Pancreatic Cancer: "A Riddle Wrapped in a Mystery inside an Enigma"

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most difficult-to-treat cancers. With an increasing incidence and inability to make major progress, it represents the very definition of unmet medical need. Progress has been made in understanding the basic biology—systematic genomic sequencing has led to the recognition that PDAC is not typically a heavily mutated tumor, although there are exceptions. The most consistently mutated genes are *KRAS*, *CDKN2A*, *TP53*, and *SMAD4/DPC4*. Study of familial PDAC has led to the recognition that a variety of defects in DNA repair genes can be associated with the emergence of pancreatic cancer. Recent studies suggest that epigenetics may play a larger role than previously recognized. A major new understanding is the recognition that PDAC should be considered a composite of tumor cells, as well as pancreatic stellate cells, immune cells, and extracellular matrix. The individual components contribute to metabolic aberration, immune dysfunction, and chemotherapy resistance, and therapeutic innovations may be needed to address them individually. It has also been recognized that metastatic seeding from PDAC occurs very early in the disease course—in an estimated 73% of cases, once the tumor reaches 2 cm. The implication of this is that therapies directed toward micrometastatic disease and increasing fractional cell kill are most needed. Neoadjuvant approaches have been taken to increase resectability and improve outcome. So much work remains, and most critical is the need to understand how this tumor originates and develops. *Clin Cancer Res; 23(7); 1629–37. ©2017 AACR.*

See all articles in this *CCR Focus* section, "Pancreatic Cancer: Challenge and Inspiration."

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a deadly disease despite decades of cancer research and treatment advances. It is estimated that in 2017 in the United States, pancreatic cancer will be the third leading cause of cancer-related deaths, with more than 53,000 individuals diagnosed and more than 43,000 deaths (1). Only 9% of newly diagnosed pancreatic cancer is localized, and the 5-year overall survival (OS) rate is 8%, lagging behind other solid tumor malignancies (1). It is estimated that by the year 2030, pancreatic cancer will be the second leading cause of cancer death in the United States (2). Over the past several years, thanks to better preclinical models and funding, the biology of pancreatic cancer has become better understood, and multiagent chemotherapeutic combinations have given more options in the advanced disease setting (3, 4). However, the disease remains mystifyingly difficult to treat; immunotherapy has so far disappointed; and from a high-level view, progress has not been great. Hence, PDAC remains, as in Winston Churchill's BBC broadcast on October 1, 1939, "a riddle wrapped in a mystery inside an enigma" (5). In this *CCR Focus*, we highlight recent scientific insights, some of which have already had a clinical impact, with many more under study.

The incidence of PDAC increases sharply by decade past the age of 40 years, with most cases being diagnosed beyond the age of 60 years (6). The incidence rate is greater in blacks than in whites and greater in males than in females (6). There are several known risk factors, including the preventable risk factors tobacco, alcohol, and obesity. The Health Professionals Follow-Up Study and the Nurses' Health Study showed that in individuals with a body mass index (BMI) more than 30 kg/m^2, the relative risk of pancreatic cancer was 1.72 compared with those with a BMI of less than 23 kg/m^2 (7). Tobacco use and exposure, including second-hand smoke, is associated with an increased risk of PDAC, with a relative risk of 2.2 and 1.21, respectively (8, 9). Heavy alcohol use is also associated with an increased risk, and the risk appears to be greater with associated tobacco use. One epidemiology study showed an elevated risk (1.6) for PDAC in those consuming 9 or more drinks per day compared with those who abstain or drink less than 1 drink per day (10). The risk is also significant for those who smoke and binge drink at least once per month (11). Several population studies have shown that diabetes is a risk factor for pancreatic cancer. In a meta-analysis of several prospective studies, in individuals with pre-diabetes or diabetes, a 0.35% change in their hemoglobin A1C increases the risk of pancreatic cancer by 14% (12). Non-modifiable risks include inherited genetic predisposition, greater height (a relative risk of 1.81; refs. 7, 13), and blood group. In two large prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-Up Study, individuals with blood group O were less likely to develop pancreatic cancer; blood groups A, AB, and B conferred a multivariable hazard ratio (HR) of 1.32, 1.51, and 1.72, respectively (13). Similar findings were observed in other studies (14, 15). Biological explanations

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for these associations are not understood. Other risk factors that have been reported but warrant more investigation include infectious etiologies such as hepatitis B and *Helicobacter pylori* infections (16, 17).

Genetics and Epigenetics in Pancreatic Cancer

Beginning with the fundamental observation that more than 90% of PDACs harbor a KRAS driver mutation, it is clear that a keystone for progress in PDAC is understanding its genomic and epigenomic origins, discussed by Dreyer and colleagues in this *CCR Focus* (18). It is estimated that approximately 10% of all cases of pancreatic cancer have a hereditary component (19). Genes that are associated with hereditary PDAC usually involve the DNA repair pathway (i.e., *BRCA* genes, Lynch genes, Fanconi anemia genes, ataxia telangiectasia) or cell-cycle regulation (i.e., *CDKN2A*, Li-Fraumeni). It is also well established that a series of genetic events occur for the normal pancreatic ductal epithelium to progress to PDAC (20). An early inciting event is usually a mutation in KRAS, which alone is not sufficient to fully transform cells (21). As the pancreas cells progress from pancreatic intraepithelial neoplasia (PanIN)-1 to PanIN-3, other mutations occur, commonly *p16*, *p53*, *SMAD4/DPC4*, and DNA repair genes (20). Collaborative ventures such as The Cancer Genome Atlas (TGCA) have provided tumor sequencing data in hopes of generating insight into the mechanisms underlying pancreatic cancer. Most striking, and distressing, in several analyses has been the overall low mutation rates in PDAC and absence of any new common driver mutations (Figs. 1 and 2) beyond the well-known mutations above. A TCGA study published in 2015 examined 100 different PDAC specimens, extending the analysis to include copy number variation (CNV) analysis (22). They found prevalent chromosomal rearrangements and used that information to categorize the tumors into four different subtypes of pancreatic cancer: stable (20%), scattered (36%), unstable (14%), and locally rearranged (30%; ref. 22). Interestingly, the presence of the unstable subtype correlated well with those who had a dramatic response to platinum-based therapy. The other subtypes classified had rare prevalence of actionable targets such as *ERBB2*, *CDK6*, and *PIK3CA*, and work is needed to understand whether therapy directed at these targets will be worthwhile (23). In further sequencing by Bailey and colleagues on 456 patients, additional phenotypes were identified, including the squamous subtype, characterized by inflammation, hypoxia, metabolic reprogramming, TGFβ signaling, MYC pathway activation, autophagy, and upregulated expression of TP63 (24). The other subtypes include the pancreatic progenitor subtype involving several transcription factors important for diabetes, fatty acid oxidation, steroid hormone biosynthesis, mucin modification, and drug metabolism; the ADEX subtype representing a more terminally differentiated phenotype; and the immunogenic subtype relating to infiltrating B and T cells (24). Again, these classifications are important to note but bear further analysis in translation to therapeutic opportunities.

A key question is the role of mutant KRAS, long presumed to create a sustained and unregulated proliferation stimulus. Pancreatic cancer is unique in that *KRAS* mutation is one of the earliest events and is found in the precursor PanIN lesions. This is distinct from the findings in other malignancies, for example, acute myelogenous leukemia where founder mutations create epigenetic changes, and RAS emerges as a late oncogenic driver. KRAS may trigger proliferation in pancreatic cancer, but its presence in the PanIN lesions shows that it alone is not sufficient to

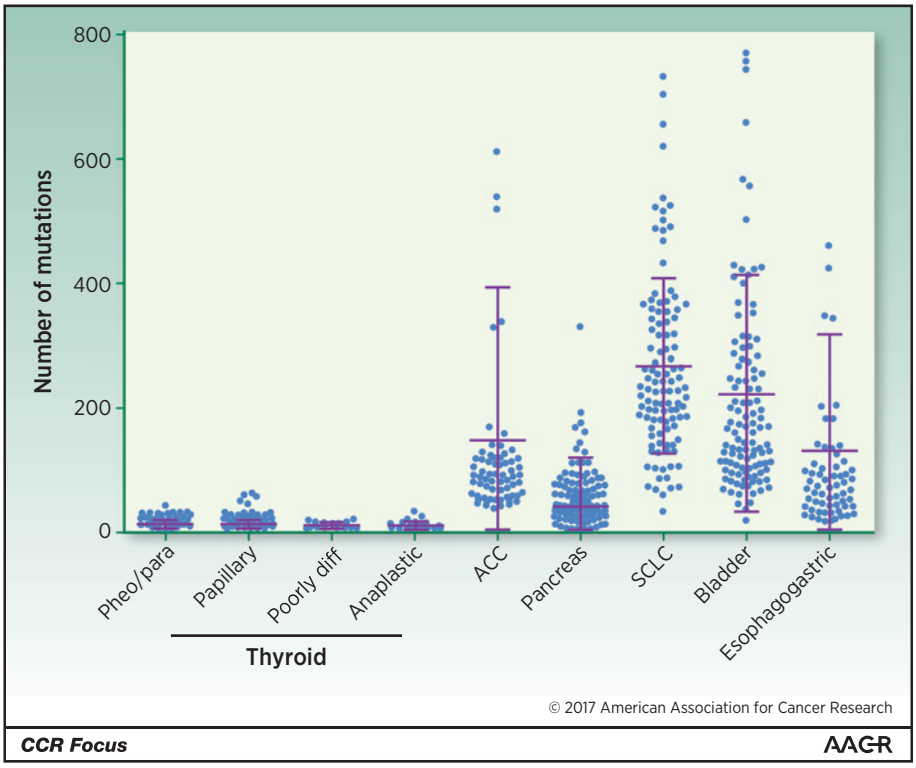

Figure 1.
Mutation burden from TCGA BioPortal [adapted from Bates (ref. 93)]. Graphs show the mutation counts for selected datasets of tumors sequenced and uploaded to the website. Note that mutation counts in pancreatic cancer exceed those in endocrine cancers but number fewer than many solid tumors. The results in the figure are based upon TCGA data and downloaded from cBioPortal (94, 95). ACC, adrenocortical cancer; Para, paraganglioma; Pheo, pheochromocytoma; Poorly diff, poorly differentiated thyroid cancer; SCLC, small-cell lung cancer.

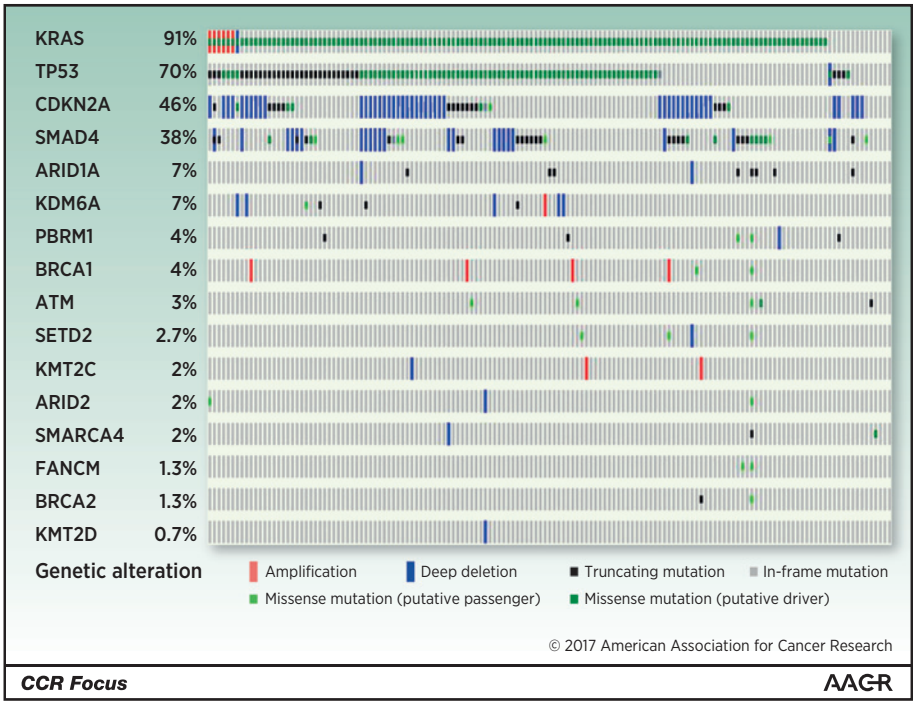

Figure 2.
Mutations in pancreatic cancer in the TCGA dataset in cBioPortal (94, 95). Shown are the four prevalent, well-known mutations in KRAS TP53, CDKN2A, and SMAD4, as well as mutations in chromatin remodeling and DNA repair genes found in the dataset.

support the malignant phenotype. As KRAS has between five and eight validated downstream signaling pathways, it is possible that pathways other than MAPK and AKT are more important, or that signaling provokes oxidative stress or inflammation, or a metabolic role. A direct KRAS inhibitor is desperately needed to resolve this question.

With the overall low mutation burden in PDAC comes the question of whether epigenomics plays a larger role than previously understood. DNA methylation may play a role in the loss of *p16* expression in pancreatic cancer development (25), and modification of histone acetylation may play a role in activating MYC to promote proliferation in pancreatic cancer (26). There are agents available to target both methylation, such as 5-azacytidine and decitabine, and histone deacetylases (HDAC), such as romidepsin, belinostat, and panobinostat (27). Another epigenetic target of interest in pancreatic cancer includes the bromodomain and extraterminal domain (BET) proteins. The BET proteins BRD2, BRD3, BRD4, and BRDT are important reader molecules that bind to acetylated histones and regulate transcription of genes involved in growth, fibrosis, inflammation, and malignancy (28). In a preclinical study examining the effects of BET inhibitors in AsPC1, Panc1, and CD18 cell lines, growth was inhibited and c-MYC and FOSL1 downregulated (28). In patient-derived tumor xenografts of pancreatic cancer, the BET inhibitor JQ1 had a significant effect on the pancreatic stroma and was synergistic with gemcitabine (29). Thus, targeting epigenetic pathways may yield further therapies for pancreatic cancer.

Genomics studies have encountered areas in the genome that have an unusually strong enrichment for binding of transcriptional coactivators (30). These so-called superenhancers in cancers such as lymphoma are responsible for activating oncogenes such as Myc. Evan and colleagues in their *CCR Focus* article postulate that normal regenerative programs that utilize superenhancers are exploited by PDAC cells (31). The role of Myc as a superenhancer regulator has been established in a variety of preclinical models in pancreatic cancer and has been shown to cooperate with KRAS to drive the progression of PanIN to pancreatic cancer and vice versa (32). Interestingly, an agent studied that has been effective in preclinical models, triptolide, has been shown to suppress Myc expression in PDAC xenografts (33). A phase I study of the prodrug of triptolide, minnelide, has been completed and a response in refractory pancreatic cancer observed (34).

Metabolism in Pancreatic Cancer

Understanding pancreatic cancer metabolism is complicated by the complexity of this cancer tissue that is comprised of PDAC cells, stromal (stellate) cells, immune cells, and an abundance of extracellular matrix (ECM; refs. 35, 36). The variability of desmoplasia triggered by stromal cells further complicates the reconstruction of a metabolic view of this cancer. At a global level, metabolic clinical positron emission tomography scanning suggests that the cancer is metabolically active when corrected for its variable low perfusion. Recent studies have led to the understanding that pancreatic cancer metabolism should be viewed as a composite picture rather than a unidimensional phenotype based on the PDAC cell itself. In this view, additional metabolic vulnerabilities may exist for therapeutic intervention beyond those of the PDAC cell (Fig. 3).

Because PDAC occurs in the context of a complex cancer tissue, deconstructing its components and their potential vulnerabilities could provide novel therapeutic strategies. At the autonomous cancer cell level, PDACs are extensively documented as having recurring oncogenic aberrations, such as *KRAS*, *TP53*, *SMAD4*, and *CDKN2A*, that are directly or indirectly linked to altered intermediary metabolism, autophagy, and macropinocytosis to

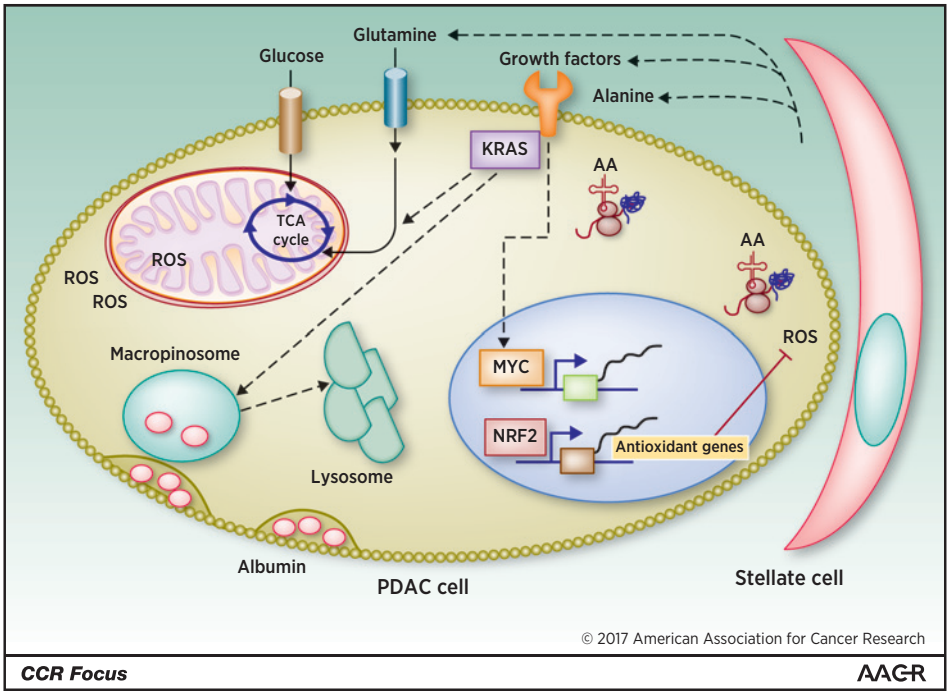

Figure 3.
PDAC metabolism: interplay between adenocarcinoma cells and stellate cells. This figure illustrates key pathways driving PDAC cell intrinsic alterations of metabolism linked to KRAS and MYC activation, which drive glutamininolysis, glycolysis, and macropinocytosis (a RAS-mediated phenotype that promotes consumption of proteins such as albumin, which is ultimately digested by lysosomal enzymes to release nutrients to support PDAC cell growth). NRF2 is depicted as a key transcription factor that modulates redox homeostasis for the survival of PDAC cells under oxidative stress of altered metabolism. The stellate cell is also depicted to modulate PDAC survival through provision of growth factors and nutrients. TCA cycle, tricarboxylic acid cycle.

sustain the metabolic needs of cancer cells (37). The stellate cells and adipocytes in the tumor microenvironment (TME) have been implicated both via metabolic synergies, producing and supplying the cancer cells with alanine and other metabolites, and via promotion of an inflammatory state. Infiltrating immune cells, such as lymphocytes, neutrophils, and macrophages, are also elements of the PDAC tumor. Each of these cells has its own metabolic profile, depending on the subtype, such as M1 (glycolytic) versus M2 (oxidative) macrophages as well as neutrophils that are permissive versus nonpermissive for tumor growth. Likewise, infiltrating lymphocytes may be a balance between cytotoxic T cells (glycolytic) versus those that are coaxed by the TME to become immunosuppressive regulatory T cells (Treg; oxidative; ref. 38).

Several approaches have targeted PDAC cell metabolism, and proof-of-concept studies have emerged to suggest that metabolic vulnerabilities do exist. The PDAC cell–intrinsic alterations in glycolysis, glutaminolysis, mitochondrial, and redox homeostasis have been potential targets. For example, KRAS-mutant cells are said to rely on a noncanonical glutamine pathway to supply redox capacity as well as micronutrients (39). Glutaminase inhibition in combination with metformin, which inhibits mitochondrial function, seems to be synergistic in highly simplified preclinical models (40). Knockdown of glutaminase in PDAC could synergize with ROS stress, but pathways involving transaminases and NRF2 are important for PDAC metabolic adaptation and may attenuate the effects of inhibiting glutaminase (39). In another example, the nonspecific lactate dehydrogenase A (LDHA) inhibitor, FX11, has been documented to diminish patient-derived pancreatic xenografts in a manner that seems to correlate with the tumor TP53 status and to be independent of KRAS status (41). Inhibition of autophagy is also being studied; as a key component for the survival of many PDACs, autophagy provides a therapeutic target already translated to clinical studies with hydroxychloroquine (42). Potential vulnerabilities of PDAC due to dependency on NRF2 for redox homeostasis and macroautophagy triggered by KRAS have not been fully exploited preclinically. It can be surmised, however, that the macroautophagy phenotype of PDACs could underlie their sensitivity to paclitaxel protein bound (Abraxane; Celgene) via inhibition of trafficking on microtubules (43–46).

Efforts to understand the stromal compartment have generated some hope with the ability of synthetic vitamin D analogues to diminish the function of stellate cells that support the survival of the PDAC cancer cells. Indeed, preclinical studies demonstrate that the active vitamin D analogue calcipotriol could diminish tumor growth and normalize the pancreatic stromal environment in preclinical models (47). Another synthetic vitamin D analogue, paricalcitol, is being studied in clinical trials (NCT02030860). Stellate cells have also been implicated in the transfer of alanine to PDAC cells in an autophagy-dependent manner, such that inhibition of autophagy clinically could deprive pancreatic cancer of nutrients (48). Adipocytes in obese animals stimulate and sustain a tumor-permissive inflammatory state by secreting IL1β that in turn recruits tumor-associated neutrophils and alters the metabolic milieu. The hypoxic PDAC TME also increases lactate that has also been implicated in providing an immunosuppressive tumor environment (49). Even though PDAC biology and the metabolic microenvironment are complex, the richer understanding of the components separately and in a reconstructed state using metabolic inhibitors in combination with standard and immunotherapeutic agents could provide paradigm-shifting therapeutic strategies for this still highly lethal disease.

Re-engineering the Pancreas TME

As discussed in the *CCR Focus* article by Evan and colleagues (31), the study of PDAC in preclinical models has led to several

Table 1. Selected strategies for immunotherapy in pancreatic cancer

Target	Rationale
CSF1R, CCR2	Inhibitors antagonize recruitment of immunosuppressive macrophages
CD40	CD40 agonists activate T cells
IDO	Inhibition of IDO enzyme leads to increase in NK cell activity
CXCR4	Inhibition of CXCR4/CXCL12 leads to mobilization of NK, T, and B cells
FAK	FAK inhibition leads to stromal remodeling
Vitamin D receptor	Vitamin D agonists affect stromal microenvironment; decrease MDSCs, M2 macrophages, and Tregs
Checkpoint inhibition combination	Inhibition of both CTLA-4 and PD-1/PD-L1 promotes T-cell activation
Chemotherapy	May decrease MDSCs and Tregs

NOTE: Discussed in detail by Johnson and colleagues (62).
Abbreviations: IDO, indoleamine-2,3 dioxygenase; NK, natural killer.

new insights. The pancreas TME promotes an anti-chemotherapeutic and protumor immune environment (50). As noted above, the pancreas TME is a result of the interplay between several different types of cells, including the pancreatic epithelial cell, cancer-associated fibroblasts (CAF), pancreatic stellate cells (PSC), and various cytokines, all promoting a favorable environment for tumor growth. CAFs produce factors that promote tumor growth including hepatocyte growth factor, VEGF, EGF, and matrix-modifying proteins (MMP) such as MMP-2 and MMP-9, inducing desmoplastic changes in the ECM (51). PSCs are the predominant fibroblastic cell type in the PDAC microenvironment and promote an epithelial-to-mesenchymal transition (EMT) in PDAC (52). Activated PSCs also promote $CD8^+$ chemotaxis toward the stroma, preventing it from accessing the tumor area (53). Activated PSCs also increase immunosuppressive myeloid-derived suppressor cells (MDSC), along with cancer-supporting M2 macrophages (54). Targeting the pancreas TME thus has the potential to improve treatment options—from chemotherapeutic to immunotherapeutic.

Immunotherapy Resistance and the Microbiome

The field of immunotherapy has generated great excitement in oncology in recent years. The use of checkpoint inhibitors such as those that block cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and PD-ligand 1 (PD-L1) has caused tumor shrinkage and long-lasting remission in individuals with advanced melanoma (55, 56), non–small cell lung cancer (57), Hodgkin lymphoma (58), head and neck squamous carcinoma (59), Merkel cell carcinoma (60), and bladder cancer (61). However, as discussed by Johnson and colleagues in this *CCR Focus*, these same results have been elusive for PDAC (62). In a phase II trial utilizing single-agent ipilimumab, an anti–CTLA-4 therapeutic, for locally advanced or metastatic PDAC, there were no responses seen and one "delayed" response (63). In a phase I trial in several different cancers being treated with an anti–PD-L1 therapy, none of the 14 individuals with PDAC had a response (64). Save for encouraging activity in a small cohort of patients with PDAC with mismatch repair–deficient tumors (65), it is clear that single-agent checkpoint inhibitor treatment in pancreatic cancer is not a viable option. Other approaches to improve immune therapy have shifted focus on the pancreas tumor environment. Focal adhesion kinase (FAK) is a cytoplasmic protein tyrosine kinase that plays a role in maintaining the PDAC stroma (66). In a preclinical model utilizing the KPC mouse model, the addition of an FAK inhibitor to gemcitabine and an anti–PD-1 inhibitor showed great synergy, along with trafficking of lymphocytes into the pancreatic tumor (66). Targeting the chemokine CXCL12 and its receptor CXCR4 has shown an effect on the immune system, mobilizing natural killer cells, T cells, and B cells, which allows the accumulation of immune cells in a tumor environment that would otherwise not exist and preclinically has exhibited synergy with checkpoint inhibition (67). Such strategies are listed in Table 1 and discussed in detail by Johnson and colleagues (62).

Other targets also include chemokines, such as CXCR2, whose inhibition in preclinical pancreas models shows synergy with PD-1 inhibition (68). Cytotoxic chemotherapies, such as gemcitabine, platinums, and taxanes (which are all agents approved for PDAC treatment), have an effect on Tregs and MDSCs and have also shown synergy with checkpoint inhibition in preclinical models (69–71). There are several other potential synergistic targets with checkpoint inhibition focusing on the TME including vitamin D receptor, TGFβ, and platelet-derived growth factor (PDGF) β, among others, currently being investigated in clinical trials (54). The microbiome is a developing area of study involving the examination of the microbial flora in humans and its effects on health. Of interest is that several gut microbiota have immunogenic effects and may be able to combine with checkpoint inhibitors to improve activity in pancreatic cancer (72). So although immunotherapy has been a disappointing option for pancreatic cancer, there remain several important lines of investigation.

New Biology and Strategies in the Clinic

Treatment for PDAC, like other malignancies, has benefited from research through better understanding of its molecular biology and subsequent clinical trials, although the gains have been modest to date. Pancreatic cancer remains a very difficult disease to treat with chemotherapy. In their *CCR Focus* article, Manji and colleagues outline strategies that are currently in clinical testing (73). The development of better models may help, including patient-derived xenograft models and the KPC mouse model derived from mutations in *KRAS* and *p53* (74, 75). Until 2011, the standard therapeutic option for advanced pancreatic cancer was single-agent gemcitabine that was shown to improve the 1-year survival rate from 2% with the previous standard, 5-fluoruracil (5-FU), to 18% (76). OS improved from 4.41 to 5.65 months. Numerous gemcitabine combinations were tested—only a combination with the EGF receptor inhibitor erlotinib improved the OS to 6.24 months compared with 5.91 months (77). The gain was modest, and its clinical impact

can be questioned despite FDA approval. In 2011, however, the combination of 5-FU with irinotecan and oxaliplatin (FOLFIRINOX) showed a median survival of 11.1 months compared with 6.8 months with gemcitabine alone (3). Subsequently, the combination of nab-paclitaxel with gemcitabine showed an OS of 8.5 months compared with 6.7 months with gemcitabine alone, supporting its FDA approval (4). This has meant there are now two accepted regimens for metastatic disease.

Recently, a second-line option gained FDA approval. Nanoliposomal irinotecan comprises irinotecan-free base encapsulated in liposome nanoparticles (78). Preclinical studies suggested that the active metabolite of irinotecan, SN-38, becomes more concentrated in tumors compared with the typical formulation of irinotecan (79). After progression on a gemcitabine-containing regimen, the combination of nanoliposomal irinotecan with 5-FU and leucovorin improved OS from 4.2 to 6.1 months compared with 5-FU and leucovorin alone (78). Thus, looking at traditional therapeutics and improving their delivery may lead to more effective treatments for individuals with pancreatic cancer.

Other avenues of interest include targeting DNA repair and the TME. As mentioned previously, sequencing introduced DNA repair as a potential therapeutic target (18). In a retrospective study in individuals with PDAC with germline *BRCA1* or *BRCA2* mutations, a survival benefit was seen when adding platinum therapy versus those treated without platinum—22 versus 9 months (80). Furthermore, a 21.7% overall response rate was observed among 23 patients with either a *BRCA1* or a *BRCA2* mutation treated with the PARP inhibitor olaparib (FDA approved for *BRCA*-mutated ovarian cancer; ref. 81). Other studies are underway that focus on treating individuals with DNA-damaging agents combined with PARP inhibitors, DNA-PK inhibitors, and other agents that target the DNA damage response.

As noted above, the pancreas tumor environment is characterized by fibrosis that is supported by PSCs, creating a barrier preventing the delivery of chemotherapy and potentially the infiltration of immune cells (50). Hyaluronan, often overexpressed in PDAC stroma, is thought to contribute (82). A phase II trial randomizing individuals with advanced pancreatic cancer to receive nab-paclitaxel plus gemcitabine with or without PEGylated recombinant human hyaluronidase (PEGPH20) to degrade hyaluronan, demonstrated a progression-free survival benefit in patients whose tumors had high hyaluronan expression (9.2 months) compared with low hyaluronan expression (5.3 months; ref. 83). A phase III study enrolling patients on the basis of tumor hyaluronan expression (NCT02715804) is ongoing.

Adjuvant and Neoadjuvant Therapies

The accepted paradigm in individuals with resectable PDAC is to proceed to surgery in a fit, healthy individual and then to follow that with adjuvant chemotherapy. Gemcitabine or 5-FU monotherapy with or without radiation therapy has been the standard-of-care for many years despite innumerable unsuccessful efforts, albeit most in the metastatic setting, to improve on gemcitabine efficacy by combining with a second agent. Reported in abstract form in 2016, the ESPAC-4 study changed that paradigm, showing improved survival in the adjuvant setting with the combination of gemcitabine and capecitabine (84). Compared with gemcitabine alone, the median OS increased from 25.5 to 28.0 months, and the 5-year survival rate increased from 16.3% to 28.8% with the combination. Results from an adjuvant trial comparing gemcitabine alone to gemcitabine in combination with nab-paclitaxel are awaited (NCT01964430).

The identification of active combinations has led to an increasing interest in the earlier introduction of chemotherapy. Pancreatic cancer is a disease that metastasizes early. In a computational model based upon 228 patients with pancreatic cancer with 101 autopsies, the risk of an individual harboring metastatic disease increased from 28% at a 1-cm pancreas tumor size to 73% at 2 cm and 94% in those with 3-cm or larger tumors (85). The argument for neoadjuvant therapy lies in concern over residual tumor left after resection or with the presence of lymph node–positive disease or for micrometastatic disease elsewhere. Furthermore, a frequent criticism of published adjuvant studies is the dropout rates of those being able to participate due to the effects of recovery from pancreatic cancer surgery. In a retrospective single-institution analysis in individuals with resectable pancreatic cancer, the use of neoadjuvant therapy resulted in a 31.5-month median survival (86). A randomized study would be needed to show that this 31.5-month survival exceeds the 28 months in ESPAC-4. In a similar report, a propensity score analysis was used to analyze observational data, matching more than 2,000 patients who received neoadjuvant therapy with patients undergoing upfront resection followed by adjuvant therapy (87). Here, neoadjuvant therapy was associated with a 26-month median survival compared with 23 months for the group undergoing upfront resection. It is intriguing to note that the neoadjuvant therapies in both studies were not optimized for current best PDAC metastatic disease regimens. Prospective studies are ongoing and examine the newer combinations of FOLFIRINOX and nab-paclitaxel plus gemcitabine in the neoadjuvant setting. Parenthetically, there are also multiple reports in the literature of a modified FOLFIRINOX regimen to reduce dose while preserving efficacy. It is not clear that modified FOLFIRINOX (mFOLFIRINOX) offers the same benefit as full dose FOLFIRINOX in the neoadjuvant setting.

Conclusions

Despite the difficulty in treating those with pancreatic cancer, there remains hope for the future. New awareness of the genetics, epigenetics, and microenvironment in pancreatic cancer has increased our understanding of the disease and offered new therapeutic approaches for study. Multiple immunotherapy strategies are in preclinical and clinical development. As detailed by Manji and colleagues (73), many clinical trials are available for those with pancreatic cancer, ranging from neoadjuvant to refractory metastatic disease. Early detection of pancreatic cancer by way of screening and the development of biomarkers is also an area of increasing research. Almost 15,000 patients have taken part in randomized clinical trials in pancreatic cancer (88–92)—evidence of the courage and determination of individuals faced with a very difficult diagnosis and prognosis. And, in that, is inspiration for those working in the field.

Disclosure of Potential Conflicts of Interest

E. Borazanci reports receiving speakers bureau honoraria from Celgene and Merrimack and is a consultant/advisory board member for Merrimack. No potential conflicts of interest were disclosed by the other authors.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. 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.
3. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
5. BBC Broadcast. The Russian enigma. London, England: The Churchill Society; 1939 [cited 1939 Oct 1]. Available from: http://www.churchill-society-london.org.uk/RusnEnig.html.
6. 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.
7. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001;286:921–9.
8. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012; 23:1880–8.
9. Villeneuve PJ, Johnson KC, Mao Y, Hanley AJ, Canadian Cancer Registries Research Group. 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.
10. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, 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.
11. Gupta S, Wang F, Holly EA, Bracci PM. 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.
12. Liao WC, Tu YK, Wu MS, Lin JT, Wang HP, Chien KL. Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis. BMJ 2015;349:g7371.
13. Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst 2009; 101:424–31.
14. Risch HA, Lu L, Wang J, Zhang W, Ni Q, Gao YT, et al. ABO blood group and risk of pancreatic cancer: a study in Shanghai and meta-analysis. Am J Epidemiol 2013;177:1326–37.
15. Greer JB, Yazer MH, Raval JS, Barmada MM, Brand RE, Whitcomb DC. Significant association between ABO blood group and pancreatic cancer. World J Gastroenterol 2010;16:5588–91.
16. Xiao M, Wang Y, Gao Y. Association between *Helicobacter pylori* infection and pancreatic cancer development: a meta-analysis. PLoS One 2013;8: e75559.
17. Hassan MM, Li D, El-Deeb AS, Wolff RA, Bondy ML, Davila M, et al. Association between hepatitis B virus and pancreatic cancer. J Clin Oncol 2008;26:4557–62.
18. Dreyer SB, Chang DK, Bailey P, Biankin AV. Pancreatic cancer genomes: implications for clinical management and therapeutic development. Clin Cancer Res 2017;23:1638–46.
19. Hruban RH, Canto MI, Goggins M, Schulick R, Klein AP. Update on familial pancreatic cancer. Adv Surg 2010;44:293–311.
20. Hruban RH, Goggins M, Parsons J, Kern SE. Progression model for pancreatic cancer. Clin Cancer Res 2000;6:2969–72.
21. Zimmermann G, Papke B, Ismail S, Vartak N, Chandra A, Hoffmann M, et al. Small molecule inhibition of the KRAS-PDEδ interaction impairs oncogenic KRAS signalling. Nature 2013;497:638–42.
22. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518:495–501.
23. Ho GY, Woodward N, Coward JI. Cisplatin versus carboplatin: comparative review of therapeutic management in solid malignancies. Crit Rev Oncol Hematol 2016;102:37–46.
24. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531:47–52.
25. Rosty C, Geradts J, Sato N, Wilentz RE, Roberts H, Sohn T, et al. p16 Inactivation in pancreatic intraepithelial neoplasias (PanINs) arising in patients with chronic pancreatitis. Am J Surg Pathol 2003;27: 1495–501.
26. Köenig A, Linhart T, Schlengemann K, Reutlinger K, Wegele J, Adler G, et al. NFAT-induced histone acetylation relay switch promotes c-Myc-dependent growth in pancreatic cancer cells. Gastroenterology 2010;138:1189–99.
27. Lomberk GA, Iovanna J, Urrutia R. The promise of epigenomic therapeutics in pancreatic cancer. Epigenomics 2016;8:831–42.
28. Sahai V, Kumar K, Knab LM, Chow CR, Raza SS, Bentrem DJ, et al. BET bromodomain inhibitors block growth of pancreatic cancer cells in three-dimensional collagen. Mol Cancer Ther 2014;13:1907–17.
29. Yamamoto K, Tateishi K, Kudo Y, Hoshikawa M, Tanaka M, Nakatsuka T, et al. Stromal remodeling by the BET bromodomain inhibitor JQ1 suppresses the progression of human pancreatic cancer. Oncotarget 2016;7:61469–84.
30. Pott S, Lieb JD. What are super-enhancers? Nat Genet 2015;47:8–12.
31. Evan GI, Hah N, Littlewood TD, Sodir NM, Campos T, Downes M, et al. Re-engineering the pancreas tumor microenvironment: a "regenerative program" hacked. Clin Cancer Res 2017;23:1647–55.
32. Ischenko I, Zhi J, Moll UM, Nemajerova A, Petrenko O. Direct reprogramming by oncogenic Ras and Myc. Proc Natl Acad Sci U S A 2013;110: 3937–42.
33. Ding X, Zhou X, Jiang B, Zhao Q, Zhou G. Triptolide suppresses proliferation, hypoxia-inducible factor-1α and c-Myc expression in pancreatic cancer cells. Mol Med Rep 2015;12:4508–13.
34. Greeno E, Borazanci EH, Gockerman JP, Korn RL, Saluja A, Von Hoff DD, et al. Phase I dose escalation and pharmokinetic study of a modified schedule of 14-o-phosphonooxymethyltriptolide. J Clin Oncol 34, 2016 (suppl 4S; abstr TPS472).
35. Halbrook CJ, Lyssiotis CA. Employing metabolism to improve the diagnosis and treatment of pancreatic cancer. Cancer Cell 2017;31:5–19.
36. Perera RM, Bardeesy N. Pancreatic cancer metabolism: breaking it down to build it back up. Cancer Discov 2015;5:1247–61.
37. Ying H, Dey P, Yao W, Kimmelman AC, Draetta GF, Maitra A, et al. Genetics and biology of pancreatic ductal adenocarcinoma. Genes Dev 2016; 30:355–85.
38. Murray PJ, Rathmell J, Pearce E. SnapShot: immunometabolism. Cell Metab 2015;22:190.
39. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 2013;496:101–5.
40. Elgogary A, Xu Q, Poore B, Alt J, Zimmermann SC, Zhao L, et al. Combination therapy with BPTES nanoparticles and metformin targets the metabolic heterogeneity of pancreatic cancer. Proc Natl Acad Sci U S A 2016;113:E5328–36.
41. Rajeshkumar NV, Dutta P, Yabuuchi S, de Wilde RF, Martinez GV, Le A, et al. Therapeutic targeting of the Warburg effect in pancreatic cancer relies on an absence of p53 function. Cancer Res 2015;75:3355–64.

42. Boone BA, Bahary N, Zureikat AH, Moser AJ, Normolle DP, Wu WC, et al. Safety and biologic response of pre-operative autophagy inhibition in combination with gemcitabine in patients with pancreatic adenocarcinoma. Ann Surg Oncol 2015;22:4402–10.
43. Michalopoulou E, Bulusu V, Kamphorst JJ. Metabolic scavenging by cancer cells: when the going gets tough, the tough keep eating. Br J Cancer 2016;115:635–40.
44. Commisso C, Davidson SM, Soydaner-Azeloglu RG, Parker SJ, Kamphorst JJ, Hackett S, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature 2013;497:633–7.
45. Davidson SM, Jonas O, Keibler MA, Hou HW, Luengo A, Mayers JR, et al. Direct evidence for cancer-cell-autonomous extracellular protein catabolism in pancreatic tumors. Nat Med 2017;23:235–41.
46. Basseville A, Bates S, Fojo T. Pancreatic cancer: targeting KRAS and the vitamin D receptor via microtubules. Nat Rev Clin Oncol 2015;12:442–4.
47. Sherman MH, Yu RT, Engle DD, Ding N, Atkins AR, Tiriac H, et al. Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. Cell 2014;159:80–93.
48. Sousa CM, Biancur DE, Wang X, Halbrook CJ, Sherman MH, Zhang L, et al. Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion. Nature 2016;536:479–83.
49. Brand A, Singer K, Koehl GE, Kolitzus M, Schoenhammer G, Thiel A, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. Cell Metab 2016;24:657–71.
50. Whatcott CJ, Han H, Von Hoff DD. Orchestrating the tumor microenvironment to improve survival for patients with pancreatic cancer: normalization, not destruction. Cancer J 2015;21:299–306.
51. Mahadevan D, Von Hoff DD. Tumor-stroma interactions in pancreatic ductal adenocarcinoma. Mol Cancer Ther 2007;6:1186–97.
52. Apte MV, Park S, Phillips PA, Santucci N, Goldstein D, Kumar RK, et al. Desmoplastic reaction in pancreatic cancer: role of pancreatic stellate cells. Pancreas 2004;29:179–87.
53. Ene-Obong A, Clear AJ, Watt J, Wang J, Fatah R, Riches JC, et al. Activated pancreatic stellate cells sequester CD8+ T cells to reduce their infiltration of the juxtatumoral compartment of pancreatic ductal adenocarcinoma. Gastroenterology 2013;145:1121–32.
54. Puré E, Lo A. Can targeting stroma pave the way to enhanced antitumor immunity and immunotherapy of solid tumors? Cancer Immunol Res 2016;4:269–78.
55. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 2015;33:1889–94.
56. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
57. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39.
58. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311–9.
59. Mehra M, Seiwert TY, Mahipal A, Weiss J, Berger R, Eder JP, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after long-term follow-up in KEYNOTE-012. J Clin Oncol 34, 2016 (suppl; abstr 6012).
60. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 blockade with pembrolizumab in advanced merkel-cell carcinoma. N Engl J Med 2016;374:2542–52.
61. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.
62. Johnson BA 3rd, Yarchoan M, Lee V, Laheru DA, Jaffee EM. Strategies for increasing pancreatic tumor immunogenicity. Clin Cancer Res 2017;23:1656–69.
63. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33:828–33.
64. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455–65.
65. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.
66. Jiang H, Hegde S, Knolhoff BL, Zhu Y, Herndon JM, Meyer MA, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. Nat Med 2016;22:851–60.
67. Fearon DT. The carcinoma-associated fibroblast expressing fibroblast activation protein and escape from immune surveillance. Cancer Immunol Res 2014;2:187–93.
68. Steele CW, Karim SA, Leach JD, Bailey P, Upstill-Goddard R, Rishi L, et al. CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. Cancer Cell 2016;29:832–45.
69. Bezu L, Gomes-de-Silva LC, Dewitte H, Breckpot K, Fucikova J, Spisek R, et al. Combinatorial strategies for the induction of immunogenic cell death. Front Immunol 2015;6:187.
70. Pfirschke C, Engblom C, Rickelt S, Cortez-Retamozo V, Garris C, Pucci F, et al. Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. Immunity 2016;44:343–54.
71. Shibuya KC, Goel VK, Xiong W, Sham JG, Pollack SM, Leahy AM, et al. Pancreatic ductal adenocarcinoma contains an effector and regulatory immune cell infiltrate that is altered by multimodal neoadjuvant treatment. PLoS One 2014;9:e96565.
72. Botticelli A, Zizzari I, Mazzuca F, Ascierto PA, Putignani L, Marchetti L, et al. Cross-talk between microbiota and immune fitness to steer and control response to anti PD-1/PDL-1 treatment. Oncotarget 2017;8:8890–9.
73. Manji GA, Olive KP, Saenger YM, Oberstein P. Current and emerging therapies in metastatic pancreatic cancer. Clin Cancer Res 2017;23:1670–8.
74. Westphalen CB, Olive KP. Genetically engineered mouse models of pancreatic cancer. Cancer J 2012;18:502–10.
75. Boj SF, Hwang CI, Baker LA, Chio II, Engle DD, Corbo V, et al. Organoid models of human and mouse ductal pancreatic cancer. Cell 2015;160:324–38.
76. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403–13.
77. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960–6.
78. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson 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.
79. Kalra AV, Kim J, Klinz SG, Paz N, Cain J, Drummond DC, et al. Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. Cancer Res 2014;74:7003–13.
80. Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer 2014;111:1132–8.
81. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33:244–50.
82. Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut 2013;62:112–20.
83. Hingorani SR, Harris WP, Seery TE, Zheng L, Sigal D, Hendifar AE, et al. Interim results of a randomized phase II study of PEGPH20 added to nab-paclitaxel/gemcitabine in patients with stage IV previously untreated pancreatic cancer. J Clin Oncol 34, 2016 (suppl 4S; abstr 439).
84. Neoptolemos JP, Palmer D, Ghaneh P, Valle JW, Cunningham D, Wadsley J, et al. ESPAC-4: A multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma. J Clin Oncol 34, 2016 (suppl; abstr LBA4006).

85. Haeno H, Gonen M, Davis MB, Herman JM, Iacobuzio-Donahue CA, Michor F. Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. Cell 2012;148:362–75.
86. Christians KK, Heimler JW, George B, Ritch PS, Erickson BA, Johnston F, et al. Survival of patients with resectable pancreatic cancer who received neoadjuvant therapy. Surgery 2016;159:893–900.
87. Mokdad AA, Minter RM, Zhu H, Augustine MM, Porembka MR, Wang SC, et al. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. J Clin Oncol 2016 Sep 12. [Epub ahead of print].
88. Xie DR, Yang Q, Chen DL, Jiang ZM, Bi ZF, Ma W, et al. Gemcitabine-based cytotoxic doublets chemotherapy for advanced pancreatic cancer: updated subgroup meta-analyses of overall survival. Jpn J Clin Oncol 2010;40: 432–41.
89. Ciliberto D, Botta C, Correale P, Rossi M, Caraglia M, Tassone P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. Eur J Cancer 2013;49:593–603.
90. Banu E, Banu A, Fodor A, Landi B, Rougier P, Chatellier G, et al. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients with advanced and metastatic pancreatic cancer. Drugs Aging 2007;24:865–79.
91. Gresham GK, Wells GA, Gill S, Cameron C, Jonker DJ. Chemotherapy regimens for advanced pancreatic cancer: a systematic review and network meta-analysis. BMC Cancer 2014;14:471.
92. Chan K, Shah K, Lien K, Coyle D, Lam H, Ko YJ. A Bayesian meta-analysis of multiple treatment comparisons of systemic regimens for advanced pancreatic cancer. PLoS One 2014;9:e108749.
93. Bates SE. Endocrine cancers: defying the paradigms. Clin Cancer Res 2016;22:4980.
94. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2:401–4.
95. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:pl1.