case reports

Novel *ALK* Fusion, *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.[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%.[2] Current systemic treatment regimens for metastatic pancreatic cancer include FOLFIRINOX (fluorouracil, folic acid, oxaliplatin, and irinotecan), gemcitabine plus nab-paclitaxel, and liposomal irinotecan with fluorouracil.[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.[7-9] In *KRAS* wild-type tumors, alternate oncogenic drivers have been identified, including *BRAF*, *ROS*, *NRG1*, *GNAS*, *CTNNB1*, and *ALK* gene fusions.[10,11] *ALK* gene fusions were first described in pancreatic adenocarcinoma in 2017.[12,13] Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase in the insulin receptor family, and *ALK* fusion genes have been characterized in multiple solid tumors, including thyroid, breast, and colorectal cancers and non–small-cell lung cancer (NSCLC).[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.[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.[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).[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.[20] However, patients can acquire resistance to ALK inhibitors through development of *ALK* resistance mutations.[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.[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).[24] Additionally, lorlatinib can overcome *ALK* G1202R and V1180L resistance mutations that are seen in acquired resistance to alectinib.[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.[12] We present a case of a young woman with a novel *ALK* fusion partner, *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. γ-glutamyl transferase and lactate dehydrogenase levels were elevated at 317 and 1,886 u/L, respectively; however, the CA 19-9 measure was normal at 3.2 u/L. The initial ultrasound showed multiple liver lesions, and follow-up positron emission tomography/computed tomography (CT) was remarkable for a 2.1 × 2.7 cm lesion in the uncinate process of the pancreas and several lesions in the liver, the largest lesion being 7.9 cm.

Biopsies of the pancreas and liver lesions were consistent with pancreatic ductal adenocarcinoma. Molecular profiling of the tumor was remarkable for *PPFIBP1-ALK* translocation, confirmed by immunohistochemistry (D5F3 companion diagnostic assay; Ventana, Roche Diagnostics, Indianapolis, IN).

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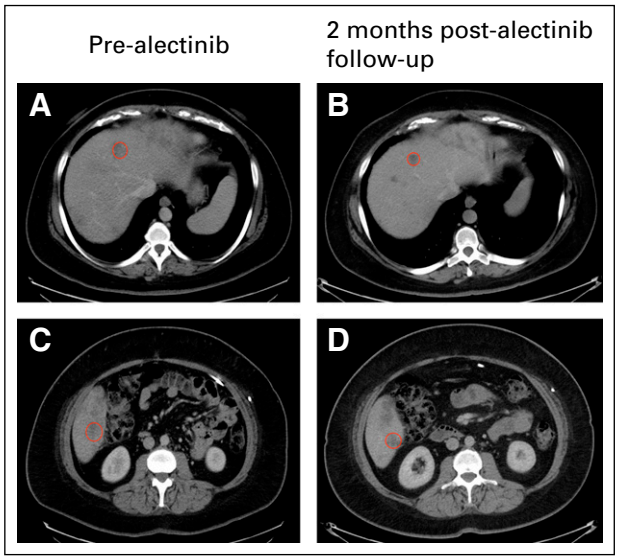

FIG 1. Computed tomography imaging of hepatic metastasis before and after alectinib. In row 1, the circled hepatic lesion in the right lobe of the liver at baseline (A) before alectinib decreased in size (B) 2 months after alectinib. Similarly, row 2 shows a different metastatic hepatic lesion (C) before alectinib with continued response seen (D) after 2 months of alectinib. The patient experienced progression during alectinib treatment after 5 months and experienced progression during fluorouracil, folic acid, oxaliplatin, and irinotecan treatment shortly thereafter.

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.[27] 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.[3] 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[12] The majority of *ALK* fusion partners seen in NSCLC includes *EML4*, but other partners include *STRN*, *KCNQ*, *KLC1*, *KIF5B*, *PPM1B*, and *TGF* genes.[28] *PPFIBP1-ALK* gene fusion was first described in 2011 in a patient with pulmonary inflammatory myofibroblastic tumor[29] and subsequently was described in epithelioid fibrous histiocytoma,[30] 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.[29] *PPFIBP1* is involved in cell adhesion and migration, and the different *ALK* fusion partners may be responsible for various invasive

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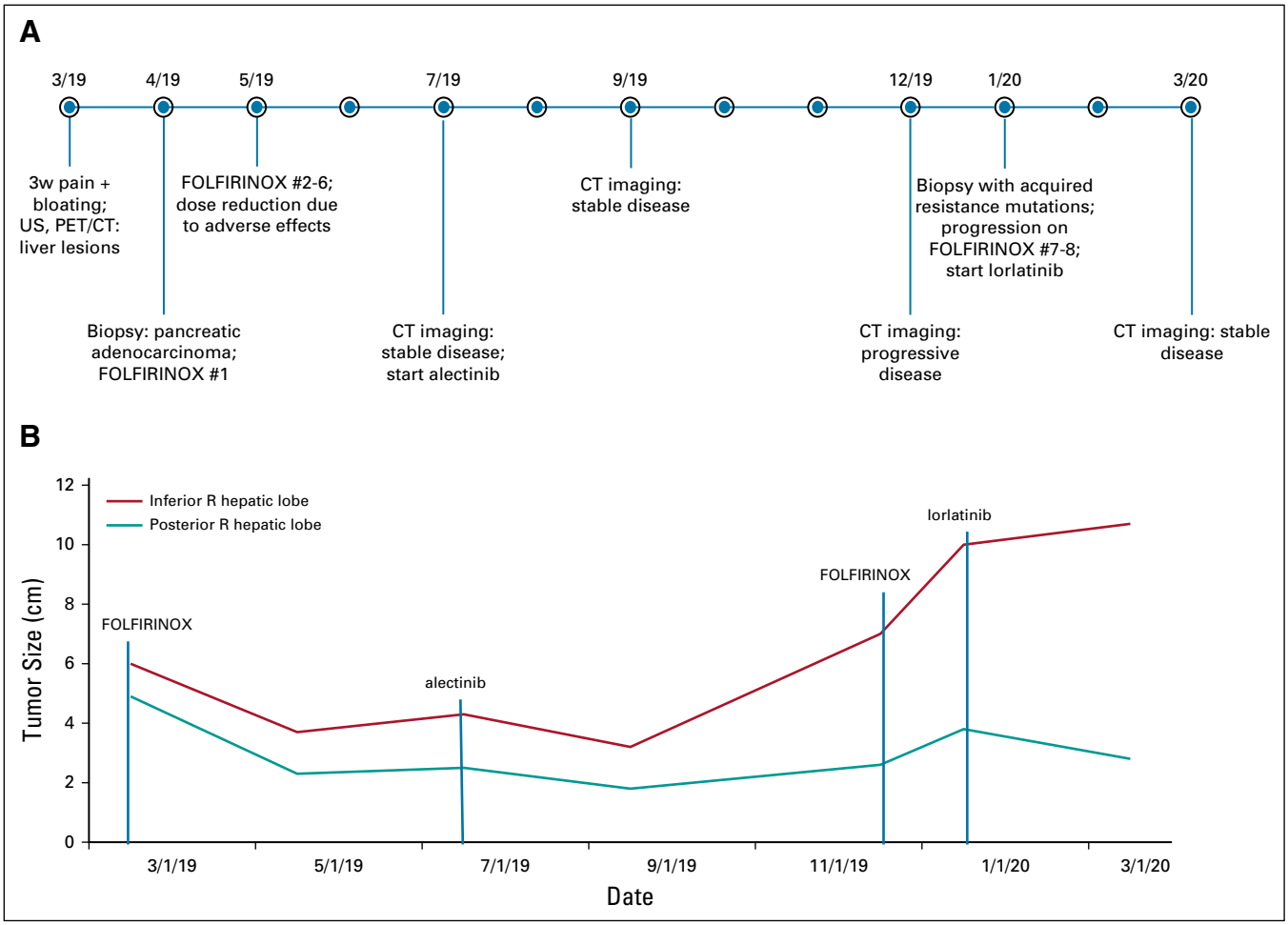

FIG 2. (A) Chronologic timeline of events including dates of initiation of anaplastic lymphoma kinase (ALK) inhibitor and radiographic imaging. (B) Graphic description of change in tumor size over time with respect to type of therapy. #, dose number; 3w, 3-week; CT, computed tomography; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin, and irinotecan; PET, positron emission tomography; R, right; US, ultrasound.

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* mutation[16]; 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

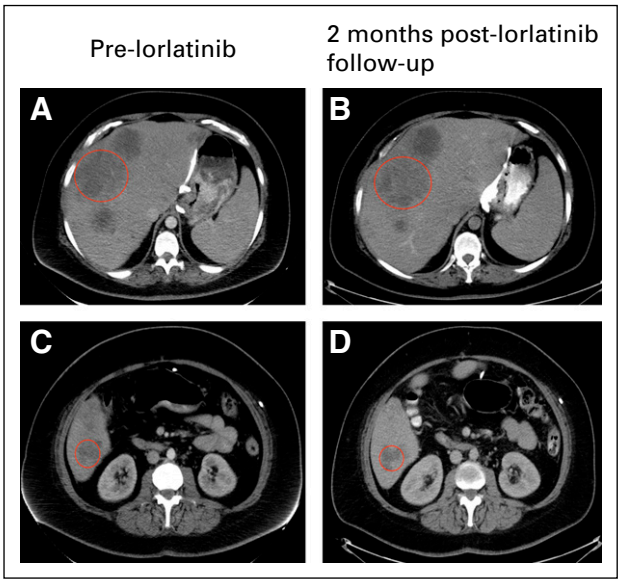

FIG 3. Computed tomography imaging of hepatic metastasis before and after lorlatinib. In row 1, the circled hepatic lesion after disease progression on fluorouracil, folic acid, oxaliplatin, and irinotecan (A) before lorlatinib was stable in size (B) 2 months after lorlatinib treatment. Similarly, row 2 shows a different metastatic hepatic lesion (C) before lorlatinib with stable disease (D) after 2 months of lorlatinib. The patient currently continues to be treated with lorlatinib.

38% of *KRAS* wild-type tumors have genomic alterations that could activate the MAPK signaling cascade.[9] 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[a]
2	32	F	Exon 6 EML4-exon 20 ALK	(1) Crizotinib	20
3	34	M	Exon 3 STRN-exon 20 *ALK*	(1) Crizotinib	10[a]
4	46	M	Exon 6 EML4-exon 20 *ALK*	(1) Crizotinib; (2) alectinib	5[a]
5	43	M	Exon 6 EML4-exon 20 *ALK*	Unknown	Unknown
6	72	F	*DCTN1-ALK*	None	Unknown
7[b]	41	F	*PPFIBP1-ALK*	(1) Alectinib; (2) lorlatinib	10[a]

NOTE. Modified from Singhi et al, 2017.[12]
Abbreviation: ALK, anaplastic lymphoma kinase.
[a]At time of report, patient was still alive.
[b]Our patient.

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