Targeting the *NTRK* Fusion Gene in Pancreatic Acinar Cell Carcinoma: A Case Report and Review of the Literature

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ABSTRACT

Pancreatic acinar cell carcinoma (PACC) is a rare pancreatic exocrine malignancy. Compared with the more common pancreatic ductal adenocarcinoma (PDAC), PACC is more common in younger White men, has earlier stages and a lower mean age (56 vs 70 years) at the time of presentation, and has a better prognosis. In addition to differences in demographic, histologic, and clinical characteristics, PACC has a genomic profile distinct from PDAC, with only rare mutations in *TP53*, *KRAS*, and *p16* that are commonly found in PDAC. This case report presents a man aged 81 years who presented with a pancreatic body mass with peripancreatic lymph node enlargement. Biopsy of the mass showed acinar cell carcinoma. The patient underwent upfront surgical resection, followed by one cycle of adjuvant gemcitabine, with stoppage of therapy due to poor tolerance. Lower-dose gemcitabine was reintroduced after disease progression 6 months later. Nab-paclitaxel was added to gemcitabine after 6 cycles because of a continued increase in the size of peripancreatic lymph nodes. Combination chemotherapy was stopped after 4 cycles because of further disease progression with new liver metastasis. Molecular testing showed the presence of an *SEL1L-NTRK1* fusion. Targeted therapy was started with the oral neurotrophic tropomyosin receptor kinase (NTRK) inhibitor larotrectinib at a dosage of 100 mg twice daily. At the time of writing, the patient has been on therapy for 13 months with an exceptional radiographic response and has not experienced any grade 3 adverse effects. To our knowledge, this is the first clinical report of an *NTRK* gene fusion in a patient with PACC. This case study highlights the significance of tumor molecular profiling in patients with pancreatic tumors, especially rare histologies.

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Background

Pancreatic acinar cell carcinoma (PACC) is a rare exocrine pancreas malignancy, accounting for <1% of primary pancreatic neoplasms. Compared with pancreatic ductal adenocarcinoma (PDAC), PACC affects mostly younger male White patients.[1] Furthermore, patients with PACC are less likely to have tumors in the head of the pancreas and tend to present with localized disease. Still an aggressive neoplasm, PACC has a more indolent course compared with PDAC and improved overall survival (OS), with the median ranging from 18 to 47 months.[1–3]

Molecular profiling of metastatic pancreatic cancer has become a routine practice. Larotrectinib and entrectinib are potent inhibitors of the neurotrophic tyrosine receptor kinase (NTRK) family of proteins, whose oncogenic rearrangements can be drivers of malignancy. The FDA approved larotrectinib in November 2018[4] and entrectinib in August 2019[5] for solid tumors harboring oncogenic *NTRK1*, *NTRK2*, or *NTRK3* fusions. These tumor-agnostic approvals followed the approval of pembrolizumab for solid tumors that show high microsatellite instability (MSI-H) or mismatch repair protein deficiency (dMMR). More recently, the FDA approved the PARP inhibitor olaparib for use in patients with PDAC who have a germline mutation in either *BRCA1* or *BRCA2*.[6]

Although these biomarker-driven therapies are recommended for patients with PDAC, their clinical utility has not yet been established in patients with PACC, despite similarities in standard-of-care therapeutic approaches. Nevertheless, a prospective randomized phase III clinical trial in a rare subtype based on even rarer molecular alterations (~1% for *NTRK1/2/3*, ~1% for MSI-H, and 5%–7% for *BRCA1/2*) is not feasible. Thus, sharing real-world experiences through case reports and case series will be critically important to ensure that the tumor-agnostic status of emerging biomarkers can be appropriately applied in the context of rare tumors such as PACC.

In a retrospective analysis of patients with pancreatic cancer who underwent molecular profiling as part of the

Pancreatic Cancer Action Network Know Your Tumor (KYT) program, highly actionable mutations were identified in 26% of patients (N=1,082; PDAC histology, n=1,005; PACC histology, n=12).[7] Notably, real-world outcomes from this registry study showed that patients receiving a molecularly matched therapy had a 1-year OS benefit and a 6-month extension in median progression-free survival (PFS) compared with those who only received unmatched therapies, either with or without actionable findings.[7] This case report presents a patient who enrolled in the KYT program and received a molecularly targeted therapy for a tumor-agnostic biomarker that had only recently been approved by the FDA at the time of initiation.

Case Description

A male patient aged 81 years with a past medical history of chronic kidney disease, hypertension, and type 2 diabetes mellitus and a family history of gastric cancer initially presented with abdominal pain. Imaging revealed a 4-cm pancreatic body mass abutting the splenic artery with no evidence of celiac artery, superior mesentery artery/vein, or portal vein encasement, along with several enlarged peripancreatic lymph nodes and no evidence of distant metastasis. An endoscopic ultrasound-guided biopsy of the mass revealed PACC (Figure 1). He underwent an uncomplicated open distal pancreatectomy with splenectomy. Pathology showed a 4.2-cm PACC with involvement of 4 of 13 retrieved lymph nodes (pT3N1). Resection margins were free of tumor.

Adjuvant gemcitabine was initiated at a dose of 1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Gemcitabine was stopped after one cycle because of poor tolerance secondary to deterioration in functional status and bilateral lower extremity edema. A surveillance CT 6 months later showed disease progression with enlarging lymph nodes. Gemcitabine was reintroduced at a lower dose of 800 mg/m^2 on days 1 and 8 of a 21-day cycle. Nab-paclitaxel was added to gemcitabine from cycle 6 onward because of further enlargement of lymph nodes. Combination chemotherapy was stopped after 4 cycles because of further disease progression, when 3 new metastatic liver lesions were identified on imaging.

Molecular profiling of the patient's tumor tissue sample was coordinated through the KYT program. Genomic testing results (FoundationOne CDx) revealed a *SEL1L-NTRK1* fusion, loss of *MEN1*, a low tumor mutational burden, and microsatellite-stable status by next-generation sequencing (NGS). This particular *SEL1L-NTRK1* fusion event showed breakpoints between *NTRK1* (chromosome 1: 156841872–156842158) and *SEL1L* (chromosome 14: 81996399–81996731). With an estimated tumor purity of 75% and a mean depth of

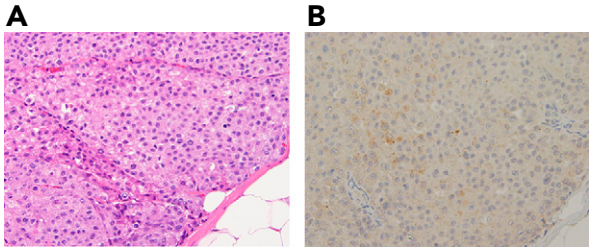

Figure 1. Biopsy of pancreatic mass showing (A) morphology consistent with acinar cell carcinoma (hematoxylin-eosin, original magnification ×100), and (B) positive immunohistochemical staining for trypsin (original magnification ×100).

853 reads from this sample, the *SEL1L-NTRK1* fusion was interpreted as in-frame and likely pathogenic with 176 reads as noted by the genomic testing laboratory. Larotrectinib on-label (which had received FDA approval for solid tumors harboring *NTRK1/2/3* fusions while genomic testing was underway) was the top-ranked therapy recommended by the Perthera molecular tumor board members, who noted that "The *NTRK1* fusion identified by this tumor profile is a compelling target for therapy, especially given the absence of a *KRAS* mutation."[8]

Of the previous patients reviewed by the Perthera molecular tumor board, the one who most closely resembled our current patient experienced a partial response to an NTRK inhibitor (entrectinib) and, at the time of study publication, had continued on therapy for >1 year.[9] Subsequently, larotrectinib, an oral NTRK inhibitor, was recommended at a dosage of 100 mg orally twice daily for our patient. However, the medication had a substantially high copay of $6,000 per month, despite insurance coverage, making the drug unaffordable for the patient. High out-of-pocket costs for novel anticancer oral therapies are one of the largest barriers to timely initiation of and adherence to treatment.[10,11] The drug was made accessible to the patient at no charge through support provided by the Bayer US Patient Assistance Foundation. At the time of writing, the patient has been on therapy with larotrectinib for 13 months. He has experienced an exceptional radiographic response with almost complete disappearance of the liver lesions (Figure 2). He has tolerated the therapy well with no dose adjustments.

Discussion

This case study anecdotally reinforces the NCCN Clinical Practice Guidelines in Oncology for Pancreatic Adenocarcinoma,[12] which recommend testing *NTRK1/2/3* for oncogenic fusion events based on the tumor-agnostic approvals of larotrectinib and entrectinib. The clinical impact that precision medicine had on this patient is

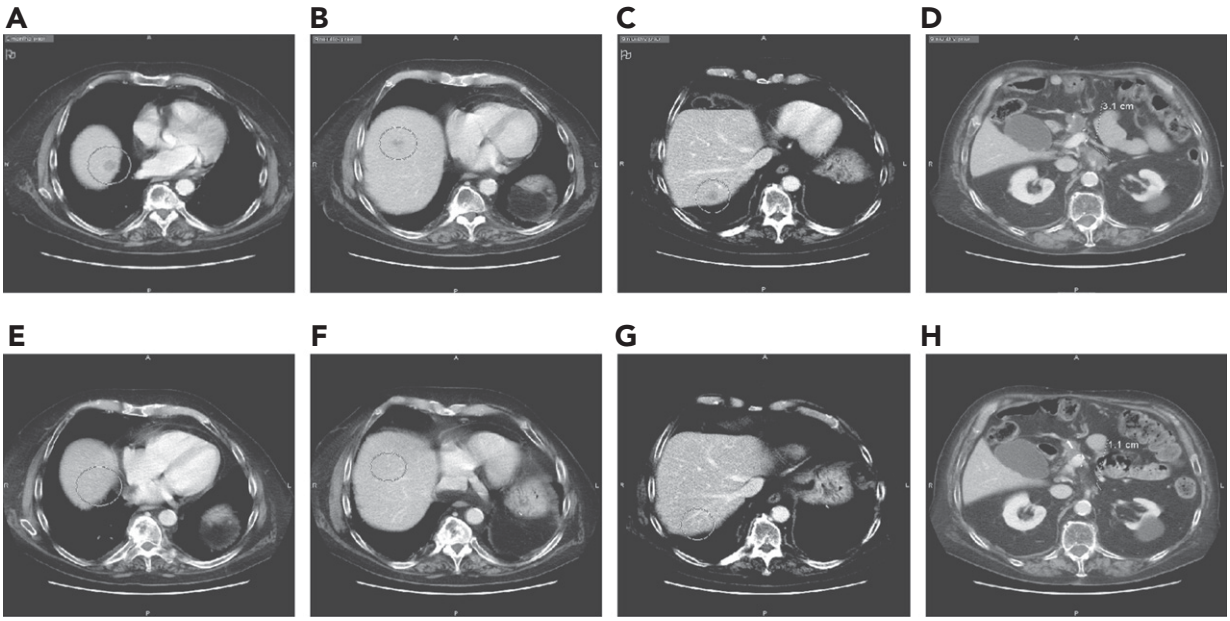

Figure 2. CT imaging of chest, abdomen, and pelvis before and after treatment with larotrectinib. Pretreatment lesions in (A) hepatic dome, (B) central liver, (C) right hepatic dome, and (D) celiac lymphadenopathy. Posttreatment improvement of (E–G) hepatic metastatic lesions and (H) celiac lymphadenopathy.

promising. Despite the rarity of *NTRK1/2/3* fusions, the role of molecular profiling in the management of PACC has not been well established. Broader efforts to harmonize real-world evidence from multiple institutions are needed to address the inability to realistically enroll a sufficient number of patients for a randomized biomarker-driven study within a rare disease such as PACC.

To estimate the potential impact that NTRK inhibitors may have across pancreatic cancer subtypes (Table 1), we analyzed genomic testing results from a combined series of patients with PACC (n=50), PDAC (n=3,316), pancreatic adenosquamous carcinoma (n=49), ampullary carcinoma (n=128), and pancreaticobiliary neuroendocrine tumors (n=319) from the Perthera real-world evidence database and the American Association for Cancer Research (AACR) Project GENIE dataset (version 6.1).[13] Oncogenic fusion events in either *NTRK1*, *NTRK2*, *NTRK3*, *ALK*, or *ROS1* were included to capture the breadth of targets thought to be selectively inhibited by NTRK/ALK/ROS1 inhibitors. Overall, each pancreatic cancer subtype had an actionability frequency <2% (0.5% in PDAC) for this class of therapy (Table 1).

Table 1. Actionable Molecular Alterations Across Pancreatic Cancer Subtypes

	***NTRK/ALK/ROS1* Oncogenic Fusions**		***KRAS/HRAS/NRAS* Driver Mutations**		***TP53* Mutations**	***CDKN2A* Alterations**
Tumor Subtype	**n (%)**	**Individual Gene-Level Alterations**	**n (%)**	**Individual Gene-Level Alterations**	**n (%)**	**n (%)**
PACC (n=50)	1 (2.0)	*NTRK1* (n=1; present patient)	5 (10.0)	*KRAS*; *NRAS* (n=3); *HRAS*	3 (6.0)	10 (20.0)
PDAC (n=3,316)	17 (0.5)	*ROS1* (n=8); *ALK* (n=6); *NTRK1* (n=3)	2,702 (81.5)	*KRAS* (n=2,694); *NRAS* (n=8)	2,127 (64.1)	1,094 (33.0)
Pancreatic adenosquamous carcinoma (n=49)	1 (2.0)	*ROS1*	39 (79.6)	*KRAS* (n=39)	35 (71.4)	17 (34.7)
Ampullary carcinoma (n=128)	1 (0.8)	*NTRK2*	68 (53.1)	*KRAS* (n=68)	68 (53.1)	29 (32.0)
Pancreatic neuroendocrine tumors (n=319)	2 (0.6)	*NTRK3*; *ROS1*	20 (6.3)	*KRAS* (n=15); *NRAS* (n=4); *HRAS*	46 (14.4)	46 (14.4)

Under each biologic pathway, the left-hand column shows the number (percent) of patients with pathway-level alterations and the right-hand column shows the number of patients with individual gene-level alterations. *RAS* mutations were constrained to known *G12/G13/Q61/A146* variants for the purposes of this analysis. Abbreviations: PACC, pancreatic acinar cell carcinoma; PDAC, pancreatic ductal adenocarcinoma.

The genomic alterations involved in the tumorigenesis of PACC are distinct from PDAC (Tables 1 and 2). Although mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* are commonly found in PDAC, each of these genes are rarely mutated in PACC (as shown in Table 1 for the same cohorts analyzed for *NTRK/ALK/ROS1* fusion frequencies). This finding is important, because the therapeutic relevance of a targetable oncogenic driver is often confounded by the presence of a co-occurring *KRAS*-activating mutation.[14]

The molecular landscape of PACC seems to be diverse. Table 2 summarizes results from several series evaluating molecular alterations in PACC, suggesting that precision oncology in PACC will evolve to targeting several uncommon genomic drivers (eg, *NTRK1/2/3* fusions) rather than a single common actionable target or pathway. PACC tumors lack the common mutations found in PDAC, such as *KRAS* and *TP53*.[15,16] Whole-exome sequencing analysis series in PACC have shown that the average number of somatic alterations in PACC is higher than in PDAC.[17,18] Myriad mutations known to have a role in tumorigenesis have been described in several PACC series, including *SMAD4*, *GNAS*, *APC*, *EGFR*, *HSP90*, *LICAM*, *MGMT*, *BRAF*, *JAK1*, *PTEN*, *GNAS*, *ARID1A*, *MLL2*, *TP53*, *RB1*, *MEN1*, *RNF43*, *KRAS*, *BRCA2*, *PALB2*, *BAP1*, and *ATM* at varying frequencies, detailed in Table 2.[15,17–21] Several series have described various chromosomal alterations in PACC, including gains in chromosomes (chromosomes 1q, 7q, 8q,12p, 17q, 20q, and Xq), loss of sequences (chromosomes 1p, 3p, 4q, 5a, 6q, 8p, 9p, 11p, 11q, 13q, 15q, 16p, 16q, and 17p), and imbalances such as *c-MYC* amplification and deleted colon cancer.[16,19,22,23] Alterations in the *APC*/β-catenin pathway have been frequently associated with PACC.[16,24] Patients with PACC have DNA dMMR[25] and MSI,[16] suggesting the possibility of an association with Lynch syndrome.

NTRK1/2/3 gene fusions have been known to be oncogenic drivers in approximately 1% of all solid tumors and could be therapeutically targeted using NTRK inhibitors.[26] In a phase I/II study, both children and adults (n=55; pancreatic tumors in 2 patients) with tropomyosin receptor kinase (*TRK*) fusion–positive tumors were treated with the highly selective TRK inhibitor, larotrectinib.[27] Larotrectinib had a remarkable clinical efficacy in that study, with an overall response rate of 75%; the median duration of response and PFS were not reached. Most adverse effects were grade 1 or 2 (93%), and the most commonly reported adverse effects were increased transaminase levels, gastrointestinal problems, fatigue, dizziness, and anemia. Dose reductions were infrequent, and there were no discontinuations of larotrectinib. Pooled analysis from phase I/II trials showed activity of another NTRK inhibitor, entrectinib, in patients with advanced/metastatic solid tumor harboring an *NTRK* fusion (n=54). Overall response rate was 57%, with a duration of response of 10 months and PFS and OS of 11 and 21 months, respectively. Similar to larotrectinib, treatment was well tolerated.[28]

The ability to detect oncogenic fusion events between *NTRK1/2/3* genes and various other partners by NGS testing has likely played an important role in accelerating the adoption of broader molecular profiling efforts across solid tumors since the FDA approvals of the NTRK inhibitors larotrectinib and entrectinib. A wide range of molecular tests is available from commercial laboratories, and it is important to consider their sensitivity and specificity, in addition to sample requirements and financial considerations. Among NGS testing methodologies, some tests rely on solely DNA-based detection (such as the test ordered for the present patient), whereas others use RNA-based sequencing at the exon level.[29] Although the coverage of each targeted NGS panel depends on each assay's technical specifications (eg, probes, alignment methods), RNA-based panels have been described as having increased sensitivity to detect fusions with less-common partner genes, particularly for *NTRK3* but less so for *NTRK1*.[30]

Table 2. Genomic Alterations Series in Pancreatic Acinar Cell Carcinoma

Study	Genetic Alteration
Hoorens et al[15]	*KRAS* (4%) and *TP53* (0%)
Rigaud et al[22]	LOH in chromosomes 1p, 4q, and 17p (>70% of pts); chromosomes 11q, 13q, 15q, and 16q (60%–70% of pts); and chromosomes 3q, 6q, 8q, 18q, and 21q (50%–60% of pts)
Taruscio et al[23]	Gains in chromosomes 1 (1q21, 66% of pts; 1q42, 50% of pts), 12 (12p11.2, 66% of pts), and X (Xq12–21, 50% of pts) and loss of sequences at chromosomes 16p (16p13.2–p13.1, 50% of pts) and 16q (16q23, 50% of pts)
Abraham et al[16]	*APC*/β-catenin pathway 23.5% (4/21 pts); allelic loss of 11p15.5, 50% (6/12 pts); MSI, 23% (3/13 pts)
Furlan et al[24]	*APC* loss (48%), methylation (56%), mutations (7%)
Liu et al[25]	dMMR in 11% (2/18 pts)
Bergmann et al[19]	*c-MYC* amplification (17% of pts) and deleted colon cancer (79% of pts) *EGFR* (42%), *HSP90* (98%), *LICAM* (72%), loss of *MGMT* (26%) and *KRAS* (3%)
Jiao et al[17]	*SMAD4* (26%); *JAK1* (17%); *TP53*, *BRAF*, *RB1* (13% each); *GNAS*, *APC*, *PTEN GNAS*, *ARID 1A*, *MLL2* (9% each); *ATM*, *BRCA2*, *PALB2*, *MEN1*, *RNF 43* (4% each)
Furukawa et al[18]	*BRCA2* (45%); *FAT1*, *FAT3*, *FAT4* (57%)
Dewald et al[42]	Gains of *CTNNB1* (80%), loss of *CTNNB1* (20%), gain of *APC* (20%), loss of *APC* (20%), gain of *CDKN2A* (20%), loss of *BRCA2* (40%), gain of *EGFR* (20%), loss of *ERBB2* (20%), loss of *TYMS* (40%), loss of *TYMP* (40%)

Abbreviations: dMMR, DNA mismatch repair deficiency; LOH, loss of heterozygosity; MSI, microsatellite instability; pts, patients.

NTRK gene fusions are rarely associated with tumorigenesis in PDAC.[9,31–33] Some of the *NTRK* fusion partners described in these pancreatic cancer studies are *LMNA-NTRK1*,[32] *ETV6-NTRK3*,[32] *TPR-NTRK1*,[9,31] *CTRC-NTRK1*,[33] *TPR-NTRK1*, and *ERC1-NTRK1*.[31] No other reports have described *SEL1L* as an *NTRK* fusion partner in pancreatic cancer. We inquired in the Perthera real-world evidence database and the AACR Project GENIE dataset to determine whether any particular *NTRK* fusion partners were found consistently across different tumor types. The most common partners found globally (n>1) were *NTRK1* with *LMNA* (n=9), *TPM3* (n=5), *IRF2BP2* (n=2), *PEAR1* (n=2), and *RBPMS* (n=2). Our patient had the only instance of an *NTRK* fusion partnered with *SEL1L* across any of the cancer types represented. In a case of a patient with metastatic PDAC with a *CTRC-NTRK1* gene fusion, O'Reilly and Hechtman[33] reported therapeutic efficacy of larotrectinib.[33] In a phase II clinical trial (ClinicalTrials.gov identifier: NCT02568267), 3 patients with pancreatic cancer with actionable gene rearrangements (2 with a *TPR-NTRK* gene fusion and 1 with an *SCL4-ROS1* gene fusion) were treated with the selective TRK and ROS1 inhibitor entrectinib. All patients had a favorable response and prolonged disease control.[34]

Although their antineoplastic efficacy seems very promising, acquired resistance mechanisms have been described in the literature. Resistance can develop through on-target or off-target mechanisms. On-target resistance mechanisms include *NTRK* kinase domain mutations that can cause interference with drug binding or adenosine triphosphate (ATP)–binding affinity.[35,36] The emergence of resistance to entrectinib in a patient with metastatic colorectal carcinoma was explained by sampling the circulating tumor DNA and xenograft samples, which showed 2 point mutations in the catalytic domain of *NTRK1*, p.G595R and p.G667C.[36] Acquired resistance to entrectinib in another patient with mammary analog secretory carcinoma was detected through an *NTRK3* p.G623R mutation, interfering with drug binding.[35] Next-generation NTRK inhibitors could overcome the on-target resistance to the first-generation NTRK inhibitors. The second-generation inhibitors are potent and highly selective, and their smaller structure allows them to accommodate an ATP-binding site while avoiding steric clashes caused by domain mutations.[37]

Currently, 2 second-generation NTRK inhibitors are in clinical development: selitrectinib/LOXO-195 and repotrectinib (TPX-0005). Preliminary analysis based on a phase I study (ClinicalTrials.gov identifier: NCT03215511) and the FDA's expanded access protocol showed the safety and efficacy of selitrectinib in patients with TRK domain mutations.[38] Repotrectinib is being evaluated in an ongoing phase I/II trial (ClinicalTrials.gov identifier: NCT03093116) in patients with rearranged *ROS1/NTRK* with relapsed disease after first-generation tyrosine kinase inhibitors.[39] Off-target resistance mechanisms could include alterations in upstream or downstream pathways, specifically involving the mitogen-activated protein kinase pathway.[40] This acquired resistance could potentially be managed with a combination of NTRK and MEK inhibitors.[40] Mutations in the insulin growth factor receptor type 1 (IGF1R) pathway could also lead to resistance and a combination of IGF1R and NTRK inhibitors to overcome the resistance.[41] Gene profiling of tumor samples is recommended for all patients with metastatic PDAC. Our case highlights the importance of genomic profiling in rare histologic variants such as acinar cell carcinoma to identify targetable alterations.

Conclusions

This case study highlights the importance of identifying targetable genetic alterations in pancreatic cancer, and specifically rare histologies such as PACC. The study describes the first reported patient with *NTRK* gene fusion in PACC. Ongoing partial response to larotrectinib was attained, and to date therapy has been tolerated with no major adverse effects.

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