Novel ALK Fusion, \textit{PPFIBP1-ALK}, in Pancreatic Ductal Adenocarcinoma Responsive to Alectinib and Lorlatinib

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INTRODUCTION

Pancreatic cancer is the seventh leading cause of cancer death among men and women worldwide, with > 430,000 deaths in 2018.\textsuperscript{1} Despite advances in surgical techniques, radiation, and systemic treatment in the past few decades, overall survival for pancreatic cancer is extremely poor, with a 5-year survival rate of 9%.\textsuperscript{2} Current systemic treatment regimens for metastatic pancreatic cancer include FOLFIRINOX (fluorouracil, folinic acid, oxaliplatin, and irinotecan), gemcitabine plus nab-paclitaxel, and liposomal irinotecan with fluorouracil.\textsuperscript{3,6}

Approximately 88%-95% of pancreatic adenocarcinomas harbor KRAS-driver mutations. However, there have been no US Food and Drug Administration (FDA)-approved targeted therapies for KRAS.\textsuperscript{7,9} In KRAS wild-type tumors, alternate oncogenic drivers have been identified, including \textit{BRAF}, \textit{ROS}, \textit{NRG1}, \textit{GNAS}, \textit{CTNNB1}, and \textit{ALK} gene fusions.\textsuperscript{10,11} \textit{ALK} gene fusions were first described in pancreatic adenocarcinoma in 2017.\textsuperscript{12,13} Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase in the insulin receptor family, and \textit{ALK} fusion genes have been characterized in multiple solid tumors, including thyroid, breast, and colorectal cancers and non–small-cell lung cancer (NSCLC).\textsuperscript{14,15} ALK translocations are seen in 3%-7% of NSCLC, causing constitutive activation of ALK and mediating oncogenesis through various signal transduction pathways, including the MAPK pathway.\textsuperscript{16} ALK inhibitors include crizotinib, the first-in-class FDA-approved targeted therapy with a greater response rate (65% v 20%) and longer progression-free survival (PFS; 7.7 months v 3 months) than standard chemotherapy in a phase III trial of previously treated ALK-positive NSCLC.\textsuperscript{17,18} In a phase III trial in treatment-naïve patients with NSCLC, crizotinib-associated PFS was notably greater than PFS with chemotherapy (10.9 months v 7.0 months).\textsuperscript{19} In the phase III ALEX trial, second-generation the ALK inhibitor alectinib greatly increased PFS compared with crizotinib in treatment-naïve patients with NSCLC—with a response rate of 82.9%—and generally is used as first-line therapy in ALK-positive NSCLC.\textsuperscript{20} However, patients can acquire resistance to ALK inhibitors through development of ALK resistance mutations.\textsuperscript{21} ALK G1202R, V1180L, and I1171 T/N/S are known alectinib-resistant mutations that were seen in 53% of patients who acquired resistance to alectinib.\textsuperscript{22,23} In a phase II trial, lorlatinib, a third-generation ALK inhibitor, was active in both treatment-naïve and previously ALK inhibitor–treated patients with ALK-positive NSCLC (objective responses of 90% and 47%, respectively).\textsuperscript{24} Additionally, lorlatinib can overcome ALK G1202R and V1180L resistance mutations that are seen in acquired resistance to alectinib.\textsuperscript{25,26}

To date, only 6 occurrences of ALK-positive pancreatic cancer have been identified. In a study of > 3,100 patients with pancreatic cancer, only 5 patients had ALK translocation, none of whom had KRAS mutations.\textsuperscript{12} We present a case of a young woman with a novel \textit{ALK} fusion partner, \textit{PPFIBP1-ALK}, in metastatic pancreatic ductal adenocarcinoma who initially experienced a response to alectinib, then experienced progression with acquired alectinib-resistant mutations, which were stabilized with lorlatinib.

CASE REPORT

A 41-year-old woman with no past medical history presented with abdominal pain and bloating for 3 weeks. She had no family history of cancer and denied smoking or alcohol use. AST, ALT, and alkaline phosphatase levels were elevated at 139, 88, 257 u/L, respectively. \(\gamma\)-glutamyl transferase and lactate dehydrogenase levels were elevated at 317 and 1,886 u/L, respectively. Biopsies of the pancreas and liver lesions were consistent with pancreatic adenocarcinoma. Molecular profiling of the tumor was remarkable for \textit{PPFIBP1-ALK} translocation, confirmed by immunohistochemistry (DSF3 companion diagnostic assay; Ventana, Roche Diagnostics, Indianapolis, IN).
Fluorescence in situ hybridization (FISH) was negative. It has been shown that FISH may have different sensitivities of detecting ALK compared with next-generation sequencing or immunohistochemistry. Of note, molecular profiling was negative for KRAS, microsatellite instability, NF1 and p53 inactivating mutations, and CDKN2A/B loss. Profiling was positive for BRCA2 c.8007A>G (silent) and CDKN1B 407A>G, both of unknown clinical significance. Patient was started on FOLFIRINOX with radiographic response. However, because of the adverse effects of chemotherapy, including nausea and neuropathy, the patient was switched to alectinib 600 mg twice daily, given her ALK fusion status. The 2-month follow-up CT imaging showed continuing response (Fig 1). However, she experienced progression on alectinib after 5 months and was placed back on FOLFIRINOX. Subsequent cell-free plasma (Guardant360; Guardant Health, Redwood City, CA) showed newly acquired ALK mutations G1202R and V1180L in addition to the PPFIBP1-ALK translocation. The patient experienced progression quickly on FOLFIRINOX and was transitioned to lorlatinib. The patient’s disease has been stable on lorlatinib on 2-month follow-up imaging, and she continues to be treated with lorlatinib (Figs 2 and 3).

**DISCUSSION**

Currently, there are no FDA-approved targeted therapies for pancreatic cancer, and standard chemotherapy (FOLFIRINOX) for metastatic pancreatic cancer is quite toxic, with a median overall survival of approximately 11 months. To our knowledge, we present the seventh case of ALK-positive metastatic pancreatic cancer with a novel PPFIBP1-ALK fusion gene and the first patient to be treated with alectinib as first-line targeted therapy. The patient ultimately acquired alectinib-resistant ALK mutations G1202R and V1180L; however, the disease has been stable on the third-generation ALK inhibitor lorlatinib.

ALK translocation in pancreatic cancer was first described in 2017, and there have been only 6 documented cases of ALK-positive pancreatic adenocarcinoma through literature review (Table 1). Although the prevalence of the ALK fusion gene is rare, at 0.16%, the prevalence increases to 1.3% among patients < 50 years old. The majority of ALK fusion partners seen in NSCLC includes EML4, but other partners include STRN, KCNQ, KLC1, KIF5B, PPM1B, and TGF genes. PPFIBP1-ALK gene fusion was first described in 2011 in a patient with pulmonary inflammatory myofibroblastic tumor and subsequently was described in epithelioid fibrous histiocytoma, but it has never been described in NSCLC or pancreatic cancer. Of the 6 patients with ALK-positive pancreatic cancer, 4 patients had EML4-ALK translocation, 1 patient had STRN-ALK, and 1 patient had a DCTN1-ALK translocation (Table 1). This patient demonstrates a novel PPFIBP1-ALK fusion gene, of which the tumorigenicity of PPFIBP1-ALK was elucidated in pulmonary inflammatory myofibroblastic tumor. PPFIBP1 is involved in cell adhesion and migration, and the different ALK fusion partners may be responsible for various invasive
and proliferative capabilities, ultimately leading to activation of different signaling pathways.28

In NSCLC, ALK fusion is an oncogenic driver that is generally mutually exclusive of KRAS mutation16; however, there are reports of concomitant KRAS and ALK fusion double alteration that may confer worse prognosis.31 All 7 patients with ALK-positive pancreatic cancer were KRAS wild type, suggesting, albeit in a small sample size, that ALK translocation drives oncogenesis and that these 2 oncogenic drivers are mutually exclusive. Overall survival ranged from 5-52 months with crizotinib treatment in ALK-positive pancreatic cancer (Table 1). This case demonstrates the first time, to our knowledge, that alectinib has been used as the first targeted therapy, and the development of known alectinib-resistant ALK mutations suggests that ALK-positive pancreatic cancer acquires resistance in a fashion similar to that of NSCLC.

There is a clear unmet medical need for novel therapeutic approaches in pancreatic cancer. A recent study in metastatic pancreatic cancer with germ-line BRCA mutations (7% prevalence) regardless of KRAS mutation status showed increased PFS with the poly ADP ribose polymerase inhibitor olaparib after first-line platinum-based chemotherapy.4 In a recent phase II basket study, 2 of 9 patients who had pancreatic cancer with HER2 amplification/overexpression experienced responses to HER2-targeted therapies trastuzumab plus pertuzumab. Additionally, a patient who had pancreatic cancer and BRAF gene fusion (CUX1-BRAF) had a partial response to the BRAF-targeted therapy vemurafenib.32 Last, 3 patients who had pancreatic cancer with NTRK1 and ROS1 gene fusions experienced responses to entrectinib, a targeted inhibitor of these genes.33 These studies are additional proof of concept that targeted therapies can be used successfully when paired with the right genomic alteration and that ALK inhibitors may be of substantial clinical benefit in the right patient. In patients with resected pancreatic cancer, KRAS mutation is associated with worse overall survival than KRAS wild-type tumors.34 Additionally, prevalence of KRAS mutation is notably less (80% v 89%) in patients < 50 years old, and
38% of KRAS wild-type tumors have genomic alterations that could activate the MAPK signaling cascade. Identification of molecular alterations in patients with KRAS wild-type status that may drive oncogenesis will help guide therapeutic intervention in a small but clinically relevant population.

ALK translocations are rare in pancreatic cancer. This is, to our knowledge, the first report of PPFIBP1-ALK rearrangement in pancreatic or NSCLC, the first reported patient with pancreatic cancer to be treated with alectinib as the first targeted therapy, and the first patient to be treated with lorlatinib after acquired resistance to alectinib with stabilization of disease. The molecular drivers of this tumor behave similarly to ALK-positive NSCLC. All 7 occurrences of ALK-positive pancreatic cancer have been KRAS wild type; given that 6 of the 7 patients were < age 50 years, there may be clinical benefit to screen young patients with pancreatic cancer who are KRAS negative for the ALK gene fusion, as they may benefit from ALK inhibitors, which may lead to improved overall survival. Last, noninvasive sampling of cell-free DNA can be used for monitoring resistance to targeted therapies in ALK-positive pancreatic cancer.

**TABLE 1.** Clinical Characteristics of Patients With ALK-Positive Pancreatic Cancer

| Patient Case | Age (years) | Sex | ALK Rearrangement | ALK Inhibitor (in order of treatment) | Duration of Survival (months) |
|--------------|-------------|-----|-------------------|--------------------------------------|-----------------------------|
| 1            | 35          | M   | Exon 13 EML4-exon 20 ALK | (1) Crizotinib; (2) ceritinib; (3) alectinib | 52* |
| 2            | 32          | F   | Exon 6 EML4-exon 20 ALK | (1) Crizotinib | 20 |
| 3            | 34          | M   | Exon 3 STRN-exon 20 ALK | (1) Crizotinib | 10* |
| 4            | 46          | M   | Exon 6 EML4-exon 20 ALK | (1) Crizotinib; (2) alectinib | 5* |
| 5            | 43          | M   | Exon 6 EML4-exon 20 ALK | Unknown | Unknown |
| 6            | 72          | F   | DCTN1-ALK | None | Unknown |
| 7*           | 41          | F   | PPFIBP1-ALK | (1) Alectinib; (2) lorlatinib | 10* |

**NOTE.** Modified from Singhi et al, 2017.12

Abbreviation: ALK, anaplastic lymphoma kinase.

*At time of report, patient was still alive.

*Our patient.
Case Report

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