Molecular landscape of pancreatic cancer: implications for current clinical trials

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ABSTRACT

Despite recent improvements, overall survival for advanced adenocarcinoma of the pancreas continues to be poor. In comparison to other tumor types that have enjoyed marked survival benefit by targeting aberrant cell signaling pathways, standard of care treatment for pancreatic cancer is limited to conventional cytotoxic chemotherapy. Multiple pathway aberrations have been documented in pancreatic cancer. A review of the COSMIC database reveals that most pancreatic cancers contain somatic mutations, with the five most frequent being *KRAS*, *TP53*, *CDKN2A*, *SMAD4*, and *ARID1A*, and multiple other abnormalities seen including, but not limited to, mutations in *STK11/LKB1*, *FBXW7*, *PIK3CA*, and *BRAF*. In the era of tumor profiling, these aberrations may provide an opportunity for new therapeutic approaches. Yet, searching clinicaltrials.gov for recent drug intervention trials for pancreatic adenocarcinoma, remarkably few (10 of 116 (8.6%)) new study protocols registered in the last three years included a molecular/biomarker stratification strategy. Enhanced efforts to target subsets of patients with pancreatic cancer in order to optimize therapy benefit are warranted.

INTRODUCTION

Pancreatic adenocarcinoma is the fourth most lethal malignancy in the United States, with 39,590 deaths expected in 2014. [1] It is one of the few malignancies where incidence approximates prevalence, as the disease is almost uniformly fatal, often within one year (Table 1). [2, 3] For patients who present with localized disease that can be surgically removed, median survival is 22.8 months due to the high-likelihood of recurrence. [4] Most patients present with metastatic disease, and treatment options are limited to chemotherapy. Median survival is about five to seven months with single-agent gemcitabine, or 8.5–11 months with more intense regimens such as gemcitabine/nab-paclitaxel and fluorouracil (5-FU)/irinotecan/oxaliplatin (FOLFIRINOX). [5–7]

Recent survival gains in the treatment of pancreatic cancer have resulted from new combinations of conventional, non-targeted chemotherapies, such as FOLFIRINOX. [7] Only one targeted agent – erlotinib, a small-molecule tyrosine-kinase inhibitor of EGFR – has been shown to improve overall survival (OS) when combined with gemcitabine. [8] This improvement was a modest 11 days compared to gemcitabine alone. Other targeted agents, such as bevacizumab, cetuximab, and sorefenib, did not improve overall survival in combination with gemcitabine. [9–11] Trials with these agents were open to all patients with pancreatic cancer, and there were no screening criteria to select patients most likely to respond to the targeted agents.

Outside the field of pancreatic cancer, significant advances in oncology therapy have emerged by identifying and intervening upon "actionable" aberrations. Advanced melanoma, which traditionally held a grave prognosis, has undergone a renaissance in treatment options. For the approximately 40% of patients that harbor a V600E *BRAF* mutation, vemurafenib produces a response rate of 48%. [12, 13] Dabrafenib, another BRAF inhibitor, and trametinib, a MEK inhibitor, have also substantially improved outcomes in *BRAF*-mutant patients. [14, 15] In advanced non-small cell lung cancer (NSCLC), median survival with traditional platinum-doublet chemotherapy is eight to nine months. [16] Targeting the EML4-ALK fusion product (~5% incidence) with crizotinib, a small-molecule kinase inhibitor, is associated with a survival

Table 1: Current treatment strategies for newly-diagnosed pancreatic cancer

Clinical Scenario	Treatment	MedianOS	1-year Survival	Comment	Reference(s)
Resectable	Surgical Resection; 6 Months Adjuvant Therapy with Gemcitabine and 5-FU Chemoradiation	20.5 Mos	73%	Pancreas head lesions only	Regine et al, 2011 [55]
	Surgical Resection; 6 Months Adjuvant Gemcitabine	22.8 Mos	72%		Oettle et al, 2007, 2013 [4, 56]
Locally-Advanced	3 Months Chemotherapy; 5-FU Chemoradiation	15.0 Mos	65%	Patients that developed mets post-chemo were excluded	Huguet at al, 2007 [57]
Metastatic	FOLFIRINOX	11.1 Mos	48%		Conroy et al, 2011 [7]
	Gemcitabine + Nab-paclitaxel	8.5 Mos	35%		Von Hoff et al, 2013 [6]
	Gemcitabine	5.7 Mos	18%		Burris et al, 1997 [5]

of about 20 months. [17] Even erlotinib, whose effect is modest in pancreatic cancer, can improve first-line progression-free survival (PFS) in patients with *EGFR*-mutations (about 8–30% depending upon ethnicity) from 4.6 to 13 months. [18–20] Further, a meta-analysis of the NSCLC literature showed responses of 49% when targeted treatments were matched to the appropriate subgroup of patients, but only 9.7% when unselected populations were treated. [21]

In this regard, a review of pancreas tumor specimens within the Catalogue of Somatic Mutations in Cancer (COSMIC) database reveals that most pancreatic cancers harbor somatic mutations (Table 2), with the five most frequent aberrations being *KRAS*, *TP53*, *CDKN2A*, *SMAD4*, and *ARID1A*. [22, 23] If specific "actionable" mutations can drive marked improvements in survival in melanoma and NSCLC, similar opportunities might reasonably be expected in pancreatic cancer. Herein we review the molecular landscape in pancreatic cancer and provide an overview of the status of current clinical trials in the field.

KRAS

Seventy-one percent of pancreatic cancer specimens in the COSMIC database harbor *KRAS* mutations. [22] KRAS is a key protein in multiple signaling pathways. When bound to guanosine triphosphate (GTP), it mediates cell survival and differentiation. Common *KRAS* mutations hinder its ability to hydrolyze GTP, leaving it constitutively active. [24] *KRAS* mutations are common in pancreatic duct lesions and are thought to play an early role in oncogenesis. [25] Thus, blocking targets downstream of KRAS is of clinical interest.

One key target downstream of KRAS is MEK, which functions as a protein kinase. Multiple MEK inhibitors are in development, and some have shown promise (Table 3). Selumetinib, a small-molecule MEK inhibitor, was randomized against single-agent capecitabine as a second-line treatment for advanced pancreatic cancer. Though there was no difference in overall survival, two of 38 (5.2%) patients in the selumetinib arm achieved a partial response (PR) [26]. Trametinib has also shown some activity. In a treatment-refractory phase I population, two of 26 patients (8%) achieved PR [27]. However, in a randomized phase II trial with trametinib given in combination with gemcitabine versus gemcitabine alone, response rate was 22% (but included one complete remission) as compared to 18%; survival was 8.4 versus 6.7 months (p, not significant).[28] The fact that some patients respond to MEK inhibitors alone is of interest, though combinations of MEK inhibitors with gemcitabine do not substantially increase the response rate. Whether or not MEK inhibitors in combination with other regimens such as FOLFIRINOX might be beneficial merits further study.

TP53

Forty-nine percent of pancreatic cancers in the COSMIC database demonstrate *TP53* mutations. [22] p53 is key tumor suppressor, and when in an inactivated state, enables cancerous cells to avoid apoptosis. Wee-1 inhibitors such as MK1775 target aberrant p53 by blocking cell cycle checkpoint regulation and increasing

Table 2: Most common mutated genes of pancreatic ductal carcinoma in COSMIC database*

Mutated Gene	Frequency		Wild-Type Gene Function**
	Percentage	Denominator	
KRAS	71%	4573	GTPase mediating cell signaling
TP53	49%	796	Tumor suppressor
CDKN2A	22%	950	Tumor suppressor
SMAD4	20%	680	Signal transduction protein
ARID1A	6%	343	Chromatin remodeling
MLL3	4%	292	Histone methylation
PIK3CA	3%	377	Protein kinase mediating cell signaling
MAP2K4	3%	294	Protein kinase mediating cell signaling
ATM	3%	190	Protein kinase mediating cell cycle checkpoint signaling
ACVR1B	3%	226	Growth factor receptor kinase
BRAF	2%	528	Protein kinase mediating cell signaling
APC	2%	267	Tumor suppressor
SF3B1	2%	206	RNA splicing
STK11/LKB1	2%	314	Tumor suppressor
FBXW7	2%	242	Component of SCF-complex mediating ubiquitination
SMARCA4	1%	291	Transcriptional regulation
ARID2	2%	189	Transcriptional regulation
CREBBP	2%	190	Histone acetylation
RNF43	2%	197	Ubiquitin ligase
EP300	1%	201	Histone acetylation
*ERBB2****	0.4%	256	Receptor tyrosine kinase

* Accessed December 1, 2014 (http://www.sanger.ac.uk/cosmic) [22].
**National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine, Gene database (http://www.ncbi.nlm.nih.gov/gene).
*** In addition to mutation, HER2 may be overexpressed or amplified in ~10 to 30% of patients [58–60].

susceptibility to cytotoxic chemotherapy. [29] In addition, retrospective analysis by Said et al [30] suggested that tumors with aberrant p53 may be more sensitive to bevacizumab. Patients with aberrant p53 had a median PFS of 11 months while the median PFS in those with wild-type p53 was 5.0 months. On multivariate analysis, the interaction between p53 mutation status and bevacizumab therapy was statistically significant [HR 0.15, 95% CI 0.05–0.44, $p < 0.001$]. [30]

Of additional clinical interest is re-activating p53 in wild-type patients. MDM2, an inhibitor of p53, is overexpressed in many cancers. [31] MDM2–p53 interaction prompts p53 degradation and blocks its tumor suppressor function. [31] Blocking MDM2 activity may prevent this degradation, thereby enabling p53-induced apoptosis of cancerous cells. [32] A search of clinicaltrials.gov lists multiple MDM2 antagonists currently under early-phase investigation, including RO5045337, RO5503781, and DS-3032b. [33]

CDKN2A

CDKN2A is aberrant in twenty-two percent of patients with pancreatic cancer. [22] It encodes multiple proteins which play roles in tumor suppression. Two transcripts, p16 and $p14^{ARF}$, are frequently abnormal in pancreatic cancer and result in loss of function. p16 inhibits the activity of cyclin-dependent kinases 4/6, thereby playing a regulatory role in the cell cycle by preventing phosphorylation of the tumor suppressor retinoblastoma protein. [34] Loss of p16 results in activation of CDK4/6 and is associated with high-grade

Table 3: Clinical trials with MEK1/2 inhibitors in metastatic pancreatic cancer

Agent	Line of Therapy	Phase of Study	Partial Remission (PR)	Comment	Reference
Trametinib + Gemcitabine	1st Line	Randomized Phase II	17/77 (22%);(includes one complete remission	PR 14/77 (18%) in placebo + gemcitabine arm	Infante et al, 2014 [28]
Trametinib + Gemcitabine	Mixed	Phase Ib	3/11 (27%)	Two patients had received prior therapy	Infante et al, 2013 [61]
Trametinib	Refractory	Phase I	2/26 (8%)		Infante et al, 2012 [27]
Selumetinib vs. Capecitabine	2nd Line	Phase II	2/38 (5%)		Bodoky et al, 2011 [26]
XL-518 / GDC-0973 + GDC-0941 (PI3K)	Refractory	Phase Ib	1 PR	Patient with PR had a *BRAF* mutation	LoRusso et al, 2012 [62]
CI-1040	1st Line	Phase II	0/15 (0%)		Rinehart et al, 2004 [63]
CI-1040	Refractory	Phase I	1/6 (17%)		LoRusso et al, 2005 [64]

pre-malignant pancreatic lesions. [35] Palbociclib, an inhibitor of CDK4/6, has been shown to suppress growth of pancreatic cancer cell lines, though with upregulation of genes associated with metastasis. [36] $p14^{ARF}$ is an inhibitor of MDM2 and stabilizes retinoblastoma protein by interfering with MDM2-mediated degradation. [37] Theoretically, either CDK4/6 or MDM2 inhibitors might be active in patients with loss of *CDKN2A* function.

SMAD4

SMAD4 is a co-factor that facilitates gene transcription and tumor suppression through the TGF-beta signaling pathway. *SMAD4* mutations are present in twenty percent of pancreatic cancers and have been associated a poorer prognosis and increased metastases. [22, 38, 39] Inactivation of *SMAD4* may enable TGF-beta signaling, which is usually suppressive, to promote cancer growth. [40, 41] To our knowledge, the role of TGF-beta inhibitors in patients with SMAD4 mutations has not been investigated.

ARID1a

ARID1a mutations are present in six percent of pancreatic cancers. [22] ARID1a plays a role in chromatin remodeling, is thought to have tumor suppressor function, and binds p53. [42] It also modulates signaling through the PI3K/AKT/mTOR axis. [43] Whether or not mutations in *ARID1a* can be targeted by using PIK3CA, AKT or mTOR inhibitors is currently unknown.

Other potentially actionable mutations

BRCA2 is a potent tumor suppressor and plays a key role in DNA repair. Murphy et al demonstrated that 5/29 patients (17%) with a strong family history of pancreatic cancer harbored *BRCA2* mutations. [44] PALB2, which binds BRCA2, also plays a role in DNA repair. *PALB2* mutations were reported in 3/96 patients (3.1%) with familial pancreatic cancer. [45]

In theory, patients with *BRCA2* or *PALB2* mutations should be more sensitive to DNA-damaging agents. Two case reports illustrate this point (Table 4). Villarroel et al reported a 61-year-old man with metastatic pancreatic cancer in the setting of a *PALB2* mutation. [46] He was initially treated with gemcitabine chemotherapy (nucleoside analogue) with no response, but then received mitomycin C chemotherapy (DNA crosslinker) and achieved a partial response that lasted twenty-two months. A 49-year-old woman with advanced pancreatic cancer in the setting of *BRCA2* mutation who was treated with mitomycin C and capecitabine after progressing through two previous regimens also achieved a partial response. [47] Mitomycin C was discontinued after six months due to toxicity. Patients with *BRCA2* mutations may also be sensitive to PARP inhibitors. Response has been seen in a variety of other tumors, including breast, prostate, and ovarian cancer harboring *BRCA2* aberrations. [48]

Abberations in *STK11/LKB1* and *FBXW7* are also potential targets. LKB1 acts through AMPK to inhibit mTOR, which regulates cell growth. [49]

Table 4: Case reports of novel therapies in advanced pancreatic cancer

Aberration	Histology	Agent	Line	Outcome	Rationale for Agent	Reference
PALB2 Mutation	Adenocarcinoma	Mitomycin C	2nd	Partial Response	Patient's tumor xenograft demonstrated sensitivity to mitomycin C	Villarroel et al, 2011 [46]
BRCA2 Mutation	Adenocarcinoma	Mitomycin C + Capecitabine	3rd	Partial Response	Pre-clinical data with mitomycin C in *BRCA2* cell lines and prior published responses to mitomycin C	Chalasani et al, 2008 [47]
STK11/LKB1 Mutation	Acinar Cell Carcioma	Everolimus	1st	Partial Response	Loss of mTOR inhibition with *STK11/LKB1* mutation	Klumpen et al, 2011 [50]

Germline *STK11/LKB1* loss-of function mutations are associated with Peutz-Jeghers Syndrome, which carries an increased risk for pancreatic neoplasms. [49] A case reported by Klumpen at al successfully used the mTOR inhibitor everolimus in a Peutz-Jeghers Syndrome patient with pancreatic cancer to obtain a partial response without additional cytotoxic chemotherapy (Table 4). [50] FBXW7 plays a role in the ubiquitin-mediated degradation of oncoproteins, and among patients with NSCLC, low *FBXW7* expression is associated with decreased survival and taxane resistance. In NSCLC cell lines with silenced *FBXW7*, taxane sensitivity can be restored when treated with the histone deacetylase inhibitor MS-275. [51]

Other potentially actionable aberrations that can be seen in small, but not insignificant subsets of patients include *PIK3CA* and *BRAF* mutations. These abnormalities occur in 2 to 3% of patients, and can theoretically be targeted by PI3K/AKT/mTOR and BRAF or MEK inhibitors, respectively.

Clinical trials for pancreatic cancer

A search of clinicaltrials.gov for new pancreatic cancer protocols registered during the past three years identified 314 protocols (search criteria: trials registered in database during the period 03/01/2011 to 03/01/2014; pancreatic cancer; drug or biological intervention studies). [33] The 314 protocol summaries were manually reviewed, and protocols containing external radiotherapy, neuroendocrine histology, and local therapy were excluded, as were protocols without the stated outcome of improved OS, PFS, or radiographic/biochemical response, leaving only 116 specific for pancreatic adenocarcinoma systemic therapy. Of these 116 protocols, 10 (8.6%) used selective inclusion criteria to identify a subset of patients based upon laboratory molecular/biomarker data and treat with a cognate therapy that was believed to impact or biologically match the biomarker. Six used tissue biomarkers to assign patients among multiple conventional chemotherapy options, two sought patients with *BRCA* mutations for PARP inhibitors, one required a specific antigen for a corresponding investigational monoclonal antibody, and one sought patients with a specific HLA marker for a vaccine study. These results suggest that there is still a remarkable paucity of trials addressing molecular/biomarker stratification in pancreatic cancer.

CONCLUSIONS

The outcome for patients diagnosed with pancreatic cancer is grim, with one year survival of 19% and 4.8% alive at five years. [52] The best therapy to date is FOLFIRINOX, and it improves median survival by four months (from 6.8 to 11.1 months) compared to gemcitabine for metastatic disease. [7] In other tumor types such as *BRAF*-aberrant melanoma, or *EGFR*- or *ALK*-aberrant NSCLC, significant improvements have been achieved by matching targeted agents with patients harboring the cognate molecular abnormality. Several theoretically "actionable" aberrations exist in pancreatic cancer including, but not limited to, *KRAS, CDKN2A, ARID1A, BRCA, PALB2, PIK3CA, BRAF* and so forth. Despite the number of aberrations that can be targeted, relatively few have been addressed in clinical trials of pancreatic cancer, with only about 9% of clinical trials of pancreatic cancer stratified by a biomarker in the last three years. Although an important step in pancreatic cancer, as in *EGFR*- or *ALK*-mutant lung cancer or BRAF-mutant melanoma might include investigation of matched targeted monotherapy, many pancreatic tumors likely contain more than one aberration. If two or more genomic aberrations exist, the role of each might need to be ascertained, and each important driver may need to be targeted (customized combination therapy) in order to prevent or circumvent resistance.[53, 54] Taken together, the data suggests that efforts to target biomarker-defined subsets of patients with pancreatic cancer in order to optimize therapy benefit are warranted.

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