abl tyrosine kinase inhibitor previously approved for chronic myelogenous leukemia in blast crisis, showed up to 43% tumor response rate in patients diagnosed with GIST (10). Since then, targeted therapies have been approved and widely utilized in renal, colorectal, gastroenteropancreatic neuroendocrine tumors, non-small cell lung cancer and malignant melanoma (11–15).

Received April 12, 2016; accepted July 21, 2016.

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Table 1 Molecular pathways and potential therapeutic targets in pancreatic adenocarcinoma

Pathway	Molecular Targets	Molecular Pathophysiology
K Ras, MAP2K and MEK pathway	MAP2K MEK	Kras encodes for GTP-binding proteins that are activated by EGFR, resulting in activation of MAP2K, PI3K-Akt. With consequent initiation of cellular transcription, translation cell cycle progression, cell survival and motility
Tyrosine kinase receptor pathway	EGFR, VEGFR, IGFR-1, PDFR	Phosphorylation of tyrosine residues results in intracellular protein recruitment with consequent activation of Ras/Raf/MEK/MAPK, PI3K-AKT/STAT family proteins with subsequent cell proliferation, oncogenesis, angiogenesis, inhibition of apoptosis, and tumor metastasis
PI3K/Akt pathway	PI3K Akt	Signaling through tyrosine kinase receptors, (EGFR, IGF-1R) activates PI3K with consequent activation of Akt, and later induction of the mTOR pathway. PI3K/Akt are involved in cell proliferation, survival, resistance to apoptosis, and angiogenesis.
mTOR signaling pathway	mTOR	Serine/threonine kinase like Akt is activated by PIK3/Akt with consequent regulation of gene transcription and cell proliferation
STAT3 signaling pathway	STAT 3	Phosphorylated by a Janus kinase (JAK), STAT3 is involved in cell proliferation, survival, motility, invasion, angiogenesis and inflammation
Poly (ADP-ribose)polymerase pathway	PARP	Family of nuclear protein enzymes involved in mediating DNA manage response and apoptosis
RET pathway	RET GDNF	Through MAPK pathway RET is associated with proliferation and invasion of pancreatic adenocarcinoma.
TP53 tumors suppressor pathway		Tp53 mutations are associated with loss of cell cycle arrest, apoptosis and DNA damage repair

Targeted therapy has also been extensively evaluated in Phase I and Ib studies in pancreatic adenocarcinoma. Strategies in this disease have included: tyrosine kinase inhibition, growth factor receptor inhibition and proto-oncogene blockers (16–22). To date, these studies have not resulted in a change from current cytotoxic based regimens, though some have shown enough promise to move on to phase II and some phase III trials. The purpose of this manuscript is to review relevant and potential therapeutic molecular targets for pancreatic adenocarcinoma and the completed and ongoing trials evaluating experimental and approved agents aimed at these targets. The following paragraphs provide a brief review of relevant and targetable pathways in pancreatic cancer and are summarized in Table 1 and Figure 1.

K-Ras

As many as 90% of patients diagnosed with pancreatic adenocarcinoma are found to have a mutated oncogenic K-Ras gene (23). This gene is involved in the early phase of pancreatic tumorigenesis. K-Ras encodes membrane bound GTP binding proteins that are activated by signaling pathways such as Epidermal Growth Factor Receptor (EGFR). When mutated, K-Ras locks the protein in an activated state, resulting in a continuous induction of signaling cascades [Mitogen-Activated Protein Kinases (MAPK/MEK), and Phosphatidylinositol 3-Kinase/AKT (PI3K-Akt)] responsible for proliferative cellular

processes including transcription, translation, inhibition of apoptosis, cell cycle progression and cellular motility (7). MAPK has also been found to promote proliferation and invasiveness of pancreatic adenocarcinoma when activated by the bond between glial derived neurotrophic factor (GDNF) and a proto-oncogene RET coded tyrosine kinase receptor (24).

Tyrosine kinase

Binding of growth factors to their respective receptors results in phosphorylation of tyrosine residues with consequent activation of signaling pathways [MAPK/MEK, PI3K-AKT, Ras, Raf, STAT]. Overexpression of EGFR, Vascular Endothelial Growth Factor Receptor (VEGFR), Platelet Derived Growth Factor Receptor (PDGFR) and the Insulin-Like Growth Factor Receptor (IGFR) due to mutations or loss of pathway regulation is associated with cellular proliferation, anti-apoptosis, anti-anoikis and angiogenesis (25). Overexpression of growth factor receptors has been documented in up to 90% of patients diagnosed with pancreatic adenocarcinoma (26,27). Growth factor receptors also play a significant role in activation of the Janus Kinase (JAK) pathway which in turn activates the STAT tyrosine phosphorylation pathway (JAK/STAT), which again promotes cell proliferation, invasion, angiogenesis and has been found to be associated with development of pancreatic metaplasia (28). HER2 is a related receptor tyrosine kinase encoded by proto-oncogenes that once activated

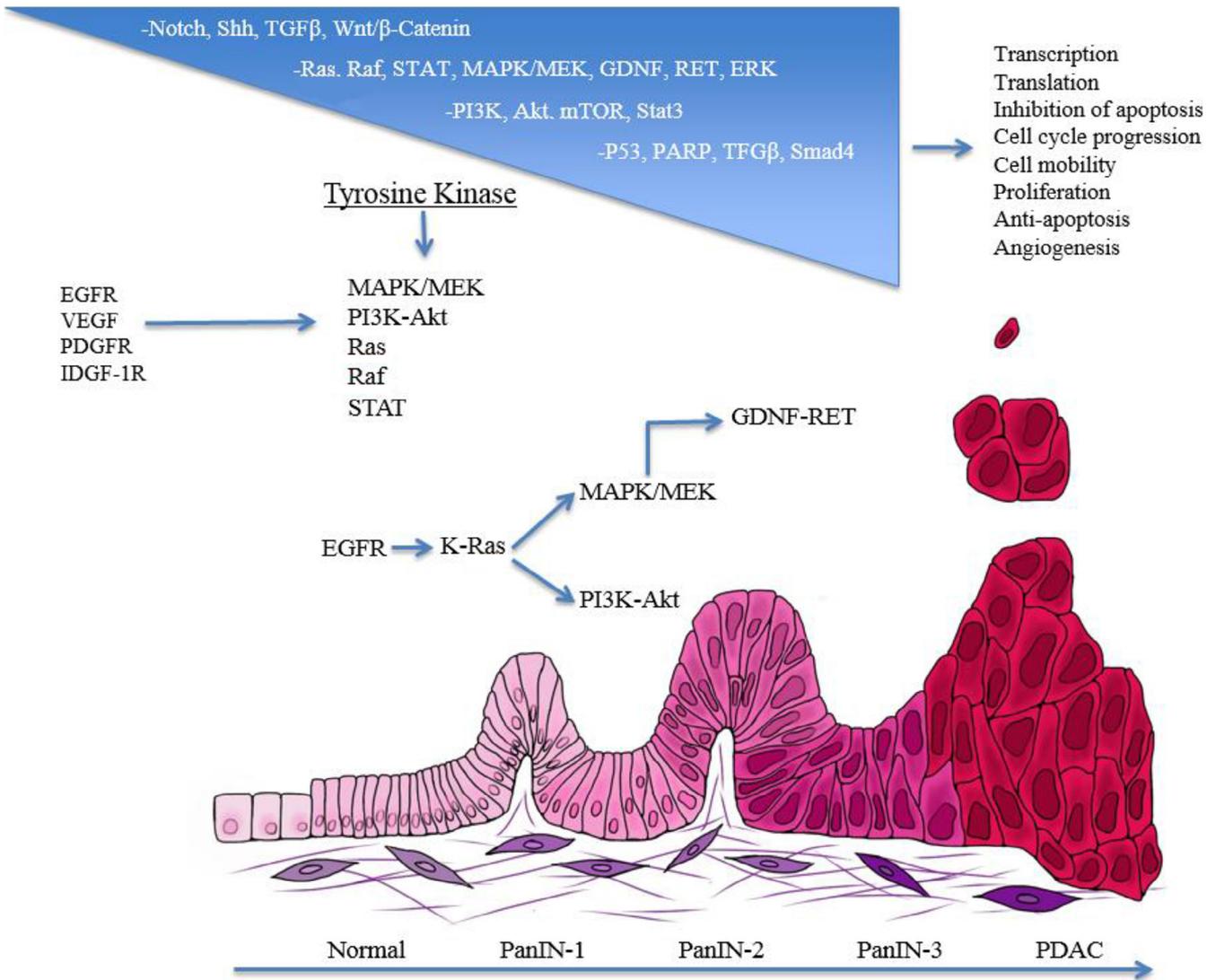


Figure 1 Molecular pathways and potential therapeutic targets in pancreatic adenocarcinoma.

promote cellular proliferation, migration and survival. HER2 expression is reported in around 50% of patients diagnosed with pancreatic adenocarcinoma (29).

PI3K/Akt and mammalian target of rapamycin (mTOR)

Signaling through tyrosine kinase receptors activates PI3K, which activates Akt with subsequent initiation of the mTOR pathway. This elaborated pathway promotes cellular proliferation, anti-apoptosis, angiogenesis and tumor invasion for which presence of the activated pathway in patients diagnosed with pancreatic adenocarcinoma has been reported to be a negative prognostic factor (30).

Poly ADP-Ribose pathway (PARP)

PARP are a group of enzymes involved in DNA damage response and apoptosis. Usually activated in cells expressing

stress or DNA damage, PARP can deplete cellular ATP during DNA repair with consequent cellular death (31).

Tumor suppressor (TP53) pathway

In oncogenic activation and stressed cells, P53 targets activation of genes involved in cell arrest, apoptosis, cellular metabolism and DNA damage repair (32). Mutations in the tumor suppressor pathway have been reported in up to 76% in patients diagnosed with pancreatic adenocarcinoma (33).

Notch ligand DLL4

Cell to cell signaling is involved in normal embryonic vascular development; the trans-membrane notch ligand receptors are fundamental in this process. Studies have shown an up-regulated expression of the delta like ligand 4 (DLL4) in pathologic angiogenesis, for which blockage of this pathway

should result in tumor angiogenic and progression of pancreatic cancer control (34).

PD-1/PDL-1

Programmed death ligand-1 (PDL-1) are ligands present on the surface of tumor cells ultimately processed and presented to the immune system by antigen presenting cells. Programmed death-1 (PD-1) is present on the surface of activated T cells and B cells and binding of this receptor by its associated ligand results in an immunosuppressive effect which allows tumors to evade immune destruction. Monoclonal antibody blockade of this cellular interaction interrupts this immuno-evasion pathway and facilitates immune system activation and destruction of tumors producing this ligand (35).

Methods

The PubMed database was queried to find completed and published studies using the key words: pancreatic cancer, molecular targeted therapy with limits on clinical trials, phase II and III trials. The NCDI clinical trial website (www.clinicaltrials.gov) was queried to identify ongoing, actively recruiting trials that evaluate agents against key molecular targets in the pathologic pathway of pancreatic cancer. Over 247 trials were identified and were limited by including only ongoing, multi-center, phase II or III trials conducted in North America.

Results—completed phase II and III clinical trials (Table 2)

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 (36)

In this trial, patients were randomly assigned 1:1 to treatment with gemcitabine + erlotinib (oral HER1/EGFR tyrosine kinase inhibitor) vs. gemcitabine + placebo. Evaluation of 569 patients with unresectable, locally advanced or metastatic pancreatic cancer demonstrated significantly longer overall survival in patients treated with gemcitabine + erlotinib (HR 0.82, 95%CI: 0.69–0.99, $p = 0.038$, median 6.24 vs 5.91 months for the gemcitabine + placebo arm). One year survival was also significantly improved in the erlotinib arm with 23% 1 year survival compared to 17% in the gemcitabine + placebo group ($p = 0.023$). Progression free survival was also significantly longer in the experimental arm (HR 0.77, 95% CI: 0.64–0.92, $p = 0.004$) with a median survival of 3.75 months vs. 3.55 months in the gemcitabine alone group. Treatment was well tolerated in both arms, but there was higher frequency of rash, diarrhea, infection, and stomatitis in the erlotinib group. The remaining adverse events were similar in both arms. There were no significant differences in global quality of life with exception of the diarrhea in the erlotinib group. Based on these data, the FDA approved erlotinib for use as a second line therapy for recurrent, metastatic pancreatic cancer.

Phase II open label study of erlotinib in combination with gemcitabine in unresectable and or metastatic adenocarcinoma of the pancreas: relationship between skin rash and survival (Pantar Study) (37)

EGFR is expressed in basal epidermal keratinocytes, hair follicles and sebaceous glands, and is also known to be over expressed in patients diagnosed with pancreatic adenocarcinoma. Erlotinib is an oral EGFR tyrosine kinase inhibitor, approved in combination with gemcitabine for the treatment of metastatic pancreatic cancer. Inhibition of EGFR is thought to be beneficial in the management of this neoplasm, but is associated with a high incidence of dermatitis. Based on this concept, the Pantar study evaluated the relationship between the skin rash produced by the use of Erlotinib and overall survival in patients diagnosed with advanced/metastatic pancreatic adenocarcinoma. The study classified the adverse event of the skin rash according to the NCI-CTC version 3. Analysis of 153 patients who received a combination of erlotinib + gemcitabine showed a significantly longer overall survival in patients who developed a grade 2 or higher rash compared to patients who developed no or a low grade rash (rash > 2, OS 11 months vs. rash < 2, OS: 5 months; $p = < 0.001$). The study confirmed a relationship between skin rash and longer overall survival in patients diagnosed with advanced pancreatic adenocarcinoma treated with combination gemcitabine and erlotinib.

Dose escalation to rash for erlotinib plus gemcitabine for metastatic pancreatic cancer: the phase II RACHEL Study (38)

The RACHEL trial was a multicenter randomized, phase II study that evaluated the impact of escalating erlotinib dose plus gemcitabine vs. gemcitabine plus standard dose erlotinib. From May 2008 to May 2010, 467 patients were enrolled in the study and 179 were randomized. Patients were given 4 weeks of treatment of 1000 mg m² gemcitabine plus 100 mg day erlotinib. Patients with grade 0-1 rash were randomized to a standard dose or escalation dose arms (erlotinib 150 mg/day with a 50 mg increase bi-weekly until development of grade 2 or higher rash or dose limiting toxicity, max dose 250 mg/day). Grade 2 or higher rash developed in 9.3% in the standard dose arm vs. 41% in the escalation arm. No difference in overall survival was encountered for standard vs. escalation dose treatment (standard OS: 8.4 vs. escalation OS: 7.0; $p = 0.20$). The authors concluded that in patients receiving erlotinib, dose escalation to skin toxicity did not result in improved survival.

Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomized phase 3 study (39)

This phase III double blinded randomized trial of gemcitabine with or without a VEGF inhibitor (axitinib) included patients with histologically or cytological confirmed metastatic or locally advanced pancreatic adenocarcinoma not amenable to curative resection. A total of 316 patients were included in each

Table 2 Clinical trials evaluating impact of chemotherapeutic agents against specific molecular targets

Target	Compound	Study Title	Group	Phase	Year	n	outcomes
EGFR	Erlotinib	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 Trial	National Cancer institute of Canada Clinical Trials Group(NCIC)	3	2007	569	Improved overall survival, (HR 0.82; 95% CI 0.69–0.99; p = 0.038) Greater one year survival (23% vs 17%), p = 0.023 Improved progression free survival, p = 0.004
	Erlotinib	Phase II Open Label Study of Erlotinib in Combination with Gemcitabine in Unresectable and or Metastatic Adenocarcinoma of the Pancreas: Relationship Between Skin Rash and Survival (Pantar Study)	European Society of Medical Oncology	2	2011	153	Longer overall survival in > grade 2 rash compared to <2 grade rash, OS: 11 months vs. 5 months; p = < 0.001.
	Erlotinib	Dose Escalation to Rash for Erlotinib plus Gemcitabine for Metastatic Pancreatic Cancer: The Phase II RACHEL Study	University Hospitals Leuven and KU Leuven	2	2014	179	No difference in overall survival for standard vs. escalation dose treatment, (standard OS: 8.4 months vs. escalation OS: 7.0 months; p = 0.20)
VEGFR	Axitinib	Axitinib plus Gemcitabine versus Placebo plus Gemcitabine in Patients with Advanced Pancreatic Adenocarcinoma: A Double-blind Randomized Phase III Study	University of Chicago Comprehensive Cancer Center	3	2011	632	No survival improvement conferred by axitinib plus gemcitabine compared to gemcitabine plus placebo. Median overall survival: 8.5 months vs 8.3 for the gemcitabine plus placebo, (HR 1.014, 95% CI 0.786–1.309, p = 0.54)
PDGFR	Imatinib	A phase II trial of Imatinib Mesylate in Patients with Metastatic Pancreatic Cancer	The Cancer Institute of New Jersey	2	2008	11	Lack of efficacy with no improvement in time to tumor progression, median survival or clinical benefit
	Vatalanib	Phase II trial of Vatalanib in Patients with Advanced or Metastatic Pancreatic Adenocarcinoma After First-line Gemcitabine Therapy	Pancreatic Cancer Research Group	2	2014	67	Good toleration to therapy and 6 moth survival rate 29%, 95% CI 18–41%, (improved compared to previous studies)
IGF-1R	Ganitumab	A Phase 3 Randomized, Double blind, Placebo-controlled Trial of Ganitumab or Placebo in Combination with Gemcitabine as First line Therapy for Metastatic Adenocarcinoma of the Pancreas: The GAMMA Trial	Dana-Farber Cancer Institute	3	2015	800	No improvement in overall survival: median OS 7.2 months for placebo, vs. 7.0 months in the 12 mg/kg ganitumab, (p = 0.49), and 7.1 months in the 20 mg/kg ganitumab, (p = 0.39) No improvement in progression-free survival: median PFS 3.7 for placebo vs. PFS 3.6, in the 12 mg/kg ganitumab, (p = 0.52), and median PFS 3.7months in the 20 mg/kg ganitumab, (p = 0.40)
mTOR	Everolimus	Oral mTOR Inhibitor Everolimus in Patients with Gemcitabine-Refractory Metastatic Pancreatic Cancer.	Dana-Farber Cancer Institute	2	2008	33	Minimal clinical activity in patients with gemcitabine-refractory metastatic pancreatic cancer with a 1.8 month progression free survival and 4.5months overall survival

(continued on next page)

Table 2 (continued)

Target	Compound	Study Title	Group	Phase	Year	n	outcomes
MEK1/2	Trametinib	A Randomized, Double-blind, Placebo-controlled Trial of Trametinib, an Oral MEK Inhibitor, in Combination with Gemcitabine for Patients with Untreated Metastatic Adenocarcinoma of the Pancreas	Sarah-Cannon Research Institute	2	2014	160	No difference in overall survival. Median OS 8.4 months for gemcitabine plus trametinib vs. 6.7 months in the gemcitabine plus placebo, (HR 0.98, 95%CI 0.67–1.44; p = 0.45) No difference in progression free survival. Median PFS 26 vs. 15 weeks. No difference in overall rate response, OR 22 vs. 18% for the placebo. No difference in duration of response, 23.1 weeks vs. 16.1 weeks in the placebo group
TK	Sorafenib	Sorafenib Does Not Improve Efficacy of Chemotherapy in Advanced Pancreatic Cancer: A GISCAD Randomized Phase II Study	Italian Group for the Study of Digestive Tract Cancer (GISCAD)	2	2013	114	No change in progression free survival. 4.3 months vs. 4.5 month in the sorafenib group, p = 0.65 No changes in overall survival. 7.5 months vs. 8.3months in the sorafenib group, p = 0.83
	Dasatinib	Phase II study of Dasatinib (BMS-354835) in Patients with Metastatic Adenocarcinoma of the Pancreas	Case Western Reserve University, National Cancer Institute	2	2013	51	No improvement in OS. Median OS 4.7 months. No improvement in progression free survival. Median PFS 2.1 months Single agent dasatinib does not have clinical activity in metastatic pancreatic adenocarcinoma
	Lapatinib	Lapatinib and Gemcitabine for Metastatic Pancreatic Cancer. A Phase II Study	Brown University Oncology Group	2	2011	29	No survival improvement compared to gemcitabine alone with a median survival 4 months (3.0–5.0 months)
PI3K	Enzastaurin	Gemcitabine Plus Enzastaurin or Single-agent Gemcitabine in Locally Advanced or Metastatic Pancreatic Cancer: Results of Phase II, Randomized, Non-comparative Study	US Oncology Research	2	2009	251	Comparable OS, PFS, RR and QOL between study arms with no increase in toxicities. OS: 5.6 vs. 5.1 months PFS: 3.4 vs 3.0 months
HER2-neu	Trastuzumab	Multicenter Phase II Trial of Trastuzumab and Capecitabine in Patients with HER2 Overexpressing Metastatic Pancreatic Cancer	Clinical Trials Unit, University Medical Center Freiburg	2	2012	17	Low HER2 expression. No improvement in overall survival (median OS 6.9 months, estimated 6 month OS: 52.9%) No improvement in progression free survival (median PFS 65 days, 23.5% at 12 weeks)

arm of the study. Efficacy of treatment was evaluated through overall survival analysis. No significant difference was encountered in survival analysis with a median of 8.5 for the gemcitabine plus axitinib group vs. 8.3 months for gemcitabine plus placebo ($p = 0.54$). The authors concluded no survival improvement with addition of axitinib to gemcitabine.

A phase II trial of imatinib mesylate (Gleevec) in patients with metastatic pancreatic cancer (40)

The authors aimed to assess the clinical efficacy and toxicity of imatinib mesylate (PGFR tyrosine kinase inhibitor at 400 mg/BID). Patients received a 28 day cycle single agent treatment. Disease progression was evaluated monthly with scans. Response was defined as lack of progression at 3 months. 11 patients were enrolled in the study, however only 9 were treated and evaluated (1 withdrew from the study after 9 days of treatment and one patient did not receive medication). Stable disease was noted in 3 patients after 2 cycles of therapy with later disease progression. Time to progression was 47 days (19–76) and median overall survival was 118 days. Medication dose had to be decreased to 600 mg/day because of unexpected grade 2–3 toxicities with good tolerance following change. With these data, the authors concluded a lack of efficacy from single agent imatinib–mesylate in terms of time to progression and survival.

Phase II trial of vatalanib in patients with advanced or metastatic pancreatic adenocarcinoma after first-line gemcitabine therapy (PCRT O4-001) (41)

Valatinib (oral tyrosine kinase inhibitor with high affinity for VEGFR and PDGFR) was evaluated in a multicenter phase II study conducted by the Pancreatic Cancer Research Team. Adverse events were included in the safety assessment and efficacy of treatment was evaluated through radiographic assessment and survival analysis. A total of 67 patients were included in the study. Adverse events included fatigue, nausea, hypertension, abdominal pain and liver function test elevation. Severe adverse events (\geq grade 3) were present in 10% of the study population. Around half of the study population (52%) was found to have progressive disease and almost 30% had stable disease. Six month survival rate was 29%. Fifteen patients survived 6 months or more and progression free survival was 8%. This trial demonstrated valatinib to be a well-tolerated second line therapy with a favorable 6 month survival rate.

A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of pancreas: the GAMMA trial (42)

The Gamma trial included 800 patients randomly assigned to one of three different groups [gemcitabine + placebo, or an IGF-1R antagonist: ganitumab (12 mg/kg) + gemcitabine, or ganitumab (20 mg/kg) + gemcitabine]. The primary end point evaluated was overall survival and secondary end points in-

cluded progression free survival, safety and efficacy. The authors report a 7.2 month median overall survival in the placebo arm vs. 7.0 month and 7.1 month in the ganitumab, 12 mg and 20 mg respectively. There was no difference in median progression free survival (3.7 months for placebo, 3.6 month for 12 mg/kg ganitumab and 3.7 months for the 20 mg/kg ganitumab). No unexpected toxicity was encountered and levels of IGF-1 were not associated with a treatment effect on overall or progression free survival. The authors established the safety of combination therapy (gemcitabine + ganitumab) but no improvement in survival.

Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer (43)

This multi-institution single arm, phase II study evaluated the effect of the oral mTOR inhibitor everolimus in patients with diagnosis of pancreatic adenocarcinoma with treatment failure to first line gemcitabine therapy. Toxicity, treatment response and survival were evaluated. A total of 33 patients were enrolled in the study. Treatment was well tolerated with thrombocytopenia and hyperglycemia being the most common adverse events. A majority of patients (67%) were removed from the study due to disease progression. 21% of patients had stable disease at 2 month follow up and 3% of patients continued to have stable disease at 4 month follow up. In the overall population the median progression free survival time was 1.8 months and the median overall survival time was 4.5 months. This trial demonstrated minimal clinical activity of everolimus on gemcitabine-refractory metastatic pancreatic cancer patients.

A randomized, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas (44)

Trametinib is an oral MEK1/2 inhibitor evaluated in this phase II study that aimed to determine its impact on overall survival as first line treatment combined with gemcitabine for patients with metastatic PCA. Secondary endpoints included: progression-free survival, overall response rate, duration of response and safety. A total of 160 patients were randomized, 80 patients received gemcitabine + trametinib and 80 patients received gemcitabine + placebo. No overall survival difference was observed between the treatment arms (median 8.4 months for the experimental arm vs. 6.7 months in the placebo + gemcitabine group, $p = 0.453$). Median progression free survival was also similar between groups (16.1 months in the gemcitabine + trametinib arm vs. 15.1 in the placebo + gemcitabine group, $p = 0.349$). Overall response rate was 22% in the gemcitabine group vs. 18% in the placebo group. Duration of response was longer in the gemcitabine + trametinib group with 23.9 weeks vs. 16.1 weeks in the placebo group. There were higher adverse events in the gemcitabine + trametinib arm (cardiac events and pneumonitis). The authors concluded no improvement in overall survival, progression free survival, overall response rate or

duration of response with addition of trametinib to gemcitabine regimen.

Sorafenib does not improve efficacy of chemotherapy in advanced pancreatic cancer: a giscad randomized phase II study (45)

This II phase study was designed to determine the activity of sorafenib (oral multikinase inhibitor RAS/RAF/MEK) as a first line treatment in patients diagnosed with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomly assigned in a 1:1 ratio to receive gemcitabine/cisplatin with or without sorafenib. A total of 114 patients were enrolled in the study. Around 3% of the patients had an objective response in both arms and 22% in the sorafenib arm had a stable response vs. 14% in the non-sorafenib group; 74.6% in the sorafenib group had progressive disease vs. 82.4% in the non-sorafenib group. Median progression free survival was similar between both arms ($p = 0.65$). No significant differences in overall survival were observed between arms ($p = 0.83$).

Phase II study of dasatinib (BMS-354835) in patients with metastatic adenocarcinoma of the pancreas (46)

Dasatinib is a multi-target kinase inhibitor that was evaluated in a phase II trial by Case Western Reserve University and the National Cancer Institute aiming to determine agent activity as first line monotherapy in patients diagnosed with metastatic pancreatic adenocarcinoma. The study included 51 patients and the authors reported no clinical benefit from single agent therapy in metastatic pancreatic adenocarcinoma. Median overall survival was 4.7 months.

Lapatinib and gemcitabine for metastatic pancreatic cancer, a phase II study (47)

Lapatinib is a reversible HER1–HER2 tyrosine kinase inhibitor that was given to 29 patients with histological confirmation of metastatic pancreatic adenocarcinoma. In this trial, 25 patients received combination therapy with lapatinib + gemcitabine and four patients were treated with single agent lapatinib. Treatment related toxicities were evaluated, the most common of which were hematologic (9/29pts), followed by infectious (cholangitis and pneumonia), diarrhea, dehydration, biliary obstruction, elevation of liver enzymes and renal failure (secondary to dehydration and contrast) in patients receiving lapatinib and gemcitabine for 3 consecutive weeks. Partial response was reported in 10% of patients. The 4 patients treated with single agent lapatinib progressed within one month.

Gemcitabine plus enzastaurin or single-agent gemcitabine in locally advanced or metastatic pancreatic cancer: results of phase II, randomized, non-comparative study (48)

This is a multicenter, randomized, non-comparative, open label trial evaluating the impact of enzastaurin (competitive inhib-

itor of protein kinase beta, and the related PI3K/AKT pathway) plus gemcitabine in patients diagnosed with advanced pancreatic adenocarcinoma. In this study, 86 patients were assigned to the gemcitabine + enzastaurin arm, and 44 patients to the gemcitabine alone group. No significant improvements or worsening quality of life were reported. Overall survival and progression free survival were similar in both groups: 5.1 and 3.4 months in the enzastaurin group vs. 5.1 and 3.0 months in the gemcitabine alone arm.

Multicenter phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer (49)

This study attempted to determine the potential impact of HER2 inhibition in patients diagnosed with pancreatic adenocarcinoma. A total of 212 patients were screened for HER2 expression, only 17 of which were included in the study. Trastuzumab (HER2 inhibitor) in combination with capecitabine was found to be well tolerated in the study population, however no improvement in overall survival (median 6.9 months, estimated 6 month OS: 52.9%) and progression free survival (23.5% at 12 weeks, median 65 days) was reported compared to standard therapy. The study was also closed prematurely due to the low HER2 expression encountered. The authors reported a surprisingly low expression of HER2 and conclude that even in HER2 amplifying tumors, combination therapy with trastuzumab plus capecitabine does not improve overall and progression free survival compared to treatment with gemcitabine or capecitabine alone.

Ongoing phase II and III trials (Table 3)

Study of gemcitabine, abraxane plus placebo versus gemcitabine, abraxane plus 1 or 2 truncated courses of demcizumab in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma (YOSEMITE) (50)

This randomized double blind, 3 arm study sponsored by OncoMed Pharmaceuticals attempts to determine the efficacy and safety of demcizumab (a delta-like ligand 4 notch blocker) when given in combination with gemcitabine/abraxane compared to placebo. The study started to recruit patients in the spring of 2015 and has an estimated completion date in June 2017. This trial expects to enroll 201 patients in whom progression free survival will be the primary outcome measure.

A phase 2 study of MM-141 plus nab-paclitaxel and gemcitabine in front-line metastatic pancreatic cancer (CARRIE) (51)

MM-141 is a tetravalent bispecific antibody antagonist of IGF-IR and ErbB3 currently being evaluated in the CARRIE trial. This randomized double blind study expects to enroll 260 patients between May 2015 and November 2017. Progression free survival is the primary outcome measure.

Table 3 Ongoing clinical trials evaluating impact of chemotherapeutic agents against specific molecular targets

Study	Agent	Target	Phase	Sponsor	Population	Start date	End date	Study design	Est. enroll
Yosemite	Demcizumab	Notch ligand DLL4	II	OncoMed, Pharmaceuticals	1st line metastatic	4/2015	6/2017	Randomized double blind, Gem/ Abraxane ± agent	201
Carrie	MM-141	IGF-1R	II	Merrimack, Pharmaceuticals	1st line metastatic	5/2015	11/2017	Randomized double blind, Gem/ Abraxane ± agent	260
POLO	Olaparib	PARP	III	AstraZeneca	gBRCA mutated metastatic, 2nd line therapy	12/2014	10/2017	Randomized double blind, Monotherapy vs. Placebo	145
1	Veliparib	PARP	II	NCI	LA / Met.	4/2012	7/2017	Randomized, Gem/cisplatin ± agent	107
2	ACP-196	Bruton's TK	II	Acerta, Pharmaceuticals	1st line metastatic	10/2015	12/2017	Randomized, Gem/Abraxane ± agent	120
3	Dasatinib	Bcr-Abl TK	II	University of Florida	1st line metastatic	7/2012	8/2018	Interventional, single group assignment, FOLFOX + Agent	42
4	PBI-05204	mTOR	II	Phoenix Biotechnology	1st line metastatic	4/2015	7/2016	Interventional, Single group assignment, Agent	50
5	SGT-53	Liposome p53 Complex	II	SynerGene Therapeutics	1st line metastatic	1/2015	6/2018	Interventional, Single group assignment, Gemcitabine + Abraxane + Agent	28
RESOLVE	Ibrutinib	Bruton's TK	II-III	Pharmacyclics	1st line metastatic	5/2015	3/2018	Randomized double blind Gemcitabine + Abraxane ± agent	326
6	Momelotinib	JAK1/JAK2	III	Gilead Sciences	1st line metastatic	6/2014	8/2020	Randomized double blind Gemcitabine + Abraxane ± agent	430
ACCEPT	Afatinib	EGFR/ErbB	II	Volker Heinemann	1st line metastatic	4/2013	4/2017	Randomized Gemcitabine ± agent	117
7	Trametenib	MEK1/MEK2	II	U. Health Network, Toronto	1st line metastatic	6/2015	12/2017	Interventional, Single group assignment GSK2256098 + Agent	24

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Table 3 (continued)

Study	Agent	Target	Phase	Sponsor	Population	Start date	End date	Study design	Est. enroll
8	Ramucirumab	VEGFR	II	Walid Shaib	1st line metastatic	3/2016	10/2019	Randomized double blind m-FOLFIRINOX ± agent	95
9	Nivolumab	PD-1	I/II	Sidney Kimmel Comprehensive Cancer Center	1st line surgically resectable	2/2016	2/2020	Randomized, Parallel assignment, GM-CSF ± agent	50
10	Nivolumab	PD-1	II	Sidney Kimmel Comprehensive Cancer Center	2nd line metastatic	12/2014	1/2019	Randomized, G-VAX + CRS-207 ± agent	94
11	Pembrolizumab	PD-1	II	Sidney Kimmel Comprehensive Cancer Center	1st line locally advanced	7/2016	7/2020	Interventional, Single group assignment. GM-CSF + SBRT + agent	54
12	Pembrolizumab	PD-1	II	Acerta, Pharmaceuticals	1st line metastatic	4/2015	9/2017	Randomized, parallel assignment, ACP-196 ± agent	76

Abbreviations: LA, locally advanced.

1. A Randomized Phase II Study of Gemcitabine, Cisplatin +/- Veliparib in Patients With Pancreas Adenocarcinoma and a Known BRCA/PALB2 Mutation (Part I) and a Phase II Single Arm Study of Single-Agent Veliparib in Previously Treated Pancreas Adenocarcinoma (Part II).
2. Study of Nab Paclitaxel/Gemcitabine Alone and in Combination With ACP-196 in Subjects With Previously Untreated Metastatic Pancreatic Cancer.
3. Phase II Study of 5-Fluorouracil, Oxaliplatin Plus Dasatinib (FOLFOX-D) in First-line Metastatic Pancreatic Adenocarcinoma.
4. A Phase II, Single-arm, Open-label, Bayesian Adaptive Efficacy and Safety Study of PBI-05204 in Patients With Stage IV Metastatic Pancreatic Adenocarcinoma.
5. Phase II Study of Combined Targeted p53 Gene Therapy (SGT-53) Plus Gemcitabine/Nab-Paclitaxel for Treatment of Metastatic Pancreatic Cancer.
6. A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Gemcitabine and Nab-paclitaxel Combined With Momelotinib in Subjects With Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma Preceded by a Dose-finding, Lead-in Phase.
7. Molecular Basket Trial In Multiple Malignancies With Common Target Pathway Aberrancies: A Phase II Trial of GSK2256098 and Trametinib in Patients With Advanced Pancreatic Cancer.
8. Phase II Randomized, Double-Blind Study of FOLFIRINOX Plus Ramucirumab Versus FOLFIRINOX Plus Placebo in Advanced Pancreatic Cancer Patients: Hoosier Cancer Research Network GI14-198.
9. Neoadjuvant/Adjuvant GVAX Pancreas Vaccine (with CY) or Without Nivolumab Trial for Surgically Resectable Pancreatic Cancer.
10. GVAX Pancreas Vaccine (with CY) and CRS-207 with or without Nivolumab.
11. Study with CY, Pembrolizumab, GVAX and SBRT in Patients with Locally Advanced Pancreatic Cancer.
12. ACP-196 Alone and in Combination with Pembrolizumab in Subjects with Advanced or Metastatic Pancreatic Cancer.

Olaparib in gbrca mutated pancreatic cancer whose disease has not progressed in first line platinum based chemotherapy (POLO) (52)

The POLO trial is a phase III multicenter, randomized double-blind study aimed at determining the efficacy of the PARP inhibitor olaparib as monotherapy in patients with germline BRCA mutated metastatic pancreatic cancer with stable disease after first line platinum based chemotherapy. The study is sponsored by AstraZeneca and hopes to enroll 145 patients from December 2014 to August 2018.

Gemcitabine hydrochloride and cisplatin with or without veliparib alone in treating patients with locally advanced or metastatic pancreatic cancer (53)

This two part National Cancer Institute sponsored trial attempts to determine whether veliparib (PARP inhibitor) + gemcitabine/cisplatin demonstrates improved survival in patients diagnosed with locally advanced or metastatic pancreatic adenocarcinoma compared to gemcitabine/cisplatin alone. The trial started enrolling patients in April 2012 and will be completed by July 2017. The first part aims to determine the optimal dose of veliparib, as well as the response rate compared to gemcitabine and cisplatin alone. The second part is aimed to determine the response rate of veliparib as a single agent therapy.

Study of nab paclitaxel/gemcitabine alone and in combination with ACP-196 in subjects with previous untreated metastatic pancreatic cancer (54)

The impact of inhibition of the Bruton's tyrosine kinase is assessed in this randomized single blind trial, recruiting patients from October 2015 to December 2017. The study attempts to evaluate the safety and efficacy (overall response rate) of ACP-196 and nab paclitaxel/gemcitabine as first line therapy in patients diagnosed with metastatic pancreatic adenocarcinoma.

Phase II study of 5-FU, oxaliplatin plus dasatinib in metastatic pancreatic adenocarcinoma (FOLFOX-D) (55)

The purpose of this single site phase II trial is to determine if dasatinib (a Bcr-Abl tyrosine kinase inhibitor) given in combination with FOLFOX will work as first line treatment in metastatic pancreatic adenocarcinoma. The University of Florida has been recruiting patients since July 2012 and will continue until June 2018, expecting to enroll a total of 42 patients. Dasatinib activity will be measured as well as therapeutic response rate, freedom from metastasis, time to progression, overall survival and patient quality of life.

Efficacy and safety study of PBI-05204 in patients with stage IV metastatic pancreatic adenocarcinoma (56)

This study evaluates the efficacy of an mTOR inhibitor in patients diagnosed with stage IV pancreatic cancer. The study is designed as an interventional single arm, open label study that will evaluate the overall survival of 50 patients enrolled from April 2015 to November 2016.

Study of combined SGT-53 plus gemcitabine/nab-paclitaxel for metastatic pancreatic cancer (57)

The safety, tolerability, toxicity and efficacy of SGT-53 (a p53 targeted agent) combined with gemcitabine and nab-paclitaxel are the aims of this trial. This intervention single group assignments study will evaluate the progression free survival, antitumor activity, time to disease progression, duration of disease control and disease control rate of 28 patients diagnosed with metastatic pancreatic cancer enrolled from January 2015 to June 2018.

Study of ibrutinib vs placebo, in combination with nab-paclitaxel and gemcitabine, in the first line treatment of patients with metastatic pancreatic adenocarcinoma (RESOLVE) (58)

RESOLVE is a phase II/III randomized multicenter, double blind trial to evaluate the efficacy of a Bruton's tyrosine kinase inhibitor (ibrutinib) in combination with nab-paclitaxel and gemcitabine as first line of treatment of patients with metastatic pancreatic adenocarcinoma. The trial estimates to include 326 patients from May 2015 to March 2018, in whom progression free survival, overall survival and adverse events will be evaluated.

Gemcitabine and nab-paclitaxel combined with momelotinib in participants with previous untreated metastatic pancreatic ductal adenocarcinoma (59)

This phase 3 study will evaluate the Janus Kinase inhibitor (mometinib) in two phases. The lead phase will determine safety, pharmacokinetics and maximum tolerated dose of momelotinib combined with nab-paclitaxel/gemcitabine. The follow up phase will randomized patients to an experimental arm that will include nab-paclitaxel/gemcitabine + momelotinib or to a nab-paclitaxel/gemcitabine + placebo arm. In this last phase, efficacy, safety and tolerability of combination therapy will be determined. Patients have been enrolled since June 2014 and study is anticipated to continue until August 2020.

Afanib as cancer therapy for exocrine pancreatic tumors (ACCEPT) (60)

Afanib is an irreversible EGFR1, inhibitor that is currently being evaluated in the ACCEPT trial. This study aims to compare the impact in overall survival, progression free survival, duration of response, toxicity and quality of life of afanib in

combination with gemcitabine vs gemcitabine alone. Patients have been randomized (2:1) since April 2013 and by April 2017, 117 patients are expected to be recruited.

A study of GSK2256098 and trametinib in advanced pancreatic cancer (61)

The University Health Network of Toronto is currently recruiting patients to determine the antitumor activity of trametinib (MEK1/MEK2 blocker) in combination with GSK2256098 (FAK inhibitor). This is an intervention, single arm study intending to include 24 patients from June 2015 to December 2017. This trial hopes to determine the number of patients with advanced pancreatic cancer that, after 24 weeks of experimental treatment, demonstrate treatment response.

Phase II randomized trial of FOLFIRINOX ± ramucirumab in advanced pancreatic cancer (62)

This phase II, multicenter, double blind, randomized, 2-arm trial evaluates the efficacy and safety of ramucirumab (VEGFR inhibitor) + FOLFIRINOX vs. placebo and FOLFIRINOX in patients with advanced pancreatic cancer not amenable to curative treatment. Progression free survival, overall survival, response rate and adverse events will be analyzed in 95 patients recruited from March 2016 to October 2019.

Neoadjuvant/adjunct GVAX pancreas vaccine (with CY) or without nivolumab trial for surgically resectable pancreatic cancer (63)

This phase II study is designed to measure the impact of nivolumab, a PD-1 blockade antibody, when added to a GM-CSF secreting allogeneic PCA vaccine with cyclophosphamide before or after surgery for resectable PCA. The primary outcome will be IL17A expression in vaccine induced lymphoid aggregates in resected tumors. The study opened at Sydney Kimmel Cancer Institute in Baltimore in February of 2016 and is expected to enroll patients for 2 years.

GVAX pancreas vaccine (with cy) and CRS-207 with or without nivolumab (64)

This study, similar to that previously described, adds a *Listeria monocytogenes*-expressing mesothelin (CRS-207) boost to the Hopkin's vaccine with and without PD-1 blockade in patients with previously treated metastatic PCA. It opened at 4 sites in North America in September of 2014 and is actively enrolling patients.

Study with CY, pembrolizumab, GVAX and SBRT in patients with locally advanced pancreatic cancer (65)

This is another trial sponsored by Kimmel Cancer Institute evaluating a different PD-1 antibody (pembrolizumab) combined with the GVAX vaccine and radiation therapy in patients with locally advanced non-metastatic PCA. The primary end-

point is Distant Metastasis Free Survival (DMFS). It is expected to begin enrolling patients in July of 2016.

ACP-196 alone and in combination with pembrolizumab in subjects with advanced or metastatic pancreatic cancer (66)

This phase II study combining Bruton's tyrosine kinase inhibitor ACP-196 with pembrolizumab in patients with locally advanced or metastatic PCA is designed to establish the proof of concept of this novel drug combination. It began enrollment in April of 2015 but is currently not recruiting participants.

Summary and conclusions

Recent advances in the treatment of advanced pancreatic cancer are characterized by novel combinations of conventional cytotoxic chemotherapy (FOLFOX, FOLFIRINOX, GEMCITABINE/ABRAXANE). Unfortunately, with the exception of erlotinib, no recently completed and published later phase trials have resulted in approved targeted strategies for patients with advanced pancreatic cancer. Most of these trials (including erlotinib) were compared using gemcitabine with or without the experimental agent as the study group. Now, with the adoption of Folfirinox or Gem/Abraxane in the advanced stage setting, the pace of discovery in pancreatic cancer therapeutics has accelerated, and prior studies demonstrating a survival benefit of these agents combined with gemcitabine alone are no longer relevant. Ongoing trials now include Folfirinox or Gem/abraxane as the control arm. It would seem improbable, however, that those agents that failed to show efficacy or synergy when combined with gemcitabine alone will demonstrate significant benefit in the setting of newer multimodal cytotoxic regimens.

Notably scarce are late phase trials evaluating the burgeoning class of agents that target PD-1 (nivolumab/OPDIVO and pembrolizumab/Keytruda) and soon to be released anti PDL-1 agents. These immune checkpoint inhibitors have shown efficacy in other tumor types, the most noteworthy of which are melanoma and non-small cell lung cancer. As such, the rationale of combining these agents with other effective immunotherapy regimens makes biologic sense. There are currently 17 trials on the clinicaltrials.gov website evaluating these agents that can enroll patients with solid tumors in various stages. Seven of these trials are looking specifically at patients with pancreatic cancer, four of which are phase II (and included in Table 3). Looking forward, one can anticipate that these agents will be studied in the setting of metastatic pancreatic cancer as Phase I and Ib data in ongoing trials begin to surface. At least in the foreseeable future however, single agent targeted therapy will not supplant combination cytotoxic regimens that have nudged months of survival in these patients into double digits.

In contrast to colorectal cancer, where many of these strategies have created 3rd and sometimes 4th lines of therapy for patients with refractory disease, demonstrated efficacies in these trials have not yet justified their application as adjuncts of single agents in pancreatic adenocarcinoma. Continued exploration of novel agents such as nivolumab/pembrolizumab, alone or in combination with conventional agents, will hopefully offer additional options in the future. The

use of such agents together with an altogether different strategy such as immunotherapy may provide the synergy necessary to push both strategies into the clinical arena.

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