Pancreatic Cancer—the Current Landscape

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Pancreatic ductal adenocarcinoma (PDA) is a devastating disease with a very poor prognosis that is set to become the second leading cause of cancer death in the next decade. Unlike other cancer types, treatments developed for PDA have generated only marginal survival gains over recent years. Most patients (as many as 80%) present at an advanced stage, when the disease is beyond curative resection. There are currently no reliable biomarkers that could enable earlier diagnosis of PDA, and widespread population screening is not feasible. However, targeted screening of high-risk groups is being undertaken, since up to 10% of PDA cases are associated with an inherited component. Genotyping of PDA is becoming increasingly important to identify patients with potentially actionable mutations. However, most frequent mutations in PDA are in the *KRAS*, *CDKN2A*, *TP53* and *SMAD4* genes, which are challenging therapeutic targets. The tumor microenvironment is highly relevant to PDA, which has a large stromal component. The stroma is increasingly recognized as important in disease development, while cancer stem cells play a vital role in promoting metastasis and are therefore important new therapeutic targets. Current PDA standard management relies on surgical resection when feasible in the minority and, for the majority, cytotoxic chemotherapy which extends survival by a few months only. Despite this bleak outlook, recent advances in understanding PDA pathophysiology and the development of new treatments such as anti-PD1 antibodies, PARP inhibitors, and pegvorhyaluronidase alfa, which targets the stroma, are offering new hope to specific patient subgroups identified by relevant biomarkers.

Keywords

Pancreatic cancer, pancreatic ductal adenocarcinoma, hyaluronan, biomarkers, pathophysiology, metastasis, diagnosis, treatment

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Pancreatic ductal adenocarcinoma (PDA) is an aggressive disease with a persistently high mortality that has only marginally decreased in recent decades.[1–4] The disease typically presents with nonspecific symptoms in the early stages, often leading to delayed diagnosis and a poor prognosis. Approximately 80% of patients with PDA present at a late stage.[5,6] Consequently, most patients have advanced disease (stages III or IV) at diagnosis that is beyond curative resection.[7–9] As there is a lack of reliable blood borne or other biomarkers for PDA, early diagnosis is difficult.[10] Effective non-surgical treatment for all stages of PDA continues to be an urgent unmet medical need.[1,8] Improved understanding of the disease is yielding new approaches to treatment which may lead to better prospects in the future for managing PDA.[8] Here, we summarize the prevalence, pathophysiology, diagnosis and current standards of care and discuss novel treatment options in clinical development for PDA.

Pancreatic cancer demographics

PDA represents over 90% of cancers arising in the pancreas and carries an extremely poor prognosis.[8] PDA is the third leading cause of cancer death in the US, the fourth leading cause in Europe and the fourth or fifth in Asian nations.[11–13] It is projected to become the second leading cause of cancer-related death in the USA by 2030.[14] Mortality rates vary throughout the world according to GLOBOCAN 2012 estimates, with 6.9/100,000 in the USA, 6.8/100,000 in Western Europe, decreasing to less than 1.0/100,000 in Middle Africa and South Central Asia.[15] The National Cancer Institute's estimates for new diagnoses of pancreatic cancer in the USA in 2018 is 55,440 (12.6/100,000, 3.2% of all new cancer cases) with 44,300 deaths (10.9/100,000, accounting for 7.3% of all cancer deaths).[11] The estimated prevalence in the USA in 2015 was 68,615 (17.1/100,000).[11] In Europe, the incidence in 2018 is estimated as 132,559 (17.8/100,000) with 128,045 deaths (17.2/100,000). The incidence in Asia in 2018 is estimated as 214,499 (4.7/100,000) with 200,681 deaths (4.4/100,000).[16]

Table 1: Risk factors for pancreatic ductal adenocarcinoma

Risk factor	Supporting information
Race	Risk of PDA is higher in black versus white populations. Age-adjusted incidence: blacks = 16.4, whites = 10.8, other races: 9.8[20]
Sex	Risk greater in men than women—age-adjusted incidence rate of 13.0 in men and 9.8 in women[20]
BMI	Study[21] of 46,648 men and 117,041 women showed relative risk of 1.72 for those with a BMI >30 kg/m^2 versus those <23 kg/m^2
Smoking	In one study on a population of 6,507 PDA cases and 12,890 controls, the RR for tobacco use and exposure to secondary smoke were 2.2 and 1.21, respectively[22]
Alcohol consumption	Heavy alcohol consumption increased the risk of PDA, RR=1.19 for individuals consuming >50gms/day in a meta-analysis of 39 studies.[34] A combination of two other large population studies showed that smoking and binge-drinking also increases PDA risk[25]
Diabetes	Long-standing diabetes increases risk. A meta-analysis found that a 0.35% change in HbA1c increases the risk of PDA by 14%.[26] However the relationship between diabetes and PDA is complex and can be differently affected by drug treatments and duration. New onset diabetes in individuals >50 years of age can be an early symptom of PDA[27]
Blood group	A large population study showed an increased risk of PDA for blood groups A, AB, and B versus group O; HRs 1.32, 1.51, and 1.72, respectively.[28] These finding are supported by other large studies[29,30]
Infections	Hepatitis B virus or helicobacter pylori infections are associated with PDA[31,32]
Family history of PDA	Slightly increased risk (family history of PDA reported in 5–10% of cases)[7]
Germline mutations	Presence of *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CDKN2A, TP53*, *MLH1* and many others can also increase PDA risk[33]

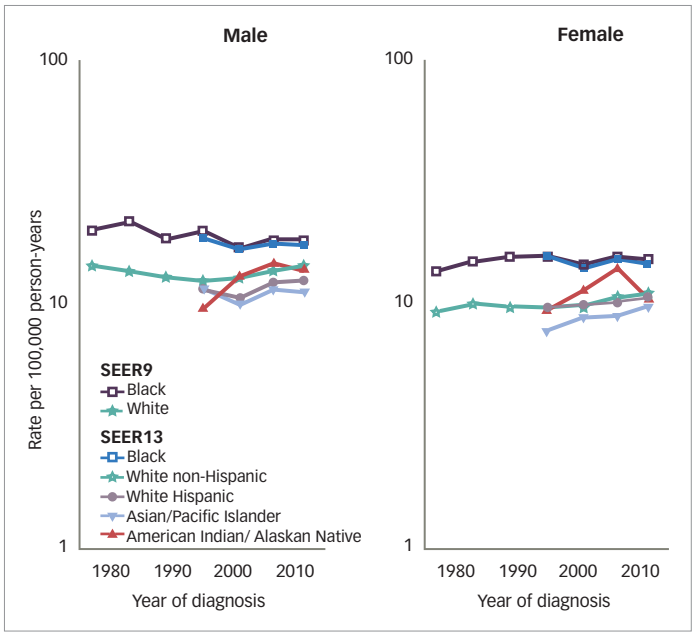
ATM = serine/threonine protein kinase - activated by DNA double-strand breaks; BMI = body mass index; BRCA = breast cancer susceptibility gene; CDKN2A = gene encoding several tumor-suppressing proteins; HbA1c = glycated hemoglobin; HR = hazard ratio; OR = odds ratio; PALB2 = partner and localizer of BRCA2; PDA = pancreatic ductal adenocarcinoma; RR = relative risk.

Data from the U.S. Surveillance Epidemiology and End Results registries show that among white males, the incidence of pancreatic cancer decreased from 1975 to 1994 (annual percentage change [APC]: -0.98%) but increased during 1994–2013 (APC: +0.95%).[17] Among non-Hispanic white and Hispanic males, the incidence APC between 1992 and 2013 was +0.84% and +0.73%, respectively. Incidence during this period also increased in white non-Hispanic, Hispanic and Asian females (APC: +0.81%, +0.56% and +1.23%, respectively), and even more rapidly among females aged 25–34 years (APC >+2.5%). Incidence among black males and females remained unchanged, but was higher than amongst white, Hispanic and Asian populations (*Figure 1*).[17]

The PDA mortality rate is remarkably similar to incidence; survival rates have only improved slightly over the past 40 years.[11] According to EUROCARE-5, the fifth cycle of the EUROCARE study of cancer survival in Europe, the 1-, 3-, and 5-year survival rates of patients with pancreatic cancer diagnosed during 1999–2007 were only 26%, 9%, and 7%, respectively.[18] More recent data from a study of European and USA patients diagnosed during 2003–2014 shows little change in this figure, with a 1-year survival of 19–34% and 5-year survival of 4–11%.[19] Survival of patients with stages III (locally advanced) and IV (distant metastatic) PDA was much worse than for stage I–II patients with potentially resectable disease. Median overall survival (OS) for stage III and IV PDA was <1 year and <6 months, with a 5-year survival of only ~2%.[19] By comparison, the 5-year survival rates for other common cancers are much higher: prostate cancer 98.2%, breast cancer 89.7%, colorectal cancer 64.5%. Even outcomes from lung cancer (5-year survival 18.6%)[11] exceed those for PDA, reflecting introduction of effective treatments over the last decade.

Several different risk factors for PDA have been identified: there are associations with lifestyle (e.g. smoking, obesity, and alcohol consumption), infection and disease history, as well as genetic factors, blood group, and family history (*Table 1*).[7,20–34] Type 2 diabetes (T2D) is frequently associated with PDA,[20,26,27,35,36] although the nature of the relationship is not clear.

Figure 1: Pancreatic cancer incidence trends by sex and racial/ethnic group (1974–2013) for black and white populations



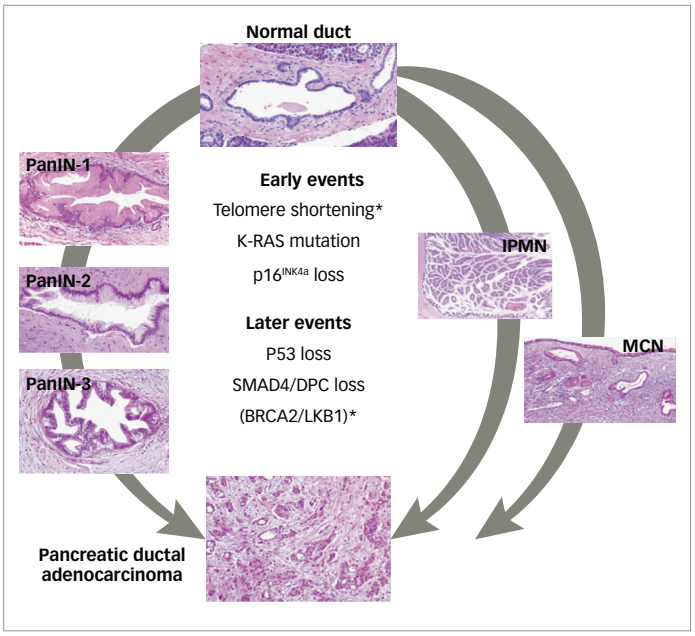
Reused with permission from Gordon-Dseagu et al., 2018.[17]

Recent-onset T2D appears to be a manifestation of PDA whereas long-term T2D may be a risk factor for PDA.[36]

Pathophysiology and natural history of pancreatic cancer

Approximately 95% of all pancreatic cancers are exocrine adenocarcinomas, most of which originate in the ducts and at the head end of the pancreas.[35] Evidence suggests that it can take many

Figure 2: Pancreatic precursor lesions and genetic events involved in pancreatic adenocarcinoma progression



Pictured are three known human PDA precursor lesions: PanIN, MCN, and IPMN. The PanIN grading scheme is shown on the left; increasing grade (1–3) reflects increasing atypia, eventually leading to frank adenocarcinoma. The right side illustrates the potential progression of MCNs and IPMNs to PDA. The genetic alterations documented in adenocarcinomas also occur in PanIN, and to a lesser extent MCNs and IPMNs, in an apparent temporal sequence, although these alterations have not been correlated with the acquisition of specific histopathologic features. The various genetic events are listed and divided into those that predominantly occur early or late in PDA progression. Asterisks indicate events that are not known to be common to all precursors (telomere shortening and BRCA2 loss are documented in PanIN and LKB1 loss is documented in a subset of PDAs and IPMNs).
IPMN = intraductal papillary mucinous neoplasm; MCN = mucinous cystic neoplasm; PanIN = pancreatic intraepithelial neoplasia; PDA = pancreatic ductal adenocarcinoma. Reused with permission from Hezel et al., 2006.[39]

years for an initiating abnormal pancreatic cell to become malignant.[37] However, PDA may progress rapidly through the clinical stages; a study of 13,131 patients calculated that the average T1-stage PDA advances to T4 stage in just over a year.[38] The tumor arises from ductal cells via pancreatic intraepithelial neoplasia (PanIN) precursor lesions (*Figure 2*).[39]

Epidemiologic studies have shown that 5–10% of PDAs are associated with an inherited component.[40] A recent case-control study found that 5.5% of patients with PDA (167/3,030) had deleterious mutations in six genes which were associated with a predisposition to PDA (*CDKN2A*, *TP53*, *MLH1*, *BRCA2*, *ATM*, and *BRCA1*). Among all tested patients in this study, 7.9% (27/343) with a family history of PDA and 5.2% (140/2,687) with no family history of PDA had a mutation in one of these six genes.[33]

The most frequent somatic alterations in PDA are in the *KRAS*, *CDKN2A*, *TP53*, and *SMAD4* genes.[41,42] *KRAS* alterations are observed in >90% of PDAs and occur early in tumor development.[42] In addition to these prevalent gene alterations, a "long tail" of gene mutations is observed, including those involved in axon guidance and DNA repair.[43–45] These mutations often alter the metabolism of pancreatic tumors. PDA cells also have a notable genomic instability phenotype that enables the rapid development of treatment resistance.[9]

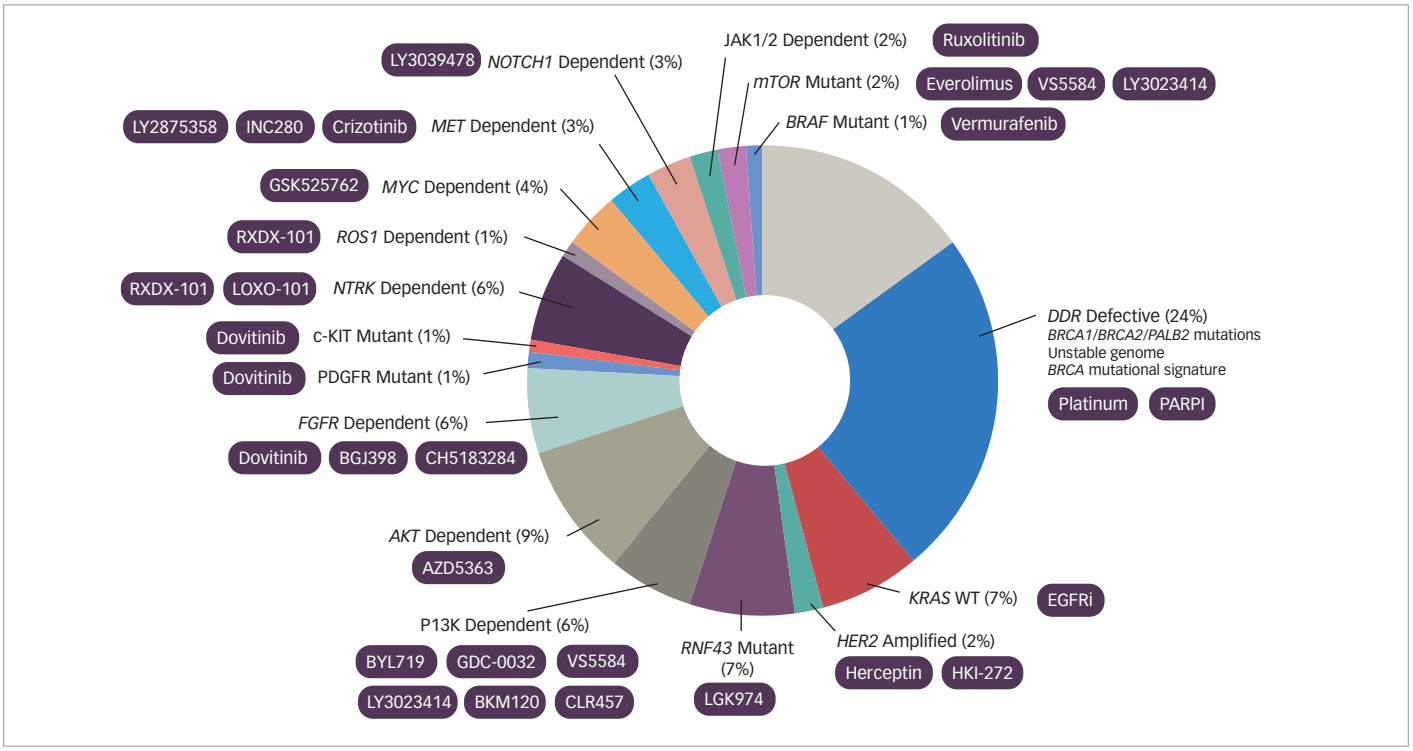
Molecular analysis of metastatic PDA tumors using real-time genomic characterization can identify clinically relevant alterations that can potentially guide treatment of PDA and the development of new treatment (*Figure 3*).[42–44,46] Studies by the Australian Pancreatic Cancer Genome Consortium on whole genomes in 100 different PDAs found that chromosomal rearrangements could be classified as stable (20%), scattered (36%), unstable (14%), and locally rearranged (30%) and these types affect response to treatment. The study also identified a mutational signature of DNA damage repair deficiency, which may be useful in predicting therapeutic response.[47] Defining patients with hypermutation, i.e., a high mutation burden, may help predict a patient's response to immunotherapy.[48] Next-generation sequencing can identify mismatch repair deficiency, which is also predictive of tumor response to immunotherapy.[49] Up to 7% of PDAs have loss-of-function mutations in either *BRCA1*, *BRCA2*, or both *BRCA* genes and germline *BRCA* mutation may be a biomarker for response to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors.[50]

Tumor genotyping and gene expression assessments are likely to become increasingly useful in defining which patients are more likely to respond to chemotherapy and immunotherapy.[51,52] The US Pancreatic Cancer Action Network 'Know your Tumor®'[53] initiative allows patients to receive molecular profiling of their tumor to facilitate a personalized approach. In this initiative, patients have undergone multiomic profiling involving genomic, proteomic, and phosphoprotein-based analysis. Initial findings from 640 participating patients showed highly actionable findings in over 25% of tumors. Among these patients, those who had received matched therapy had significantly longer progression-free survival (PFS) than those who received unmatched therapy (4 months versus 2 months; hazard ratio [HR] 0.47; adjusted p=0.03). These findings indicated that molecular profiling has considerable potential in PDA diagnosis and treatment selection.[52]

In addition to genomic alterations, other fundamental features of PDA have started to guide ongoing research efforts. In PDA, the tumor microenvironment is created by interactions between cells such as pancreatic epithelial cells, cancer-associated fibroblasts, stellate cells, adipocytes, and infiltrating immune cells. Such interactions are believed to promote tumor growth and metastasis (*Figure 4*) and may contribute to resistance to systemic therapy.[54–56] Stellate cells and adipocytes in the tumor microenvironment are believed to act synergistically to supply the cancer cells with metabolites such as glutamate and other micronutrients.[57,58] These cells also maintain an inflammatory state which is accompanied by the infiltration of the tumor by inflammatory cells such as lymphocytes, neutrophils and macrophages.[59,60] Metabolism is altered within PDA cells and this is affected by the stroma which limits perfusion of the tumor tissues.[61,62] The stroma surrounding PDA tumors is rich in hyaluronan which has been implicated in increasing intertumoral pressure, collapsing blood vessels, and preventing access by therapeutic agents and immune cells.[63,64] The stroma may also promote metastasis, with the possibility that tumors having a high-extracellular hyaluronan level (hyaluronan-high, defined as hyaluronan staining in the extracellular matrix ≥50% of the entire tumor surface at any intensity) may be more aggressive than tumors with low hyaluronan (*Figure 4*).[54,55,65–67] Overcoming this barrier using enzymatic depletion of hyaluronan is an important development in current treatment approaches.[66,68]

Within PDAs, cancer stem cells have an important role and have unique metabolic, autophagic, invasive, and chemoresistance properties, enabling

Figure 3: Molecular subtypes of pancreatic ductal adenocarcinoma



AKT = ATP-dependent tyrosine kinase; c-KIT = tyrosine-protein kinase kit; DDR = DNA-damage response; EGFRi = epidermal growth factor receptor inhibitor; FGFR = fibroblast growth factor receptor; HER2 = human epidermal growth factor receptor 2; JAK = janus kinase; MET = tyrosin-protein kinase Met; mTOR = mammalian target of rapamycin; MYC = family of oncogenes carried by the avian virus myelocytomatosis and a human gene overexpressed in various cancers; NTRK = neurotrophic tyrosine receptor kinase; PARPi = poly ADP ribose polymerase inhibitor (e.g. olaparib); PDGFR = platelet-derived growth factor receptor; WT = wild type. Reused with permission from Dreyer et al., 2017.[44]

continuous self-renewal and allowing the cells to evade elimination from chemotherapies. They also promote metastases.[69] Current treatment options do not target cancer stem cells, but improved understanding of the characteristics and signals that maintain and drive this cancer stem cell population is vital for the development of more effective treatments.

Diagnosis

Symptoms of PDA include weight loss, jaundice, loss of appetite, malabsorption, severe pain in mid abdomen and back, light-colored stools or dark urine, dyspepsia, fatigue, and nausea.[70] In many cases, however, the disease creates mild or non-specific symptoms during its early stages, and as a result, appropriate investigation is delayed and <20% of pancreatic cancers are amenable to complete surgical resection at diagnosis.[9,71] In advanced PDA, symptoms such as pain and thromboembolic events are highly prevalent[72–74] and are associated with increased morbidity and mortality.[72] In addition, cachexia develops in approximately 80% of patients with PDA during their disease course, and up to one-third of patients die from complications from cachexia.[75] Diagnosis of PDA involves multiple imaging techniques. Initial investigations of abdominal symptoms may include ultrasound and computed tomography (CT) examinations. Endoscopic ultrasound is the optimal modality to assess and stage primary tumors as well as to obtain a tissue diagnosis.[76] Positron emission tomography is potentially of value in improving selection of patients for surgical resection.[77]

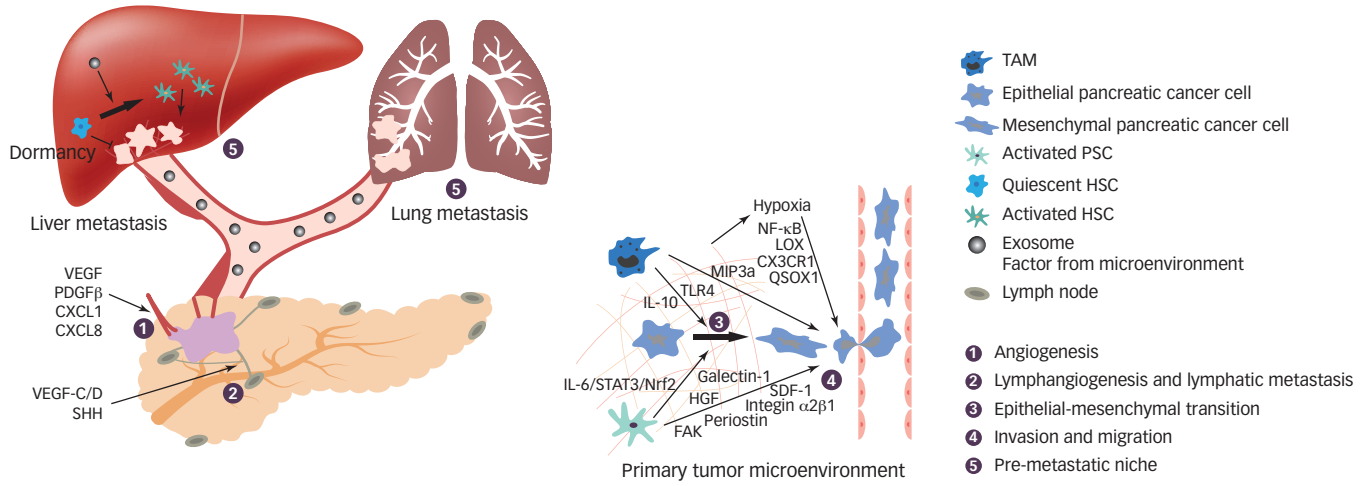
Detecting PDA earlier would be advantageous but there are no reliable diagnostic circulating biomarkers for the disease.[10] Serum CA 19-9 is widely used as a marker for metastatic PDA, but is non-specific and is not recommended for diagnostic use.[78] Serum macrophage inhibitory cytokine 1 (MIC-1) also has some potential as a biomarker, especially in combination with CA 19-9.[79] A recent study in a large cohort of patients with PDA found that a signature of 29 biomarkers can reliably discriminate individuals with stage I and II PDA from control subjects and this was validated in a further prospective study at a separate treatment center.[80] A combined analysis of a panel of serum proteins and microRNAs showed improved sensitivity and specificity in the detection of PDA-initiating cells and other biomarkers in patients with PDA compared with healthy controls but further development of the technique in a larger population is needed.[81,82]

In the general population, widespread screening is not feasible at present due to the lack of suitable biomarkers and the comparative rarity of the disease. Surveillance, however, is warranted in individuals >50 years of age with one first-degree relative, two family members who are affected by PDA, or in those carrying a mutation in a known cancer predisposition gene.[33,83,84] Recent results from a long-term (16 years) surveillance study indicated that 9 of 10 PDAs detected during surveillance were resectable and 85% of these patients survived for 3 years, suggesting a benefit of surveillance in high-risk PDA.[85]

Current standards of care and their efficacy

Current treatment in PDA is based on disease stage at diagnosis (*Table 2*).[86] Given the relative recalcitrance of PDA to current treatments, the National Comprehensive Cancer Network in the USA indicates that clinical trials are a preferred treatment option at every stage of pancreatic cancer diagnosis.

Figure 4: The pancreatic cancer microenvironment participates in metastasis[55]



The diagram shows that the pancreatic cancer microenvironment influences every step of metastasis via multiple signaling pathways. 1. The pancreatic cancer microenvironment can stimulate angiogenesis by cytokines to favor cancer cell survival and proliferation. 2. Molecules from the pancreatic cancer microenvironment can induce lymphangiogenesis to establish a pathway for lymphatic metastasis. 3. The pancreatic cancer microenvironment can facilitate the epithelial-mesenchymal transition to cause cancer cells to enter lymphatic vessel. 4. The pancreatic cancer microenvironment can play important roles in invasion and migration to facilitate metastasis. 5. Factors and exosomes derived from the pancreatic cancer microenvironment can induce pre-metastatic niche formation in liver and lung. These molecules or exosomes can activate hepatic stellate cells (HSCs) in liver for desmoplasia. CXCL = chemokine ligand; CX3CR = chemokine receptor; FAK = focal adhesion kinase; HGF = hepatocyte growth factor; HSC = hepatic stellate cells; IL-10 = interleukin-10; LOX = lysyl oxidase; MIP3 = macrophage inflammatory protein-3; NF-kB = nuclear factor kB; Nrf2 = nuclear respiratory factor 2; PDGFβ = platelet-derived growth factor β; PSC = pancreatic stellate cells; QSOX = quiescin-sulfhydryl-oxidase-1: quiescin Q6/sulfhydryl oxidase; SDF-1 = stroma-derived factor-1; SHH = sonic hedgehog; STAT3 = signal transduction activator of transcription-3; TAM = tumor-associated macrophage; TLR4 = toll-like receptor-4; VEGF = vascular endothelial growth factor.
Source: Ren et al., 2018.[55]

Table 2: Staging of pancreatic ductal adenocarcinoma

T1	Tumor ≤2 cm
T1a	Tumor ≤0.5 cm
T1b	Tumor >0.5 cm and <1 cm
T1c	Tumor >1 cm but <2 cm
T2	Tumor >2 cm but <4 cm
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves coeliac axis, superior mesenteric artery, and/or common hepatic artery
N1	Metastases in 1–3 nodes
N2	Metastases in 4 or more nodes

M catergory unchanged

Stage

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Source: Amin et al., 2017.[86]

Potentially resectable primary pancreatic ductal adenocarcinoma (stages I, II, and III)

Stage I and II PDAs, and stage III PDAs that are not invading local vessels, are potentially resectable. The standard operation for tumors of the pancreatic head is the pancreaticoduodenectomy (Whipple procedure); tumors of the body or tail are resected using distal pancreatectomy.[87] Surgery is the only means of curing PDA and radical surgery achieving R0 resections offers the best outcomes when combined with optimal adjuvant chemotherapy.[88] Outcomes are less favorable for those patients with larger tumors and involved surgical margins, and they represent the majority of patients undergoing surgery.[88] Therefore, the overall median survival for all patients undergoing resection of PDA has been reported at 18–27 months, and the 5-year survival rate ranges from 12–35%.[89–91] Around 30% of patients undergoing resection may die within 1 year of surgery,[92] indicating that PDAs invade and metastasize early. Since patients with involved resection margins have much poorer survival,[93] patient selection for surgery is critical to optimize outcomes and avoid morbidity associated with major surgery. Development of novel strategies of perioperative adjunctive therapy is essential to reduce recurrence after surgery.

Following surgical resection of PDA, adjuvant chemotherapy can substantially prolong OS compared to surgery alone. In 2004, the European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial demonstrated that adjuvant chemotherapy with 5-fluorouracil achieved 5-year OS of 21%, versus 8% for with surgery alone (p=0.009).[94] Subsequent studies confirmed gemcitabine was as effective as fluorouracil as an adjuvant therapy and better tolerated.[95,96] In 2017, the ESPAC-4 study results concluded that the addition of capecitabine to gemcitabine further improved outcomes, with estimated 5-year OS reaching 28.8%. Median OS was 28.0 months for patients receiving adjuvant gemcitabine + capecitabine and 25.5 months for those receiving gemcitabine alone (HR 0.82; p=0.032).[88]

Table 3: Different definitions of borderline resectable pancreatic cancer

Vessel	MDACC	AHPBA/SSO/SSAT	NCCN
CA	No contact	No contact	Pancreatic body/tail: solid tumor contact ≤180° or >180° without involvement of aorta or gastroduodenal artery
CHA	Short-segment encasement/abutment	Abutment or short segment encasement	Pancreatic head: solid tumor contact without extension to CA or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction
SMA	Tumor abutment ≤180°	Tumor abutment ≤180°	Pancreatic head: solid tumor contact ≤180°
SMV/PV	Short-segment occlusion amenable to resection and reconstruction	Abutment with or without impingement; or encasement but without encasement of nearby arteries; or short-segment occlusion amenable to resection or reconstruction	Solid tumor contact >180° or ≤180° with contour irregularity or vein thrombosis but with suitable vessel proximally and distally to site of involvement, allowing for safe and complete resection and vein reconstruction*

** The most recent version of the NCCN resectability criteria also considers cases with solid tumor contact with the inferior vena cava as borderline resectable. AHPBA/SSO/SSAT = Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; CA = celiac axis; CHA = common hepatic artery; MDACC = MD Anderson Cancer Center; NCCN = National Comprehensive Cancer Network; PV = portal vein; SMA = superior mesenteric artery; SMV = superior mesenteric vein. Source: Toesca et al. 2018.*[93]

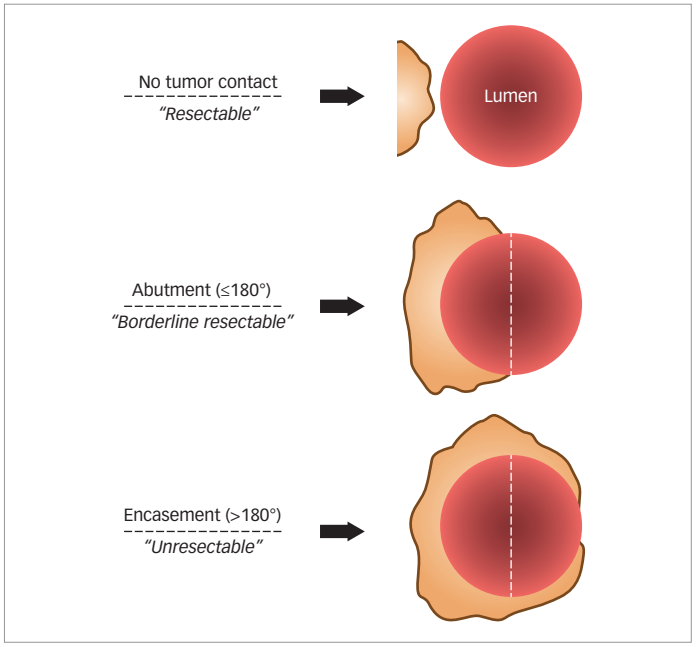
Initial results from the phase III PRODIGE 24/CCTG PA.6 trial showed improved efficacy for modified fluorouracil and folinic acid, oxaliplatin, leucovorin and irinotecan (FOLFIRINOX) compared with gemcitabine. After a median follow-up of 30.5 months, the median disease-free survival for modified FOLFIRINOX versus gemcitabine was longer (22 versus 13 months), as was the median OS (54 versus 35 months).[97] As in the metastatic setting, combination chemotherapy appears superior to single-agent gemcitabine in terms of efficacy, but careful patient selection is needed in view of greater associated toxicity. In addition, as *nab*-paclitaxel + gemcitabine demonstrated a clinically significant survival benefit versus gemcitabine alone in metastatic disease, it is also under investigation in patients with surgically resected PDA (APACT trial; NCT01964430).[98] A total of 866 patients have been randomized, and primary results of disease-free survival and safety will be available at the American Society of Clinical Oncology (ASCO) 2019 annual meeting. However, according to the recent press release by the sponsoring company, the study did not meet the primary endpoint of disease-free survival by blinded independent review; although the secondary endpoint of OS at the time of this data cut off was improved, reaching nominal statistical significance.[99,100] The safety profile observed in the study was consistent with previously reported studies of *nab*-paclitaxel.

The population with early PDA is a heterogeneous patient group and it is now clear that not all stage II tumors are actually resectable. Improvements in multidetector CT scanning with protocols optimized for PDA imaging offer higher resolution images of the tumor vessel interface, which has enabled evaluation of the extent of abutment and encasement of adjacent vessels. Tumors with no arterial contact are resectable, tumors abutting major pancreatic arteries ≤180° are termed "borderline resectable", and tumors encasing major pancreatic arteries ≥180° are unresectable (*Table 3*, *Figure 5*).[93]

The significance of refining PDA resectability has been the rationale for neoadjuvant therapy aimed at improving outcomes from primary cancer surgery. One of the first major reviews evaluating this approach suggested that as many as one-third of unresectable tumors could be rendered resectable by neoadjuvant therapy.[101] A 2017 propensity score-matched analysis of 15,237 stage I/II patients from the National Cancer Database, found that patients who received neoadjuvant therapy followed by resection had improved survival compared with those who received upfront resection (median survival, 26 months versus 21 months, respectively; HR 0.72; 95% confidence interval [CI], 0.68–0.78).[102] A single-arm study presented at ASCO 2018 found that preoperative FOLFIRINOX chemotherapy was feasible in patients with resectable PDA and allowed for better selection of patients with more advanced tumors who were not initially suitable for resection,[103] and a randomized trial of 364 patients presented at ASCO-GI 2019 found that neoadjuvant chemotherapy using gemcitabine and S1 resulted in improved OS compared to those receiving upfront surgery (median OS 36.7 versus 26.6 months, respectively; HR 0.72; 95% CI 0.55–0.94; p=0.015 stratified log-rank test).[104]

Neoadjuvant therapy is a promising exploratory approach, but a number of issues need to be addressed, including optimal treatment regimen and modalities. Additional randomized controlled trials in large patient populations are needed to properly evaluate this approach.

Figure 5: Magnified section of a computed tomography axial slice of a borderline resectable pancreatic adenocarcinoma



Artery representation shown in axial slice view. Dark yellow represents the tumor
Reused with permission from Toesca et al., 2018[93]

Locally advanced pancreatic ductal adenocarcinoma (unresectable stage III)

Diagnosis of locally advanced PDA confirms unresectability. Whether chemotherapy or chemoradiotherapy should be offered as treatment for this disease stage is an ongoing debate. However, combination systemic chemotherapy using in the setting of metastatic disease may be considered as initial therapy prior to chemoradiation for appropriate patients with locally advanced disease. The phase III LAP07 clinical trial found no significant difference in OS with chemoradiotherapy compared with chemotherapy alone. The same study found no significant survival advantage in patients with locally advanced PDA when erlotinib was added to gemcitabine as maintenance therapy.[105]

Results from the SCALOP phase II study showed that capecitabine was a more effective radiosensitizer compared with gemcitabine when used after induction chemotherapy, but the difference in the primary endpoint of PFS was not significant (15 months in the capecitabine group versus 13 months in the gemcitabine group; p=0.012).[106] On the other hand, a meta-analysis of 11 studies involving 315 patients with locally advanced PDA reported that FOLFIRINOX chemotherapy was associated with a median OS of 24 months, which is superior to that achieved with single agent gemcitabine. The percentage of patients down-staged to enable surgical resection ranged from 0–43%, while the rate of serious or life-threatening adverse events associated with treatment reached 60%. The authors concluded that prospective randomized trials are needed to evaluate optimal chemotherapy and chemoradiotherapy in this patient group.[107] In clinical practice, combination chemotherapy is being routinely offered to patients, with the option for consolidation chemoradiotherapy in those cases where surgical downstaging has not been achieved.[108]

Metastatic pancreatic ductal adenocarcinoma (stage IV)

Standard optimal first-line combination chemotherapy for metastatic PDA is based on the results of the MPACT (nab-paclitaxel + Gemcitabine in Metastatic Pancreatic Adenocarcinoma) and PRODIGE/ACCORD (FOLFIRINOX versus Gemcitabine as First-line Treatment for Metastatic Pancreatic Adenocarcinoma) trials.[2,109,110] The MPACT trial showed that, in patients with metastatic PDA, nab-paclitaxel + gemcitabine significantly improved OS, PFS, and response rate, but rates of peripheral neuropathy and myelosuppression were increased. The median OS was 9 months in the nab-paclitaxel + gemcitabine group versus 7 months in the gemcitabine group (p<0.001).[110] The PRODIGE/ACCORD study showed that first-line FOLFIRINOX produced a greater survival advantage in appropriately selected patients with metastatic PDA over gemcitabine (the median OS was 11 months in the FOLFIRINOX group versus 7 months in the gemcitabine group (p<0.001).[109] Although FOLFIRINOX is now one of the preferred first-line options for patients with metastatic PDA, debate persists whether the survival benefits of the combination regimen in metastatic disease outweigh the associated toxicities. These include thrombocytopenia, febrile neutropenia, diarrhea, and neuropathy. Therefore, FOLFIRINOX is usually reserved for patients aged ≤76 years who have a good PS (ECOG 0 or 1).[109] Modifications of the FOLFIRINOX regimen can provide comparative survival benefits to the conventional regime with fewer adverse events.[111] Gemcitabine monotherapy remains an acceptable treatment option for those patients unable to tolerate combination regimens.

Second-line treatment may be offered to carefully selected patients, according to ECOG PS and other clinical factors, such as bilirubin levels and comorbidities. However, the advantage of second-line therapy is very limited and the optimum regimen not established.[112] The German Charité Onkologie (CONKO) 003 phase III study found that second-line oxaliplatin + fluorouracil significantly extended OS compared with fluorouracil alone (6 months versus 3 months; p=0.01) in patients with advanced gemcitabine-refractory PDA. However, the oxaliplatin + fluorouracil group showed an increased rate of mild to moderate neurotoxicity (38.2% versus 7.1%).[113] On the basis of these findings, fluorouracil/leucovorin + oxaliplatin was considered as the best option following failure of gemcitabine-based treatment. Conversely, the PANCREOX (Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy) phase III study found that the addition of oxaliplatin to fluorouracil/leucovorin as modified FOLFOX6 (infusional fluorouracil, leucovorin, and oxaliplatin) had a detrimental effect compared with fluorouracil/leucovorin.[114]

The phase III NAPOLI-1 (nanoliposomal irinotecan with fluorouracil and folinic acid) study showed a survival advantage for nanoliposomal irinotecan fluorouracil + folinic acid compared with flurouracil/folinic acid (6 months versus 4 months; p=0.012) in patients with metastatic PDA after previous gemcitabine-based therapy.[115] This represents another useful second-line treatment option.

Early evidence is emerging that subgroups of patients identified by a molecular signature may benefit from a targeted therapeutic approach. Up to 7% of PDAs harbour a germline *BRCA* mutation. *BRCA* genes code for proteins involved in homologous recombination repair of DNA double-strand breaks. Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors which prevent repair of DNA single strand breaks have demonstrated antitumour efficacy in ovarian and breast cancer patients with a germline *BRCA* mutation. Very recently, the PARP inhibitor, olaparib, was reported to maintain response and delay disease progression after platinum-based chemotherapy in *BRCA* mutant advanced pancreatic cancer patients.[50] Patients with *BRCA*-associated locally advanced PDA can benefit from targeted therapy with olaparib as a second-line therapy after treatment failure with another line of therapy.[116]

In May 2017, the anti-programmed cell death protein 1 (PD1) checkpoint inhibitor, pembrolizumab, was licensed in the USA to treat patients with DNA mismatch repair deficiency, determined either by genetic mutation analysis or immunohistochemical assessment of microsatellite instability. Researchers reported an objective response rate of 51% across 12 different tumor types and complete responses in 21% of patients.[117] All patients were heavily pre-treated, having received two or more prior regimens. Mismatch repair deficiency of microsatellite instability is not routinely tested for in PDA and the license has not been extended outside the USA. However, these data are the first to identify a potential role for immune checkpoint inhibitors as treatment of PDA and many research studies are currently exploring novel immunotherapy approaches for this disease (*Table 4*). Further investigation of an immune checkpoint inhibitor combination for PDA treatment was conducted in a recent phase Ib/II study which investigated the use of the PD-L1 inhibitor durvalumab and the Bruton tyrosine kinase inhibitor ibrutinib given every two weeks to patients with pretreated solid tumours including 49 individuals with stage III/IV PDA.[118] The results indicate that the combination was well tolerated but showed only limited anti-tumour activity in this study population.

Table 4: Ongoing pancreatic ductal adenocarcinoma clinical trials investigating immunotherapeutic approaches

Intervention	Phase	Cancer stage	ClinicalTrials.gov identifier	Estimated completion date
Cabiralizumab plus nivolumab with and without nab-paclitaxel, onivyde, fluorouracil, gemcitabine, oxaliplatin, leucovorin	II	Locally advanced or metastatic PDA, ECOG performance 0 or 1	NCT03336216	December 2020
Azacitidine and pembrolizumab	II	Advanced pancreatic cancer after failure of first-line therapy	NCT03264404	September 2019
Durvalumab and stereotactic ablative body radiotherapy	I/II	Borderline resectable and locally advanced PDA	NCT03245541	September 2021
CY/GVAX pancreas vaccine followed by CRS-207 or CRS-207 alone	II	Metastatic PDA, ECOG performance 0 or 1	NCT03190265	October 2019
Olaptesed pegol (NOX-A12) alone and in combination with pembrolizumab	I/II	Metastatic PDA with liver metastases of the primary pancreatic cancer after failure of first-line therapy	NCT03168139	March 2022
Nivolumab and ipilimumab and radiation therapy	II	PDA	NCT03104439	October 2024
Durvalumab following successful R0/R1 resection of PDAs and neoadjuvant chemotherapy	II	Borderline resectable and locally advanced PDA	NCT03038477	December 2019
Pembrolizumab and BL-8040	II	Metastatic PDA	NCT02907099	December 2019
Nivolumab or nivolumab plus ipilimumab plus RT	II	Metastatic PDA	NCT02866383	November 2019
BL-8040 alone and in combination with pembrolizumab	II	Metastatic PDA	NCT02826486	December 2018
Nivolumab or nivolumab plus ipilimumab administered concurrently with high dose RT	II	Metastatic PDA, after failure of first-line therapy	NCT02866383	November 2019
Combined cyclophosphamide, pembrolizumab, GVAX (pancreatic cancer vaccine), and SBRT	II	Locally advanced PDA	NCT02648282	July 2020
Durvalumab alone or in combination with tremelimumab	II	Metastatic PDA after failure of first-line therapy	NCT02558894	June 2017
Cyclophosphamide/GVAX plus nivolumab	I/II	Newly diagnosed stage I/II PDA	NCT02451982	February 2020
Pembrolizumab plus neoadjuvant chemoradiation	I/II	Resectable or borderline resectable PDA	NCT02305186	June 2019
Ibrutinib plus durvalumab*	I/II	Relapsed/refractory solid tumors	NCT02403271	August 2017
nab-paclitaxel and gemcitabine with or without olaratumab	I/II	Metastatic or unresectable PDA	NCT03086369	May 2022
RO7009789 plus nab-paclitaxel and gemcitabine*	I	Newly diagnosed resectable PDA	NCT02588443	October 2018
Pexidartinib plus durvalumab	I	Metastatic/advanced PDA	NCT02777710	June 2019
Galunisertib (LY2157299) and durvalumab	I	Recurrent or refractory metastatic PDA	NCT02734160	June 2019

** Study NCT02403271 has completed. Efficacy results are not yet available but safety results have been posted at ClinicalTials.gov. Study NCT02588443 has completed but efficacy and safety results are not yet available.*
BL-8040 = an immunotherapy agent—CXCR4 antagonist; CRS-207 = an immunotherapy agent (Aduro Biotech, Berkeley, California, USA) against specific tumor-associated antigens; ECOG = Eastern Cooperative Oncology Group; GVAX = irradiated, autologous pancreatic cancer vaccine; mFOLFIRINOX = a modified fluorouracil and folinic acid, oxaliplatin, and irinotecan regimen; PDA = pancreatic ductal adenocarcinoma; RT = radiotherapy; SBRT = stereotactic body radiation therapy.

According to the ASCO pancreatic cancer guidelines[119] and a more recent update,[120] the following options are updated or newly recommended for the treatment of metastatic PDA in 2018:

- For patients with Eastern Cooperative Oncology Group performance status (ECOG PS) ≥3, the major emphasis should be on optimizing best supportive care measures (evidence quality: intermediate).
- Routine testing for deficiency in mismatch repair or high microsatellite instability is recommended (evidence quality: low). For patients who tested positive for deficiency in mismatch repair or microsatellite instability, the checkpoint inhibitor such as pembrolizumab is recommended (evidence quality: intermediate).
- Gemcitabine + nab-paclitaxel can be given as second-line therapy to patients who have received first-line FOLFIRINOX and have an ECOG PS of 0–1 and a favorable comorbidity profile (evidence quality: low).
- Fluorouracil + nanoliposomal irinotecan, or fluorouracil + irinotecan as second-line therapy for patients who received first-line gemcitabine + nab-paclitaxel, have an ECOG PS of 0–1 and a favorable comorbidity profile (evidence quality: low).
- Fluorouracil + oxaliplatin may be considered as second-line therapy for patients who received first-line gemcitabine + nab-paclitaxel, have an ECOG PS of 0–1 and a favorable comorbidity profile (evidence quality: low).
- Gemcitabine or fluorouracil can be considered as second-line therapy for patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more aggressive regimens and want to continue anticancer therapy (evidence quality low).
- No data available supporting third-line (subsequent-line) cytotoxic therapy.

Supportive care

PDA is a debilitating disease associated with multiple complex symptoms. In addition to anticancer therapies, patients diagnosed with PDA often

Table 5: Ongoing pancreatic ductal adenocarcinoma clinical trials investigating chemotherapeutic approaches

Intervention	Phase	Cancer stage	ClinicalTrials.gov identifier	Estimated completion date
SOXIRI (S-1, oxaliplatin and irinotecan)	II	Inoperable/metastatic PDA (previous systemic chemotherapy, neoadjuvant or adjuvant allowed if not irinotecan, oxaliplatin, or S1).	NCT03403101	December 2019
FOLFOX-A (fluorouracil, oxaliplatin, leucovorin and Abraxane®, Celgene, Summit, New Jersey, USA)	II	Metastatic PDA without previous chemotherapy	NCT02080221	December 2018
mFLOX regimen (fluorouracil bolus and oxaliplatin)	II	Metastatic or unresectable PDA without previous chemotherapy	NCT02896803	August 2018
EndoTAG-1 (liposomes carrying embedded paclitaxel) plus gemcitabine	III	Metastatic PDA	NCT03126435	July 2020
Alternating cycles of gemcitabine monotherapy followed by nab paclitaxel/ gemcitabine	II	Metastatic PDA	NCT02564146	June 2019

PDA = pancreatic ductal adenocarcinoma; S1 = tegafur/gimeracil/oteracil.

need interventions to provide relief of biliary and/or duodenal obstruction, malnutrition, and pain.[69] The endoscopic placement of self-expandable metal stents can be used to palliate biliary and duodenal obstruction.[121] Patients with PDA are at high risk of thrombo-embolic events, which increase morbidity and mortality.[71] Results from a randomized controlled trial indicate that anticoagulation may be useful for preventing serious morbidity, but did not improve survival.[122] Pain management is an important priority for patients with advanced PDA. Key sources of pain are from an enlarging primary tumor and/or liver capsular pain associated with metastatic disease. Celiac plexus neurolysis blocks the pain signals transmitted along the celiac plexus infiltrated by primary PDA and has been shown to provide a high level of pain relief in the majority of patients.[123] The technique tends to be reserved for patients refractory to opioids or those suffering a high level of toxicity; the benefits of early intervention have never been formally tested.

Weight loss in pancreatic cancer can be due to anorexia, malabsorption, and/or cachexia.[124] Palliative interventions include pancreatic enzyme replacement therapy[125] and the use of thalidomide to attenuate weight loss in patients with cachexia.[126] In addition, PDA is associated with high rates of depression and suicide,[127] emphasizing the need to monitor patient distress.

Discussion and future perspectives

Current PDA treatments offer limited benefits; at best, they delay progression and extend survival for very short durations.[1,9,128] Among 35 different agents or combinations that have been tested in phase III studies in the last 25 years, only 11% have entered clinical practice.[129] Resistance to conventional chemotherapy and radiotherapy is often innate, rather than acquired.[9] In addition, the majority of patients diagnosed with PDA are older and frailer compared with patient groups diagnosed with more common cancers. They also tend to have poor functional status associated with late presentation, including biliary and bowel obstruction, cachexia and abdominal pain, thus limiting their tolerance of anticancer therapies. Improving outcomes for patients with PDA is therefore a global urgent unmet need and the focus for both preclinical and clinical research. A search of the US National Library of Medicine (ClinicalTrials.gov) in October 2018 identified multiple ongoing trials of chemotherapy agents aiming to adapt doublet (gemcitabine + nab-paclitaxel) and triplet (FOLFIRINOX) therapies to improve outcomes in PDA (*Table 5*). Biologically targeted agents have been extensively evaluated as a therapeutic strategy in PDA. Despite promising early studies, agents targeting epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), insulin-like growth factor 1 receptor (IGF-1 R), vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR), NOTCH and WNT have proved ineffective.[129] New targets are being evaluated particularly focusing on the microenvironment and mechanisms to amplify T-cell immune response (*Table 6*).

Immune checkpoint blockade has, to date, proved a disappointing therapeutic strategy for PDA. Neither anti-CTLA4 nor anti-PD1 antibodies have shown activity as single agents overall.[130] The only exception so far is the slight activity of pembrolizumab in microsatellite instability-high tumors,[119] which represent <5% of all PDA.[131,132] One serious challenge for immunotherapy in PDA is that it has a non-inflamed microenvironment with a dearth of T cells and the tumor mutational burden is low relative to other cancers, such as melanoma and lung cancer, against which checkpoint inhibitors are proving most effective. Despite this, numerous clinical trials are currently investigating immunotherapy approaches, most of which are at early stages of development and results are awaited with much interest (*Table 4*).

An integrated approach using both germline testing and somatic analyses of tumor tissues and next-generation sequencing may assist with the choice of treatment for individual patients in the future.[49,133] Some key novel comprehensive national research strategies are currently aiming to develop molecular stratified treatment approaches within clinical trials and in regular clinical practice. These initiatives include Precision Promise in the USA, which is a coordinated and adaptive randomized clinical trial platform that allows multiple novel therapies to be evaluated and aims to expedite their approval for use in PDA.[134] In the UK, Precision Panc is establishing a coordinated system aiming to increase the speed of scientific discovery and clinical trials and to develop personalized treatments in order to rapidly improve survival in PDA.[135] These systematic approaches to molecular profiling and molecular stratification of PDA involve considerable investment and may well yield significant benefits in the longer term.

Table 6: Ongoing PDA clinical trials investigating biological targeted agents

Intervention	Target	Phase	Cancer stage	ClinicalTrials.gov identifier	Estimated completion date
BVD-523 plus nab paclitaxel and gemcitabine	MEK/ERK	I	Newly diagnosed metastatic PDA	NCT02608229	December 2021
GSK2256098 and trametinib	FAK/MEK	II	Advanced PDA that is not responsive to standard therapies	NCT02428270	December 2018
Ibrutinib plus nab-paclitaxel and gemcitabine	BTK	I/II	Metastatic PDA	NCT02562898	June 2019
Plerixafor	CXCR4	I	Locally advanced or metastatic PDA refractory to conventional chemotherapy	NCT03277209	December 2020
Palbociclib plus gedatosilib	CDK 4/6 P13K/mTOR	I	Advanced PDA	NCT03065062	January 2023
LGK974	Wnt/β-catenin	I	BRAF mutant locally advanced or metastatic PDA hat has progressed despite standard therapy	NCT01351103	January 2020
PEGPH20 plus gemcitabine and nab-paclitaxel	HA	III	HA-high Stage IV previously untreated PDA	NCT02715804	December 2019

BTK = Bruton's tyrosine kinase; CDK4/6 = cyclin D dependent kinase 4 and 6; CSF1R = colony stimulating factor 1 receptor; ERK = extracellular signal-regulated kinase; FAK = focal adhesion kinase-1; HA = hyaluron; MEK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; PDA = pancreatic ductal adenocarcinoma; S1 = tegafur/gimeracil/oteracil; TGF-β = transforming growth factor-β.

Conclusion

PDA has been described as an 'insidious clinical syndrome'[9] that has one of the worst cancer outcomes. Although some environmental and lifestyle factors are implicated in cause, no systematic preventative strategies are in place. Biomarkers to aid detection and treatment are lacking. Most patients present with unresectable disease and despite optimal systemic therapy, life expectancy for most patients remains <1 year. Despite this poor experience, research into PDA molecular pathophysiology is generating increasing understanding of how this cancer grows and evades intervention. In addition, many new targets are emerging which are being exploited as novel therapeutic targets. Clinical trials, some of which have been summarized here, therefore offer our patients the best hope for the future. ❑

1. Borazanci E, Dang CV, Robey RW, et al. Pancreatic cancer: "a riddle wrapped in a mystery inside an enigma". *Clin Cancer Res*. 2017;23:1629–37.
2. Martin AM, Hidalgo M, Alvarez R, et al. From first line to sequential treatment in the management of metastatic pancreatic cancer. *J Cancer*. 2018;9:1978–88.
3. Puckett Y, Garfield K. Cancer, Pancreas. [Updated 2019 Mar 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan. Available at: www.ncbi.nlm.nih.gov/books/NBK518996/ (accessed April 27, 2019)
4. The Lancet Gastroenterology Hepatology. Pancreatic cancer: how can we tackle the lack of progress? *Lancet Gastroenterol Hepatol*. 2017;2:73.
5. Chatterjee D, Katz MH, Rashid A, et al. Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer*. 2012;118:3182–90.
6. Karmazanovsky G, Fedorov V, Kubyshkin V, et al. Pancreatic head cancer: accuracy of CT in determination of resectability. *Abdom Imaging*. 2005;30:488–500.
7. Hidalgo M. Pancreatic cancer. *N Engl J Med*. 2010;362:1605–17.
8. Hidalgo M, Cascinu S, Kleeff J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. *Pancreatology*. 2015;15:8–18.
9. Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? *Therap Adv Gastroenterol*. 2013;6:321–37.
10. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. *World J Gastroenterol*. 2018;24:2047–60.
11. National Cancer Institute, Surveillance, Epidemiology and End Results Program (SEER) U.S. Cancer Stat Facts: Pancreatic Cancer. Availiable at: https://seer.cancer.gov/statfacts/html/pancreas.html (accessed August 23, 2018).
12. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356–87.
13. Thompson CA, Gomez SL, Hastings KG, et al. The burden of cancer in Asian Americans: a report of national mortality trends by Asian ethnicity. *Cancer Epidemiol Biomarkers Prev*. 2016;25:1371–82.
14. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74:2913–21.
15. Ilic M, Ilic I. Epidemiology of pancreatic cancer. *World J Gastroenterol*. 2016;22:9694–705.
16. International Agency for Research on Cancer (IARC), GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012, 2017. Available at: http://globocan.iarc.fr/Pages/summary_table_pop_sel.aspx (accessed August 23, 2018).
17. Gordon-Dseagu VL, Devesa SS, Goggins M, et al. Pancreatic cancer incidence trends: evidence from the Surveillance, Epidemiology and End Results (SEER) population-based data. *Int J Epidemiol*. 2018;47:427–39.
18. Lepage C, Capocaccia R, Hackl M, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999–2007: results of EUROCARE-5. *Eur J Cancer*. 2015;51:2169–78.
19. Huang L, Jansen L, Balavarca Y, et al. Stratified survival of resected and overall pancreatic cancer patients in Europe and the USA in the early twenty-first century: a large, international population-based study. *BMC Med*. 2018;16:125.
20. Shaib YH, Davila JA, El-Serag HB, The epidemiology of pancreatic cancer in the United States: changes below the surface. *Aliment Pharmacol Ther*. 2006;24:87–94.
21. Michaud DS, Giovannucci E, Willett WC, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA*. 2001;286:921–9.
22. Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol*. 2012;23:1880–8.
23. Villeneuve PJ, Johnson KC, Mao Y, et al. Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study. *Can J Public Health*. 2004;95:32–7.
24. Lucenteforte E, La Vecchia C, Silverman D, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol*. 2012;23:374–82.
25. Gupta S, Wang F, Holly EA, et al. Risk of pancreatic cancer by alcohol dose, duration, and pattern of consumption, including binge drinking: a population-based study. *Cancer Causes Control*. 2010;21:1047–59.
26. Liao WC, Tu YK, Wu MS, et al. Blood glucose concentration and risk of pancreatic cancer: systematic review and doseresponse meta-analysis. *BMJ*. 2015;349:g7371.
27. Sharma A, Chari ST. Pancreatic Cancer and Diabetes Mellitus. *Curr Treat Options Gastroenterol*. 2018;16:466–78.
28. Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and the risk of pancreatic cancer. *J Natl Cancer Inst*. 2009;101:424–31.
29. Greer JB, Yazer MH, Raval JS, et al. Significant association between ABO blood group and pancreatic cancer. *World J Gastroenterol*. 2010;16:5588–91.
30. Risch HA, Lu L, Wang J, et al. ABO blood group and risk of pancreatic cancer: a study in Shanghai and meta-analysis. *Am J Epidemiol*. 2013;177:1326–37.
31. Hassan MM, Li D, El-Deeb AS, et al. Association between hepatitis B virus and pancreatic cancer. *J Clin Oncol*. 2008;26:4557–62.
32. Xiao M, Wang Y, Gao Y, Association between Helicobacter pylori infection and pancreatic cancer development: a meta-analysis. *PLoS One*. 2013;8:e75559.
33. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *JAMA*. 2018;319:2401–9.
34. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112:580–93.
35. Becker AE, Hernandez YG, Frucht H, et al. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. *World J Gastroenterol*. 2014;20:11182–98.
36. Tan J, You Y, Guo F, et al. Association of elevated risk of pancreatic cancer in diabetic patients: A systematic review and meta-analysis. *Oncol Lett*. 2017;13:1247–55.
37. Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature*. 2010;467:1114–7.
38. Yu J, Blackford AL, Dal Molin M, et al. Time to progression of pancreatic ductal adenocarcinoma from low-to-high tumour stages. *Gut*. 2015;64:1783–9.
39. Hezel AF, Kimmelmann AC, Stangler BZ et al. Genetics and biology of pancreatic ductal adenocarcinoma. *Genes and Development*. 2006;20:1218–49.
40. Brentnall TA. Cancer surveillance of patients from familial pancreatic cancer kindreds. *Med Clin North Am*. 2000;84:707–18.
41. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science*. 2008;321:1801–6.
42. Pelosi E, Castelli G, Testa U. Pancreatic cancer: molecular characterization, clonal evolution and cancer stem cells. *Biomedicines*. 2017;5:pii:E65.
43. Aguirre AJ, Nowak JA, Camarda ND, et al. Real-time genomic characterization of advanced pancreatic cancer to enable precision medicine. *Cancer Discov*. 2018;8:1096–11.
44. Dreyer SB, Change DK, Bailey P, et al. Pancreatic cancer genomes: implications for clinical management and therapeutic development. *Clin Cancer Res*. 2017;23:1638–46.
45. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature*. 2012;491:399–405.
46. Ho J, Li X, Zhang L, et al. Translational genomics in pancreatic ductal adenocarcinoma: A review with re-analysis of TCGA dataset. *Semin Cancer Biol*. 2019;55:70–77.
47. Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature*. 2015;518:495–501.
48. Humphris JL, Patch AM, Nones K, et al. Hypermutation in pancreatic cancer. *Gastroenterology*. 2017;152:68–74e2.
49. Hu ZI, Shia J, Stadler ZK, et al. Evaluating Mismatch Repair Deficiency in Pancreatic Adenocarcinoma: Challenges and Recommendations. *Clin Cancer Res*. 2018;24:1326–36.
50. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for

germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381:317–27.
51. Gleeson FC, Levy MJ. Genomic profiling and potentially targetable alterations in pancreatic ductal adenocarcinoma. *Curr Treat Options Gastroenterol*. 2018;16:441–8.
52. Pishvaian MJ, Bender RJ, Halverson D, et al. Molecular profiling of patients with pancreatic cancer: initial results from the Know Your Tumor Initiative. *Clin Cancer Res*. 2018;24:5018–27.
53. Pancreatic Cancer Action Network, Know your tumor - powerful knowledge - personalized treatment, 2018. Available at: www.pancan.org/facing-pancreatic-cancer/patient-services/know-your-tumor/ (accessed October 23, 2018).
54. Gore J, Korc M. Pancreatic cancer stroma: friend or foe? *Cancer Cell*. 2014;25:711–2.
55. Ren B, Cui M, Yang G, et al. Tumor microenvironment participates in metastasis of pancreatic cancer. *Mol Cancer*. 2018;17:108.
56. Whatcott CJ, Diep CH, Jiang P, et al. Desmoplasia in primary tumors and metastatic lesions of pancreatic cancer. *Clin Cancer Res*. 2015;21:3561–8.
57. Son J, Lyssiotis CA, Ying H, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature*. 2013;496:101–5.
58. Zhan HX, Zhou B, Cheng YG, et al. Crosstalk between stromal cells and cancer cells in pancreatic cancer: New insights into stromal biology. *Cancer Lett*. 2017;392:83–93.
59. Chang JH, Jiang Y, Pillarisetty VG. Role of immune cells in pancreatic cancer from bench to clinical application: An updated review. *Medicine (Baltimore)*. 2016;95:e5541.
60. Murray PJ, Rathmell J, Pearce E. SnapShot: Immunometabolism. *Cell Metab*. 2015;22:190-e1.
61. Halbrook CJ, Lyssiotis CA. Employing metabolism to improve the diagnosis and treatment of pancreatic cancer. *Cancer Cell*. 2017;31:5–19.
62. Perera RM, Bardeesy N. Pancreatic cancer metabolism: breaking it down to build it back up. *Cancer Discov*. 2015;5:1247–61.
63. Chauhan VP, Boucher Y, Ferrone CR, et al. Compression of pancreatic tumor blood vessels by hyaluronan is caused by solid stress and not interstitial fluid pressure. *Cancer Cell*. 2014;26:14–5.
64. Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell*. 2012;21:418–29.
65. Cheng XB, Kohi S, Koga A, et al. Hyaluronan stimulates pancreatic cancer cell motility. *Oncotarget*. 2016;7:4829–40.
66. Hingorani SR, Zheng L, Bullock AJ, et al. HALO 202: Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. *J Clin Oncol*. 2018;36:359–66.
67. Lipponen P, Aaltomaa S, Tammi R, et al. High stromal hyaluronan level is associated with poor differentiation and metastasis in prostate cancer. *Eur J Cancer*. 2001;37:849–56.
68. Shepard HM. Breaching the castle walls: hyaluronan depletion as a therapeutic approach to cancer therapy. *Front Oncol*. 2015;5:192.
69. Hermann PC, Sainz B, Jr. Pancreatic cancer stem cells: a state or an entity? *Semin Cancer Biol*. 2018;53:223–31.
70. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26:v56–68.
71. Dabizzi E, Assef MS, Raimondo M. Diagnostic management of pancreatic cancer. *Cancers (Basel)*. 2011;3:494–509.
72. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006;166:458–64.
73. Koulouris AI, Banim P, Hart AR. Pain in patients with pancreatic cancer: prevalence, mechanisms, management and future developments. *Dig Dis Sci*. 2017;62:861–70.
74. Mushin M, Dabbous, O Morrison B, et al. Thromboembolic events in advanced pancreatic cancer: A systematic review. *J Clin Oncol*. 36:4;461.
75. Tan CR, Yaffee PM, Jamil LH, et al. Pancreatic cancer cachexia: a review of mechanisms and therapeutics. *Front Physiol*. 2014;5:88.
76. Goncalves B, Soares JB, Bastos P. Endoscopic ultrasound in the diagnosis and staging of pancreatic cancer. *GE Port J Gastroenterol*. 2015;22:161–71.
77. Ghaneh P, Hanson R, Titman A, et al. PET-PANC: multicentre prospective diagnostic accuracy and health economic analysis study of the impact of combined modality 18fluorine-2-fluoro-2-deoxy-d-glucose positron emission tomography with computed tomography scanning in the diagnosis and management of pancreatic cancer. *Health Technol Assess*. 2018;22:1–114.
78. Marrelli D, Caruso S, Pedrazzani C, et al. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. *Am J Surg*. 2009;198:333–9.
79. Koopmann J, Buckhaults P, Brown DA, et al. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. *Clin Cancer Res*. 2004;10:2386–92.
80. Mellby LD, Nyberg AP, Johansen JS, et al. Serum biomarker signature-based liquid biopsy for diagnosis of early-stage pancreatic cancer. *J Clin Oncol*. 2018;36:2887–94.
81. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*. 2018;359:926–30.
82. Madhavan B, Yue S, Galli U, et al. Combined evaluation of a panel of protein and miRNA serum-exosome biomarkers for pancreatic cancer diagnosis increases sensitivity and specificity. *Int J Cancer*. 2015;136:2616–27.
83. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62:339–47.
84. Capurso G, Signoretti M, Valente R, et al. Methods and outcomes of screening for pancreatic adenocarcinoma in high-risk individuals. *World J Gastrointest Endosc*. 2015;7:833–42.
85. Canto MI, Almario JA, Schulick RD, et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. *Gastroenterology*. 2018;155:740–51e2.
86. American Joint Committee on Cancer - Exocrine Pancreas. In Amin MB, Edge SB, Greene FL (eds.), *Cancer Staging Manual*. 8th ed, New York, New York, USA: Springer, 2017, 337–47.
87. Bachmann J, Michalski CW, Martignoni ME, et al. Pancreatic resection for pancreatic cancer. *HPB (Oxford)*. 2006;8:346–51.
88. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011–24.
89. Yamamoto T, Yagi S, Kinoshita H, et al. Long-term survival after resection of pancreatic cancer: a single-center retrospective analysis. *World J Gastroenterol*. 2015;21:262–8.
90. Zacharias T, Jaeck D, Oussoultzoglou E, et al. Impact of lymph node involvement on long-term survival after R0 pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas. *J Gastrointest Surg*. 2007;11:350–6.
91. Ferrone CR, Brennan MF, Gonen M, et al. Pancreatic adenocarcinoma: the actual 5-year survivors. *J Gastrointest Surg*. 2008;12:701–6.
92. Barugola G, Partelli S, Marcucci S, et al. Resectable pancreatic cancer: who really benefits from resection? *Ann Surg Oncol*. 2009;16:3316–22.
93. Toesca DAS, Koong AJ, Poultsides GA, et al. Management of borderline resectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2018;100:1155–74.
94. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200–10.
95. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297:267–77.
96. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA*. 2010;304:1073–81.
97. Conroy T, Hammel, P. Hebbar, M. et al Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. *J Clin Oncol*. 2018;36:LBA4001.
98. Tempero MA, Dana Backlund Cardin, Goldstein D, et al. APACT: Phase III randomized trial of adjuvant treatment with nab-paclitaxel (nab-P) plus gemcitabine (Gem) versus Gem alone in patients (pts) with resected pancreatic cancer (PC). *J Clin Oncol*. 2016;34:TPS473.
99. Celgene, Celgene Provides Update on ABRAXANE® Combination Therapy in the Treatment of Metastatic Triple-Negative Breast Cancer and Pancreatic Cancer, 2019. Available at: https://ir.celgene.com/press-releases/press-release-details/2019/Celgene-Provides-Update-on-ABRAXANE-Combination-Therapy-in-the-Treatment-of-Metastatic-Triple-Negative-Breast-Cancer-and-Pancreatic-Cancer/default.aspx (accessed March 19, 2019).
100. Columbus G, Nab-Paclitaxel Plus Gemcitabine Misses DFS Endpoint in Pancreatic Cancer, 2019. Available at: www.onclive.com/web-exclusives/nabpaclitaxelgemcitabine-combo-misses-dfs-endpoint-in-pancreatic-cancer (accessed 19 March 2019).
101. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med*. 2010;7:e1000267.
102. Mokdad AA, Minter RM, Zhu H, et al. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. *J Clin Oncol*. 2017;35:515–22.
103. Shahda S, Garrett House M, Zyromski N, et al. Prospective trial of preoperative FOLFIRINOX in patients with resectable pancreatic ductal adenocarcinoma (PDAC): Report of early endpoints. *J Clin Oncol*. 2018;36:4118.
104. Unno M, Motoi F, Matsuyama Y, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05). Presented at: American Sciety for Clinical Oncology Gastrointestinal Cancers Symposium, San Francisco CA USA, January 17–19, 2019.
105. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *JAMA*. 2016;315:1844–53.
106. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol*. 2013;14:317–26.
107. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol*. 2016;17:801–10.
108. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34:2654–68.
109. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817–25.
110. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691–703.
111. Tong H, Fan Z, Liu B, et al. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. *Sci Rep*. 2018;8:8666.
112. Rahma OE, Duffy A, Liewehr DJ, et al. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. *Ann Oncol*. 2013;24:1972–9.
113. 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;32:2423–9.
114. Gill S, Ko YJ, Cripps C, et al. PANCREOX: a randomized phase iii study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. *J Clin Oncol*. 2016;34:3914–20.
115. Wang-Gillam A, Li CP, Bodoky G, et al. 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;387:545–57.
116. Kowaleski A, Szylberg Ł, Saganek M, et al. Emerging strategies in BRCA-positive pancreatic cancer. *J. Cancer Res & Clin Oncol*. 2018;144:1503–7.
117. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357:409–13.
118. Hong D, Rasco D, Veeder M, et al. A phase 1b/2 study of the Bruton Tyrosine Kinase inhibitor ibrutinib and the PD-L1 inhibitor durvalumab in patients with pretreated solid tumors. *Oncology*. 2019;97:102–11.
119. Sohal DP, Mangu PB, Khorana AA, et al. Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34:2784–96.
120. Sohal DPS, Kennedy EB, Khorana A, et al. Metastatic pancreatic cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36:2545–56.
121. Stark A, Hines OJ, Endoscopic and operative palliation strategies for pancreatic ductal adenocarcinoma. *Semin Oncol*. 2015;42:163–76.
122. Pelzer U, Opitz B, Deutschinoff G, et al. efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. *J Clin Oncol*. 2015;33:2028–34.
123. Wyse JM, Carone M, Paquin SC, et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol*. 2011;29:3541–6.
124. Hendifar AE, Petzel MBQ, Zimmers TA, et al. Pancreas cancer associated weight loss. *Oncologist*. 2018;pii:theoncologist.2018-0266. [Epub ahead of print].
125. Berry AJ. Pancreatic enzyme replacement therapy during pancreatic insufficiency. *Nutr Clin Pract*. 2014;29:312–21.
126. Gordon JN, Trebble TM, Ellis RD, et al. Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut*. 2005;54:540–5.
127. Turaga KK, Malafa MP, Jacobsen PB, et al. Suicide in patients with pancreatic cancer. *Cancer*. 2011;117:642–7.
128. Matrisian LM, Berlin JD. The past, present, and future of pancreatic cancer clinical trials. *Am Soc Clin Oncol Educ Book*. 2016;35:e205–15.
129. Andrikou K, Peterle C, Pipitone S, et al. Emerging antibodies for the treatment of pancreatic cancer. *Expert Opin Emerg Drugs*. 2017;22:39–51.
130. Hilmi M, Bartholin L, Neuzillet C. Immune therapies in pancreatic ductal adenocarcinoma: Where are we now? *World J Gastroenterol*. 2018;24:2137–51.
131. Eatrides JM, Coppola D, Al Diffalha S, et al. Microsatellite instability in pancreatic cancer. *J Clin Oncol*. 2016;34:15.
132. Knudsen ES, O'Reilly EM, Brody JR, et al. Genetic diversity of pancreatic ductal adenocarcinoma and opportunities for precision medicine. *Gastroenterology*. 2016;150:48–63.
133. Kamps R, Brandao RD, Bosch BJ, et al. Next-generation sequencing in oncology: genetic diagnosis, risk prediction and cancer classification. *Int J Mol Sci*. 2017;18:308.
134. Pancretic Cancer Action Network, Precision Promise - changing medicine -changing history - changing lives, 2018. Available at: www.pancan.org/research/precision-promise/ (accessed October 23, 2018).
135. Cancer Research UK, Precision Panc, 2018. Available at: www.precisionpanc.org (accessed October 23, 2018).