

Identification of Targetable *ALK* Rearrangements in Pancreatic Ductal Adenocarcinoma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers, with a 5-year survival of 8%. Current therapeutic regimens are largely ineffective and underscore the need for novel treatment strategies. Chromosomal rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene have been identified in several neoplasms. In addition, *ALK* protein inhibitors have proven efficacy in patients with *ALK*-rearranged tumors. However, *ALK* translocations in PDAC have not been described. Through comprehensive genomic profiling of 3,170 PDACs, we identified 5 cases (0.16%) that harbored an *ALK* fusion gene: an exon 6 *EML4*–exon 20 *ALK* translocation (n=3), an exon 13 *EML4*–exon 20 *ALK* translocation (n=1), and an exon 3 *STRN*–exon 20 *ALK* translocation (n=1). Among the most prevalent PDAC-related genes, activating *KRAS* mutations were absent in all 5 cases, who were <50 years of age. Among patients aged <50 years in our study cohort, *ALK* translocations constituted 1.3% of PDACs. Four of 5 patients were treated with an *ALK* inhibitor, and 3 of these patients demonstrated stable disease, radiographic response, and/or normalization of serum CA 19-9. Although rare, *ALK* fusions occur in PDAC, and screening for *ALK* rearrangements should be considered in young patients with PDAC.

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Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer death in the United States. In 2016, the American Cancer Society estimated that 53,070 individuals would be diagnosed with PDAC and approximately 41,780 would die of this deadly disease.¹ Although surgical resection offers the only possibility of cure, >85% of patients present with inoperable disease at diagnosis. Therefore, chemotherapy is the mainstay of treatment for most patients. Unfortunately, current therapeutic regimens, including gemcitabine plus nab-paclitaxel and FOLFIRINOX (5-fluorouracil, folinic

acid, oxaliplatin, and irinotecan), have limited efficacy, with an incremental survival benefit of only a few months in unselected patients. However, significant responses have been observed in small subgroups.²

Whole-exome and whole-genome sequencing studies of large PDAC cohorts have revealed a diverse number of genetic alterations in otherwise histologically similar tumors.^{3,4} The intertumoral heterogeneity of molecular abnormalities may partly explain the poor response rates to current therapeutic regimens among unselected patients with PDAC.⁵ Thus, there has been

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a recent emphasis on a more personalized approach to the treatment of PDAC based on its underlying genetic alterations. For instance, PDACs harboring mutations in DNA repair genes, such as *BRCA2* or *PALB2*, are often sensitive to poly(ADP-ribose) polymerase inhibitors and cisplatin.⁶ Moreover, mutations in the mismatch repair genes confer susceptibility to immune checkpoint inhibitors.⁷ However, these “actionable” genetic alterations are relatively uncommon and, consequently, there is an urgent need to identify additional molecular targets.

In recent years, chromosomal rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene have been the subject of intense clinical investigation.⁸ The *ALK* protein is a receptor tyrosine kinase and physiologically expressed within the central nervous system. Translocation of *ALK* with various partner genes results in an *ALK* fusion protein and constitutive *ALK* activation. Several *ALK* fusion genes have been reported and are considered drivers of tumorigenesis for a wide range of neoplasms. In addition, the *ALK* protein inhibitors crizotinib, ceritinib, and alectinib have proven efficacy in patients with *ALK*-rearranged tumors.^{9,10} Therefore, the *ALK* fusion protein represents an attractive target for directed therapy, but, to date, has not been reported in PDACs. We examined the prevalence of *ALK* rearrangements within a large cohort of locally advanced and metastatic PDACs and identified 5 patients with an *ALK*-rearranged PDAC. We further analyzed their associated clinicopathologic features and molecular profile. Follow-up information was available for 4 patients, including treatment response data with *ALK* protein inhibitors.

Methods

Comprehensive Genomic Profiling

Ten 4-mcm unstained sections from 3,170 PDACs were submitted to a CLIA-certified and College of American Pathologists–accredited laboratory (Foundation Medicine, Inc., Cambridge, MA) for targeted next-generation sequencing and gene fusion detection (see supplemental eTable 1, available with this article at JNCCN.org).¹¹ DNA was extracted and quantitated by a PicoGreen fluorescence assay. Thereafter, approximately 50 to 100 ng of DNA was used for library construction. Hybrid selection and sequencing were performed of all coding exons of 295

cancer-associated genes and select introns of 19 genes to include 47 introns frequently rearranged in solid tumors (including *ALK*). The average depth of coverage was >500x, with >99% of exons with >100x coverage using the Illumina HiSeq 2000 (Illumina, Inc., San Diego, CA). Sequencing data were processed using a customized set of analysis tools, designed to detect all classes of genomic alterations that include base substitutions, short insertions and deletions, copy number alterations, and genomic rearrangements.

ALK Fluorescence In Situ Hybridization

Fluorescence in situ hybridization (FISH) was assessed using a break-apart probe to the *ALK* gene (Vysis LSI *ALK* Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Des Plaines, IL). Staining of tissue sections was performed using 4-mcm unstained paraffin sections. At least 60 tumor nuclei were scored with positivity, defined as >15% of tumor cells demonstrating split signals (isolated red signals and/or split red and green signals). Overlapping cells were excluded from analysis.

ALK Immunohistochemistry

Immunohistochemical labeling was performed on 4-mcm unstained sections. Slides were deparaffinized with serial xylene treatments and subjected to antigen retrieval using heated citrate solution (pH 9.0) at 100°C for 10 minutes. Immunolabeling for *ALK* (D5F3 rabbit monoclonal, Ventana Medical Systems, Inc., Tucson, AZ) was performed on the automated Benchmark XT system (Ventana Medical Systems, Inc., Tucson, AZ) using the biotin-free Ventana OptiView DAB IHC Detection Kit (Ventana Medical Systems, Inc., Tucson, AZ). Positive cases were defined by the presence of strong granular cytoplasmic staining in at least 10% of tumor cells.

Results

Targeted next-generation sequencing of 295 genes and gene fusion detection of 19 genomic rearrangements (supplemental eTable 1) to include *ALK* were performed on 3,170 PDACs in the course of clinical care.¹¹ The patient cohort consisted of 1,724 men and 1,446 women ranging in age from 19 to 88 years (median, 63 years). In most cases, patients were described as having locally advanced and/or metastatic disease. In total, 5 of 3,170 PDACs (0.16%)

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harbored an *ALK* rearrangement. Among the 5 tumors, an exon 13 *EML4*–exon 20 *ALK* translocation was detected in 1 case (Case 1), an exon 6 *EML4*–exon 20 *ALK* translocation in 3 cases (Cases 2, 4, and 5), and an exon 3 *STRN*–exon 20 *ALK* translocation in 1 case (Case 3) (Figure 1A–C). The corresponding clinicopathologic features for each patient are summarized in Table 1. The patients consisted of 4 men and 1 woman ranging in age from 32 to 46 years (mean, 38 years). Among patients <50 years of age within the cohort (n=385), *ALK* translocations were identified in 1.3%. Morphologically, 4 cases were tubular-type PDACs and 1 was a colloid carcinoma (Figure 1D–F). However, among the 4 tubular-type PDACs, 1 showed prominent extracellular mucin. Clinical presentation, treatment, and follow-up information was available for 4 of 5 patients.

Case 1

A 35-year-old man presented with fatigue, diarrhea, and jaundice. No personal or family history of cancer, pancreatitis, or liver disease was reported. The patient denied a history of tobacco, alcohol, or recreational drug use. Abdominal contrast-enhanced CT showed a 2.1-cm pancreatic head mass, which

was confirmed as PDAC through subsequent endoscopic ultrasound (EUS)–guided fine-needle aspiration (FNA). His serum CA 19-9 level was elevated at 54.2 U/mL (normal <33 U/mL). Sonographic evidence suggested invasion into the portal vein, and the patient was deemed borderline resectable. The patient completed 6 cycles of neoadjuvant FOLFIRINOX with a radiologic decrease in tumor size to 1.8 cm and CA 19-9 normalization. Due to chemotoxicity, the patient was switched to gemcitabine and nab-paclitaxel for 2 cycles. This was followed by stereotactic body radiation therapy (RT). After 7 months from initial diagnosis, a robotic-assisted classic pancreaticoduodenectomy (Whipple resection) was performed. The surgical specimen revealed a 2.0-cm moderately differentiated PDAC centered within the pancreatic head and extension into the peripancreatic soft tissue. In addition, 2 of 56 regional lymph nodes were involved via metastatic PDAC. Overall, the PDAC was pathologically staged as ypT3N1. Because of delayed surgical recovery, the patient did not receive adjuvant therapy.

Three months after surgery, the patient's CA 19-9 level was elevated at 56.3 U/mL; however, no evidence of recurrence was identified on CT

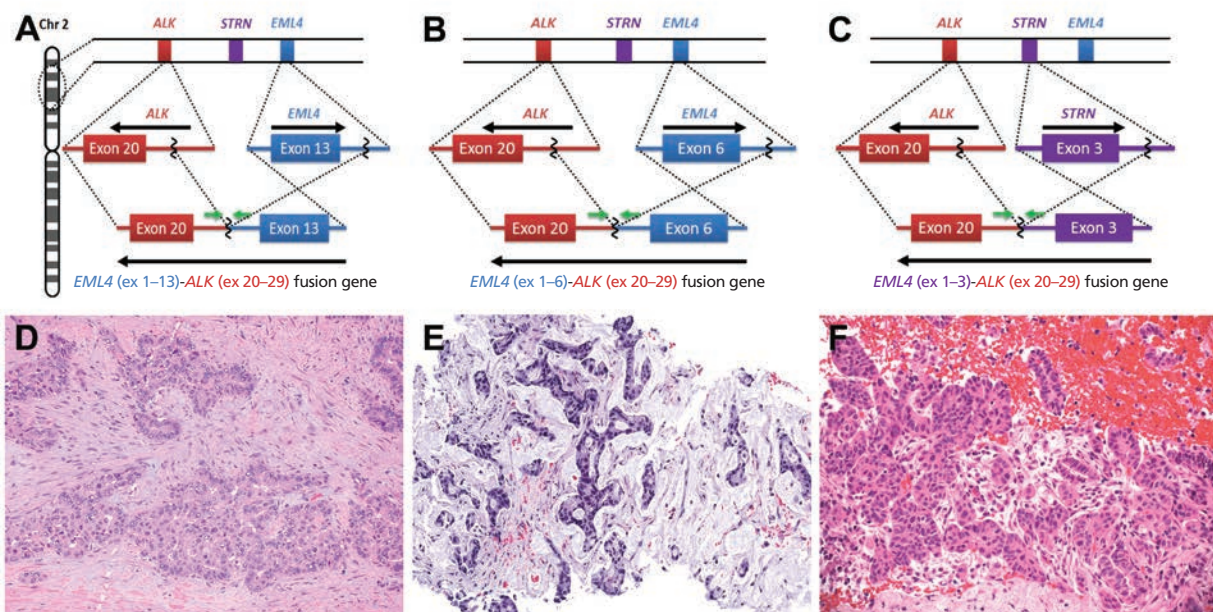


Figure 1. Comprehensive genomic profiling identified 3 *ALK* fusion genes within pancreatic ductal adenocarcinomas (PDACs). The *ALK* fusion genes consisted of (A) an exon 13 *EML4*–exon 20 *ALK* translocation (Case 1), (B) an exon 6 *EML4*–exon 20 *ALK* translocation (Cases 2, 4, and 5), and (C) an exon 3 *STRN*–exon 20 *ALK* translocation (Case 3). Green arrows depict uniquely mapped paired-end reads (of ≥ 15 primer pairs) in the intronic regions of *EML4* (introns 13 and 6) or *STRN* (intron 3) and *ALK* (intron 19). Black arrows indicate the direction of transcription of each gene. Hematoxylin and eosin–stained slides of *ALK*–positive tumors were heterogeneous and consisted of tubular-type (D, Case 1; F, Case 3) and colloid-type (E, Case 5) adenocarcinomas (original magnification $\times 200$).

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Table 1. Clinical and Pathologic Findings

Case	Age, y	Sex	Histologic Subtype	Distant Metastases	ALK Rearrangement	Other Molecular Alterations (MAF/CN)	Median Exon Coverage
1	35	M	Tubular-type adenocarcinoma	Yes	Exon 13 <i>EML4</i> –exon 20 <i>ALK</i>	<i>BAP1</i> c.1714delC (7%) ^a <i>NFE2L2</i> c.40C>T (5%) <i>MCL1</i> amplification (7)	690
2	32	F	Tubular-type adenocarcinoma with mucinous features	Yes	Exon 6 <i>EML4</i> –exon 20 <i>ALK</i>	<i>CDKN2A/B</i> homozygous deletion <i>MYC</i> amplification (82) <i>TP53</i> c.325_326insTTCC (59%)	667
3	34	M	Tubular-type adenocarcinoma	No	Exon 3 <i>STRN</i> –exon 20 <i>ALK</i>	None	896
4	46	M	Tubular-type adenocarcinoma	Yes	Exon 6 <i>EML4</i> –exon 20 <i>ALK</i>	<i>CDKN2A</i> homozygous deletion <i>TP53</i> c.994-1G>C (51%) <i>SMAD4</i> c.247C>T (51%) <i>FGFR1</i> c.422C>G (65%)	734
5	43	M	Colloid carcinoma	Unknown	Exon 6 <i>EML4</i> –exon 20 <i>ALK</i>	<i>STK11</i> c.226delG (7%)	618

Abbreviations: CN, copy number; MAF, mutation allele frequency.

^a*BAP1* mutation was present within the patient's primary tumor; however, a *PBRM1* mutation was identified within the patient's subsequent lung metastasis.

imaging. At 11 months, the patient's serum CA 19-9 level had increased to 584.9 U/mL. CT imaging revealed enlarged retroperitoneal (left periaortic and retrocaval) and posterior mediastinal lymph nodes consistent with metastatic disease. Gemcitabine and nab-paclitaxel were administered for 3 cycles, but treatment was complicated by chemotoxicity and had to be stopped.

Comprehensive genomic profiling (CGP) of the patient's primary PDAC revealed an exon 13 *EML4*–exon 20 *ALK* translocation, which was confirmed with FISH using a break-apart probe for *ALK* (Figure 2A) and *ALK* immunohistochemistry (Figure 2B). Additionally, a *BAP1* frameshift mutation (c.1714delC, p.L573fs*3), *NFE2L2* missense mutation (c.40C>T), and *MCL1* gene amplification were identified. Considering the unique genetic alterations, additional immunohistochemical stains were performed on the patient's PDAC. The tumor immunolabeled for CK7 but was negative for CK20, CDX2, TTF-1, napsin A, PAX8, GCDFP-15, mammaglobin, estrogen receptor (ER), and progesterone receptor (PR). Based on the clinical, radiographic, pathologic, and immunolabeling findings, the tumor was consistent with a PDAC.

One month after discontinuing gemcitabine and nab-paclitaxel, the patient was started on crizotinib, but experienced neutropenia and was switched to ceritinib. Within 2 months, his CA 19-9 level normalized (23.5 U/mL; Figure 3A). Moreover, there was a decrease in the size of retroperitoneal and pos-

terior mediastinal lymph nodes (Figure 3B–E). After 7 months on ceritinib, the patient's CA 19-9 level increased to 79.8 U/mL and correlated with the development of a 0.8-cm right upper lobe lung nodule. However, the patient's intra-abdominal disease remained stable. A wedge resection of the lung nodule was performed and was consistent with metastatic PDAC. Repeat genetic profiling continued to demonstrate an exon 13 *EML4*–exon 20 *ALK* translocation, *NFE2L2* missense mutation, and *MCL1* gene amplification, but lacked a *BAP1* frameshift mutation. Instead, a frameshift mutation in *PBRM1* (c.3558_3559insA, p.E1189fs*6) was identified. *ALK* secondary mutations and gene amplification were absent. Further, no alterations in *KRAS* were detected. The patient was switched to alectinib and is alive and well at the time of writing; the duration of survival from diagnosis is currently 52 months.

Case 2

A 32-year-old woman presented with increasing fatigue, shortness of breath, recurrent nausea and vomiting, lightheadedness, and distal upper extremity paresthesia. The patient denied a history of other cancers. CT imaging identified multiple masses within the pancreas, liver, ovaries, and peritoneum. The largest mass was centered within the head of the pancreas. An exploratory laparotomy confirmed the presence of a large pancreatic head mass and multiple smaller lesions within the liver, ovaries, and peritoneum. Resection of multiple liver lesions and bilateral

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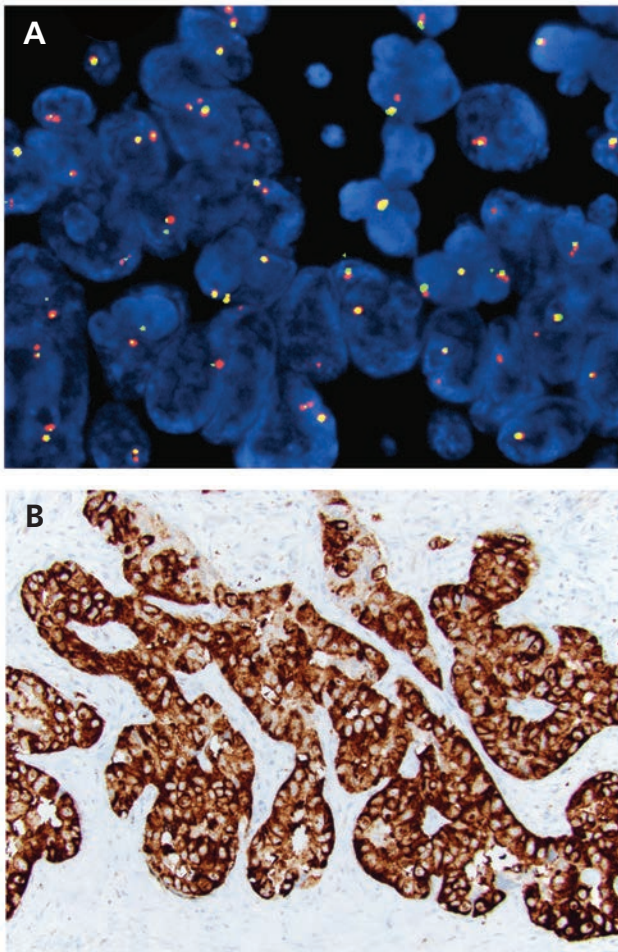


Figure 2. Both Case 1 (exon 13 *EML4*–exon 20 *ALK* fusion gene) and Case 3 (exon 3 *STRN*–exon 20 *ALK* fusion gene) were confirmed to harbor an *ALK* rearrangement by (A) *ALK* break-apart fluorescence in situ hybridization probe, which demonstrated isolated red signals in >15% of neoplastic nuclei (original magnification x1,000), and (B) *ALK* immunohistochemistry, which showed strong, diffuse, and granular cytoplasmic staining (original magnification x400).

salpingo-oophorectomy was performed for pathologic evaluation and ancillary studies. The specimens revealed a moderately differentiated adenocarcinoma with prominent mucinous features. Immunohistochemical stains were strongly positive for CK7 and CA 19.9, and negative for CK20, PAX8, CDX2, ER, and PR. Additionally, Smad4, MLH1, PMS2, MSH2, and MSH6 immunolabeling showed preserved nuclear expression. Overall, the histologic features and immunoprofile were consistent with a pancreatic primary.

Adjuvant therapy consisted of FOLFIRINOX for 2 cycles with subsequent chemotoxicity. The patient was switched to gemcitabine and nab-paclitaxel, but again experienced chemotoxicity, and progression of

her liver metastases was seen on MRI. CGP of one of her metastases revealed an exon 6 *EML4*–exon 20 *ALK* translocation, *CDKN2A/B* deletion, *MYC* gene amplification, and *TP53* frameshift mutation (c.325_326insTTTCG, p.L111fs*39). Based on these findings, the patient was started on crizotinib alone, and 2 months later was found to have stable metastatic disease on MRI. The primary site and metastases remained stable on follow-up MRI for the next 15 months. However, the patient's clinical course was complicated by repeated episodes of bacteremia and, ultimately, she died of septic shock. The duration of survival from diagnosis was 20 months.

Case 3

A 34-year-old man presented with progressive fatigue, pale skin, and anemia. The patient denied a personal or family history of cancer, pancreatitis, or liver disease. In addition, the patient denied a history of tobacco, alcohol, or recreational drug use. An abdominal CT identified a 7.5-cm pancreatic mass involving the superior mesenteric artery and vein. No evidence of distant metastatic disease was seen. A follow-up EUS-FNA confirmed the presence of a pancreatic head mass with secondary biliary obstruction, and cytopathology was consistent with a PDAC. The patient received 4 cycles of FOLFIRINOX with stable-to-slight disease progression by CT. Further, the patient's serum CA 19-9 level was elevated at 410 U/mL.

CGP of the pancreatic head biopsy revealed the presence of an exon 3 *STRN*–exon 20 *ALK* translocation; no other genetic alterations were identified. The presence of an *ALK* translocation was confirmed by *ALK* break-apart FISH and *ALK* immunohistochemistry. The patient began treatment with gemcitabine and crizotinib, and also received external-beam RT. After 2 months of chemoradiotherapy, his serum CA 19-9 level decreased to 84 U/mL. Further, repeat abdominal CT showed a decrease in tumor size to 6.9 cm. The patient is alive and continuing only crizotinib therapy at the time of writing. The duration of survival from diagnosis is currently 10 months.

Case 4

Limited clinical information was available for Case 4, a 46-year-old man who presented with a locally advanced pancreatic head mass consistent with PDAC. An exon 6 *EML4*–exon 20 *ALK* translocation

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was identified through CGP of biopsy material from the pancreatic head. Additional genetic alterations included a homozygous *CDKN2A* deletion, *TP53* splice site mutation (c.994-1G>C), *SMAD4* nonsense mutation (c.247C>T, p.Q83*), and *FGFR1* missense mutation (c.422C>G, p.T141R). The patient was treated with crizotinib alone, but experienced progression after 2 months, with development of leptomeningeal disease and secondary spinal cord compression. The patient received external-beam RT to his thoracic spine and was started on alectinib. The duration of survival from diagnosis is 5 months at the time of writing.

Discussion

To the best of our knowledge, this is the first report of targetable *ALK* translocations in PDAC. Among 3,170 PDACs, we identified 5 cases harboring either an *EML4-ALK* or *STRN-ALK* fusion gene. The patients consisted of 4 men and 1 woman ranging in age from 32 to 46 years. Morphologically, the *ALK*-rearranged PDACs were classified as either tubular or colloid, but among the tubular cases, 1 exhibited prominent extracellular mucin. Besides the presence of an *ALK* rearrangement, other genetic abnormalities included somatic alterations in *BAP1*, *CDKN2A/B*, *FGFR1*, *MCL*, *MYC*, *NFE2L2*, *SMAD4*, *STK11*, and *TP53*. Of note, the most frequently mutated gene in PDAC is *KRAS*. However, *KRAS* mutations were lacking in all *ALK*-rearranged PDACs.

ALK fusion genes, including *EML4-ALK* and *STRN-ALK*, have been identified in multiple cancer types, including lung adenocarcinoma, colorectal adenocarcinoma, breast cancer, renal cell carcinoma, renal medullary carcinoma, and papillary thyroid carcinoma.^{12–15} Based on previous reports, the resulting chimeric proteins possess potent oncogenic activity in both in vitro and in vivo models.^{8,16,17} In lung adenocarcinoma, *ALK* fusions are detected in approximately 1% of tumors and are often characterized by distinct epidemiologic, demographic, and pathologic features. *ALK*-positive lung adenocarcinomas typically present at a young age, and are often characterized by prominent mucinous cells, such as signet-ring cells and goblet cells, and abundant extracellular mucin.¹⁸ Further, rearrangements involving *ALK* in lung adenocarcinomas are mutually exclusive to mutations in *KRAS* and *EGFR*.¹⁹

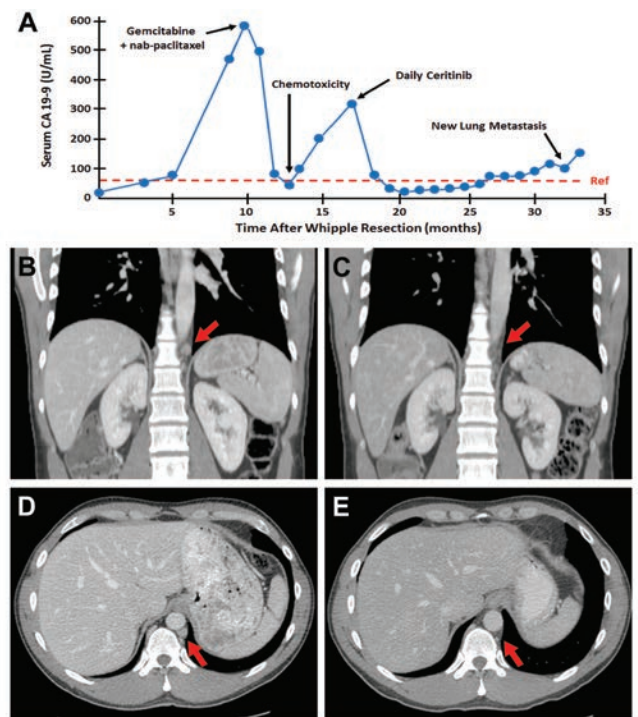


Figure 3. The clinical and treatment course of Case 1 after Whipple (classic pancreaticoduodenectomy) resection. (A) An increase in serum CA 19-9 levels was associated with disease recurrence and the disease initially responded to gemcitabine and nab-paclitaxel. The patient soon developed chemotoxicity, which necessitated cessation of therapy. On identification of an exon 13 *EML4*-exon 20 *ALK* translocation, daily ceritinib alone was started and a decrease in serum CA 19-9 levels was observed shortly thereafter. However, the patient's serum CA 19-9 levels slowly increased over the next several months with the development of a new lung metastasis. (B, D) Before ceritinib treatment, CT scan for Case 1 showed an enlarged posterior mediastinal lymph node (red arrow). (C, E) Within 2 months of treatment, a repeat CT scan showed resolution of the patient's posterior mediastinal lymph node (red arrow).

Analogous to lung adenocarcinoma, *ALK* rearrangements in PDAC were detected in a small percentage of cases, with a prevalence of 0.16%. Indeed, considering the low prevalence of *ALK* translocations, many reports have concluded that rearrangements in *ALK* are absent in PDAC.²⁰ Moreover, a striking feature of *ALK*-positive PDACs is a young age at onset, with a mean age of 38 years. In comparison, the mean age of patients with PDAC is 65 years.²¹ In contrast to *ALK*-rearranged lung adenocarcinomas, signet-ring cells and goblet cells were absent in *ALK*-positive PDACs; however, abundant extracellular mucin was identified in 2 cases. Lastly, *KRAS* mutations are nearly ubiquitous in PDAC, but none of the *ALK*-translocated PDACs harbored a mutation in *KRAS*, which may reflect the mutual exclusivity of these alterations. The similarities between *ALK*-

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positive PDACs and lung adenocarcinoma as well as other *ALK*-translocated carcinomas are intriguing and suggest not only a common pathogenesis, but possibly an equivalent response to treatment.

Several studies have demonstrated that *ALK*-rearranged tumors are highly responsive to small molecule tyrosine kinase inhibitors, such as crizotinib and ceritinib. However, despite the initial sensitivity, most patients will eventually experience relapse within 12 months.²² Mechanisms of acquired resistance include secondary mutations in the *ALK* tyrosine kinase domain, *ALK* fusion gene amplification, and activation of alternative tyrosine kinases or downstream genes, such as *KRAS* mutations.²³ Consistent with these findings, on treatment with *ALK* inhibitors, 3 of 4 patients described herein demonstrated either stable disease or radiographic response with normalization of serum CA 19-9 levels. For Case 1, within 2 months of starting ceritinib, both a radiographic and serum CA 19-9 response were identified, but after 7 months resistance was observed. However, the pattern of ceritinib resistance was heterogeneous in distribution, with development of a new metastasis within the lung and stable intra-abdominal disease. CGP of the patient's primary tumor and subsequent lung metastasis revealed discordant results. Before ceritinib treatment, in addition to an *EML4-ALK* translocation, a *BAP1* mutation was identified within the patient's primary PDAC. In contrast, the patient's pulmonary metastasis was wild-type for *BAP1* but harbored a *PBRM1* mutation. No *ALK* secondary mutations, *EML4-ALK* gene amplification, or other genetic alterations associated with receptor tyrosine kinase pathway activation were detected within the pulmonary metastasis.

PBRM1 is hypothesized to be a tumor suppressor gene and encodes for the protein BAF180, a component of the SWI/SNF chromatin remodeling complex that regulates gene expression through nucleosome repositioning.²⁴ Loss of *PBRM1* is associated with increased cell proliferation and motility. *PBRM1* is believed to have regulatory effects on *TP53*, *CDKN1A/p21*, and the *KRAS* pathway. In fact, Varela et al²⁵ found *PBRM1* inactivation cooperates with mutant *KRAS* in driving tumor development in a mouse model of PDAC. Considering the possible mutual exclusivity between *KRAS* mutations and *ALK* rearrangements in PDAC, it is

plausible that a *PBRM1* inactivation can potentiate the downstream effects of *ALK* tyrosine kinase activation. Moreover, mutations in *PBRM1* and *BAP1* with loss of heterozygosity of the wild-type allele tend to be subclonal and mutually exclusive, which could explain the lack of a *BAP1* inactivation within the patient's pulmonary metastasis.²⁶

It is important to note that there are a number of limitations in this study. Although all patients within our cohort were clinically and pathologically considered to have PDAC, confirmatory surgical resection material was only available for a single patient with an *ALK*-translocated PDAC. However, 85% patients with PDAC present with locally advanced and/or metastatic disease. Regardless, the lack of confirmatory resection specimens does not minimize the significance of our findings. Three of 4 patients with *ALK* translocations within our cohort demonstrated stable disease, radiographic response, and/or normalization of serum CA 19-9 to *ALK* inhibitors. In addition, the low prevalence of *ALK* translocations in PDAC may be viewed as insignificant to justify the expense of CGP. The young age at presentation for patients with *ALK*-positive PDAC may be used to screen patients for these targetable translocations. In fact, among patients <50 years of age within our study cohort, 1.3% of patients with PDAC harbored an *ALK* translocation. Further, similar to lung adenocarcinoma, low-cost alternatives, such as *ALK* break-apart FISH and *ALK* immunohistochemistry, may be used to screen for *ALK* rearrangements in PDAC.

Conclusions

Rearrangements in *ALK* are present in a small subset of PDACs. Similar to other *ALK* translocated cancers, PDACs with *ALK* translocations are characterized by young patient age at presentation, an absence of *KRAS* mutations, and a clinical response to *ALK* inhibitors. Considering the low prevalence of *ALK* rearrangements in PDAC, screening for these "actionable" targets may be facilitated by focusing on patients presenting with PDAC at an age of <50 years.

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