

# Durable response to selpercatinib in HOOK3-RET fusion positive, $\alpha$ -fetoprotein producing metastatic pancreatic ductal adenocarcinoma with intestinal-type differentiation

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**Abstract.** Pancreatic cancer carries a poor prognosis, with few effective treatment options available. Various rearranged during transfection (RET) proto-oncogene fusions have been found in a small fraction of pancreatic cancers; however, the hook microtubule tethering protein 3 (HOOK3)-RET fusion has not yet been reported in the medical literature. The HOOK3-RET fusion was observed in a case of  $\alpha$ -fetoprotein (AFP)-producing pancreatic ductal adenocarcinoma with widespread hepatic and lymph node metastasis in a 51-year-old South Asian male. The patient's serum carbohydrate antigen 19.9 was mildly elevated: 96.28 U/ml (normal, <37 U/ml), but the serum AFP level was very high (16,410.0 ng/ml; normal, <6.6 ng/ml). The patient did not respond to gemcitabine and cisplatin-based systemic chemotherapy. Next-generation sequencing of the patient's biopsy sample revealed a HOOK3-RET fusion. RET proto-oncogene fusions trigger a cascade of oncogenic signals, which promote the proliferation and survival of cancer cells. Selpercatinib, a selective inhibitor of receptor tyrosine kinase RET, blocks RET kinase activity by binding to its adenosine triphosphate-binding site, thus preventing the kinase from phosphorylating substrates and halting oncogenic signaling. The patient was treated with selpercatinib, which produced a durable response lasting over 15 months in this chemotherapy-refractory patient, highlighting the efficacy of selpercatinib in HOOK3-RET fusion-positive pancreatic cancer.

## Introduction

Worldwide, pancreatic cancer is the sixth leading cause of cancer-associated mortality, and it is more common in the Western and industrialized parts of the world (1). It carries a poor prognosis, with few effective treatment options. In patients with advanced disease, long-term survival remains poor, with a 5-year survival rate of ~10% despite the use of multi-agent combination chemotherapy (2). The advent of targeted therapies, matched to tumor-specific molecular alterations, has significantly expanded the range of treatment options. However, only a limited number of such actionable targets have been identified in pancreatic cancer (2). Various rearranged during transfection (RET) proto-oncogene fusions have been found in a small fraction of pancreatic cancers, with a reported incidence of 0.6% (2). However, to the best of our knowledge, hook microtubule tethering protein 3 (HOOK3)-RET fusion, as seen in the present case, has not yet been reported in pancreatic cancer in the medical literature. These RET fusions lead to constitutively active, ligand-independent signalling and oncogenesis, thus making these fusions a promising therapeutic target. This has led to the development of RET tyrosine kinase inhibitors (2). The present study reported a case of HOOK3-RET fusion in a patient with  $\alpha$ -fetoprotein (AFP)-producing metastatic pancreatic ductal adenocarcinoma of the intestinal type in a 51-year-old South Asian male. The patient was treated with selpercatinib, a selective inhibitor of receptor tyrosine kinase RET, which produced a durable response in this chemotherapy-refractory patient.

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## Case report

A 51-year-old South Asian male with a medical history of hypertension presented to Sandhu Cancer Centre (Ludhiana, India) in July 2024 with complaints of anorexia, abdominal pain and weight loss for 3 months. The patient also exhibited yellow discoloration of the body for 1 month. General physical examination revealed an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 (3) and the presence of scleral icterus. A computed tomography (CT) scan of the neck,

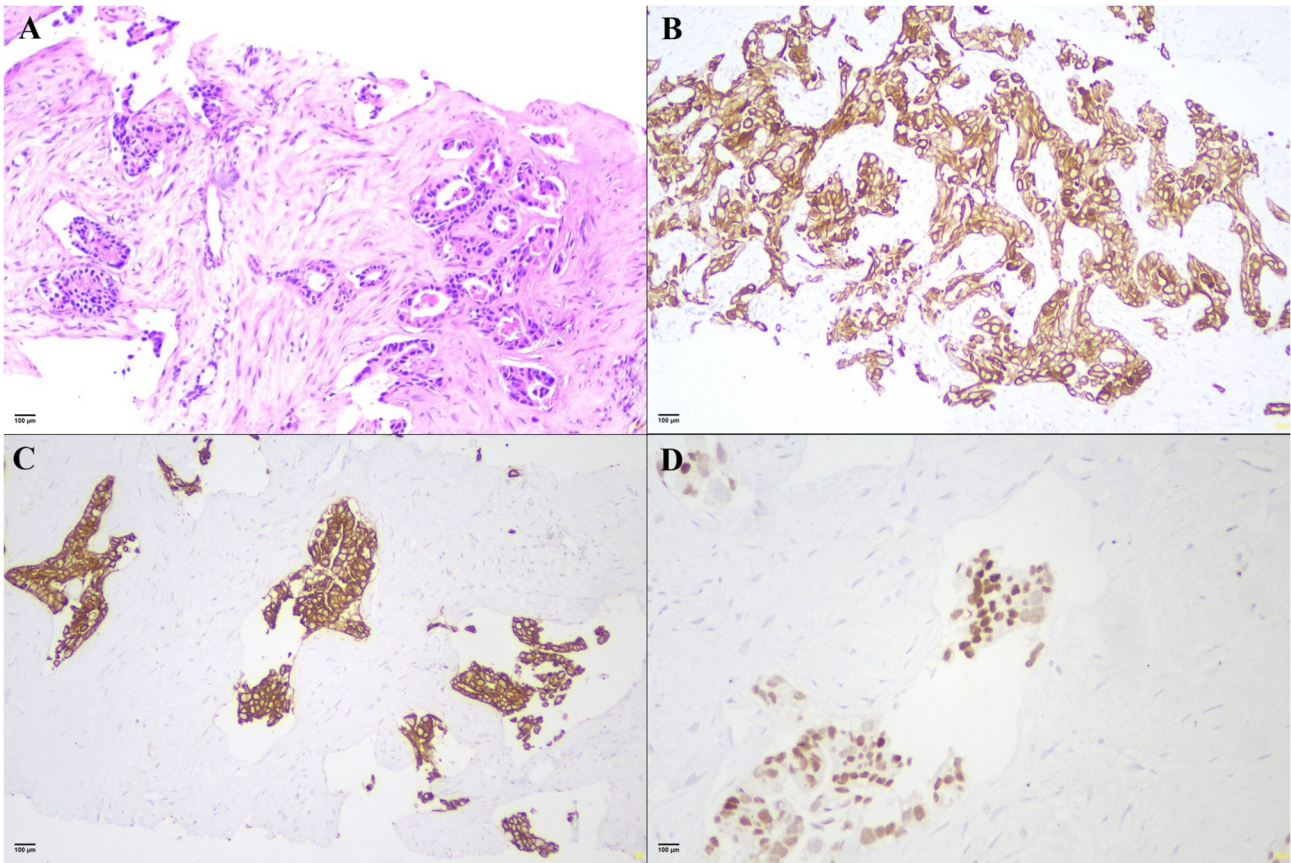


Figure 1. Liver biopsy (A) H&E stain showing foci of metastatic pancreatic ductal adenocarcinoma with significant desmoplasia, (B) CK7 IHC with membrane staining of tumor glands, (C) CK19 IHC with membrane staining of tumor glands, and (D) CDX2 IHC with nuclear positivity in tumor glands (magnification, x200; scale bar, 100  $\mu$ m). IHC, immunohistochemistry; CK, cytokeratin; CDX2, caudal-type homeobox transcription factor 2.

chest, abdomen and pelvis demonstrated a 3.3x4.8x4.4 cm heterogeneously enhancing mass lesion involving the head and uncinate process of the pancreas, along with peripancreatic, periportal and left supraclavicular lymphadenopathy, as well as multiple hepatic metastases. Tumor infiltration and thrombosis of the portal vein, superior mesenteric vein, inferior mesenteric vein and splenic vein were also observed. However, no lung or mediastinal metastases were found. The results of the liver function tests were as follows: Total serum bilirubin: 6.50 mg/dl (normal, <1.1 mg/dl); direct bilirubin, 6.20 mg/dl (normal,  $\leq$ 0.2 mg/dl); alanine aminotransferase (ALT), 259 U/l (normal, <41 U/l); aspartate aminotransferase (AST), 107 U/l (normal, <37 U/l); and alkaline phosphatase, 308 U/l (normal, <129 U/l). Serum carbohydrate antigen 19.9 (CA 19.9) was mildly elevated (96.28 U/ml; normal, <37 U/ml) and serum carcinoembryonic antigen (CEA) was normal (4.01 ng/ml; normal, <5 ng/ml). However, the serum AFP level was very high (16,410.00 ng/ml; normal, <6.6 ng/ml). Biopsy of the liver lesion was performed and histopathology (Data S1) revealed metastatic pancreatic ductal adenocarcinoma (Fig. 1A). The tumor cells were positive for cytokeratin (CK) 7 (Fig. 1B), CK19 (Fig. 1C), caudal-type homeobox transcription factor (CDX) 2 (Fig. 1D), mucin 2 (MUC2) and glypican-1, and negative for CEA, MUC5AC, hepatocyte paraffin 1 and arginase 1 on immunohistochemistry (IHC). Based on histopathology and IHC, a final diagnosis of metastatic pancreatic ductal adenocarcinoma with intestinal-type differentiation was made.

In view of the poor performance status (ECOG PS 2), and the presence of icterus and abnormal liver function tests, the decision was made not to initiate FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan and oxaliplatin) regimen, the preferred initial systemic therapy for medically fit patients with metastatic pancreatic cancer. Instead, a gemcitabine (1,000 mg/m<sup>2</sup> weekly) plus cisplatin (25 mg/m<sup>2</sup> weekly) regimen was started (4). Depending on tolerance, the drug dosages were reduced by 25-50% and the interval between cycles was extended for up to 2 weeks.

Following 10 weeks of chemotherapy, symptomatic improvement was achieved along with a biochemical response with normalisation of bilirubin, ALT and AST. The AFP level was also decreased to 5,970.00 ng/ml. However, the CA19.9 level increased to 177.48 U/ml. On the repeat CT scan, there was radiological disease progression as per the response evaluation criteria in solid tumors version 1.1 (5), with a 21% increase in the sum of the longest diameters (SLD) of the pancreatic mass (Fig. 2A), an increase in the size of liver metastases (Fig. 2B), along with persistence of peripancreatic and left supraclavicular lymphadenopathy.

In the meantime, the tissue biopsy subjected to RNA-based next-generation sequencing (NGS) revealed a rare HOOK3::RET rearrangement, as the fusion product between the exon 21 (chr8:43013400:+) of HOOK3 and exon 12 (chr10:43116584:+) of RET was visualized using Arriba, version v2.3.0 (Fig. 3). The homologous recombination deficiency status was negative

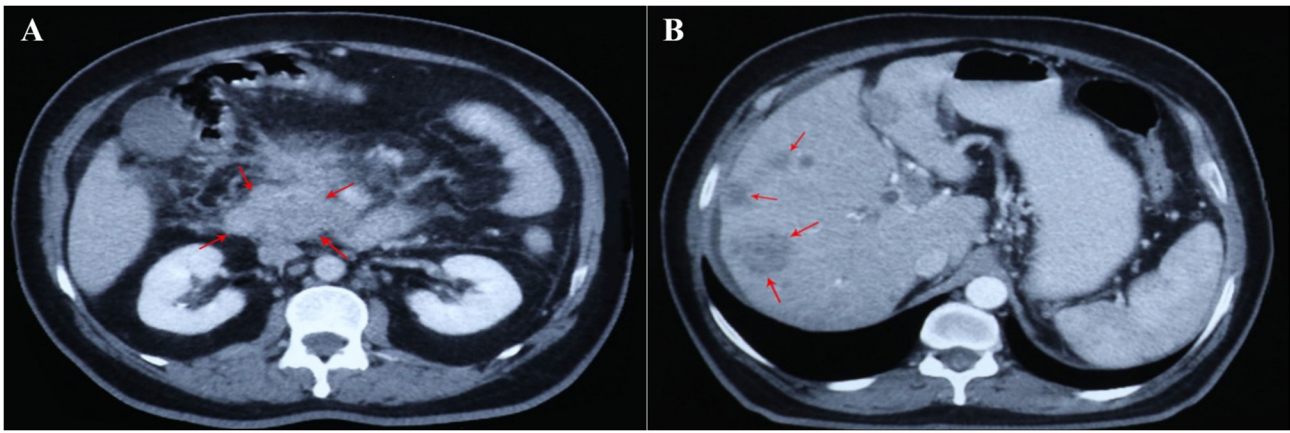


Figure 2. Pre-selpercatinib treatment contrast-enhanced computed tomography abdomen axial section (venous phase) showing (A) mildly heterogeneously enhancing primary mass lesion (red arrows) measuring ~3.8 (anteroposterior dimension) x 5.6 (transverse dimension) x 5.8 (craniocaudal dimension) cm in the head and uncinate process of the pancreas, and (B) multiple hypoenhancing hepatic metastases (red arrows), the largest measuring ~2.2x2.0 cm.

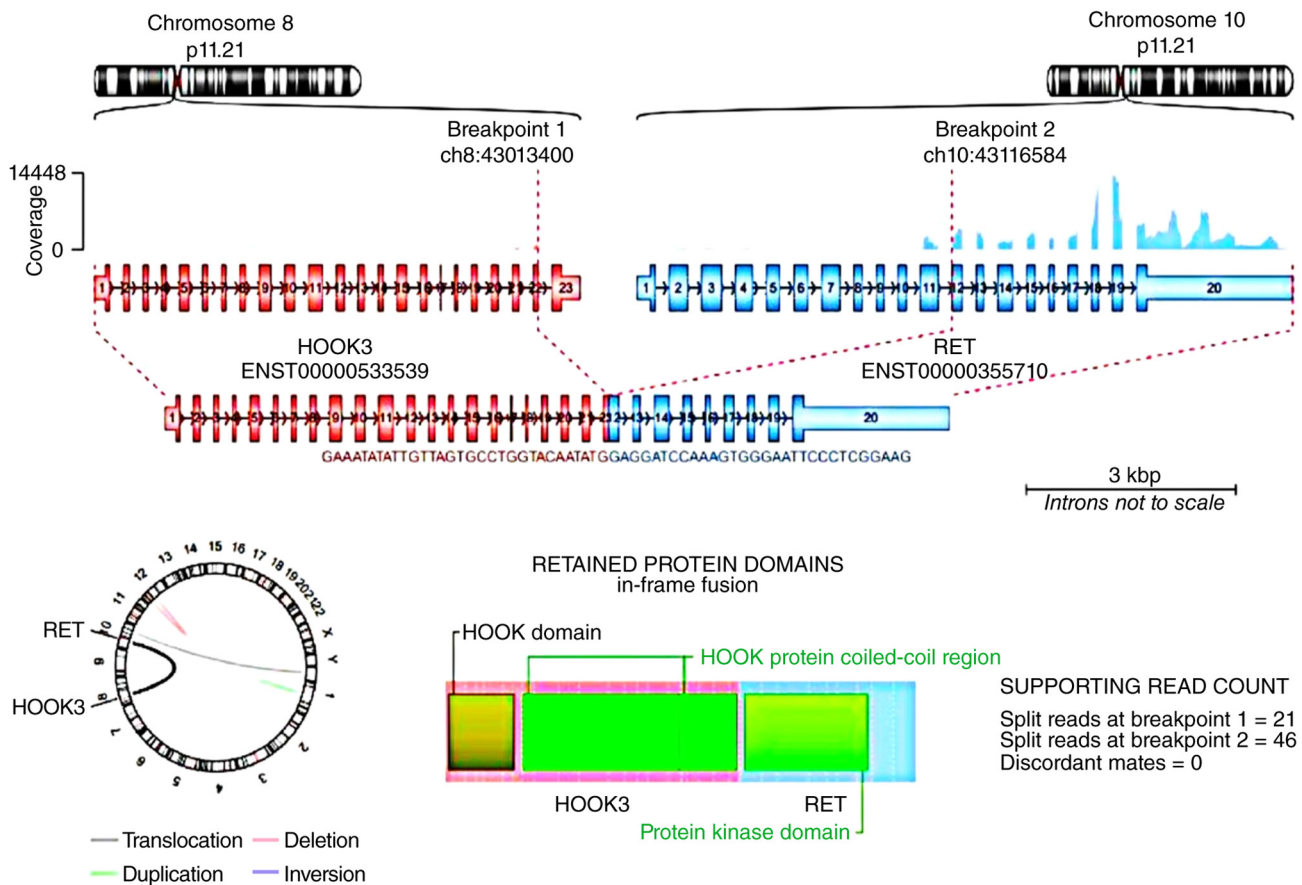


Figure 3. Schematic representation of the in-frame HOOK-RET fusion gene, with the breakpoint indicated on chromosome 8 for HOOK3 and chromosome 10 for RET, and the resulting retained protein domains from both HOOK3 and RET. The HOOK-RET fusion was visualized using Arriba, version v2.3.0. HOOK3, hook microtubule tethering protein 3; RET, rearranged during transfection.

on NGS. A comprehensive hereditary cancer gene panel using NGS from blood for single nucleotide variants, insertion/deletion polymorphisms and large deletions/duplications did not reveal any pathogenic variants. No deletions or duplications were detected in the digital multiplex ligation-dependent probe amplification. On IHC, the mismatch repair (MMR) status was proficient and programmed death-ligand 1 (PD-L1) expression

was 0%. The US Food and Drug Administration (FDA) granted accelerated approval to selpercatinib, a selective inhibitor of receptor tyrosine kinase RET, on September 21, 2022, for adult patients with locally advanced or metastatic solid tumors harboring a RET gene fusion who have progressed on or following prior systemic treatment or have no satisfactory alternative treatment options based on the LIBRETTO-001 trial (6).

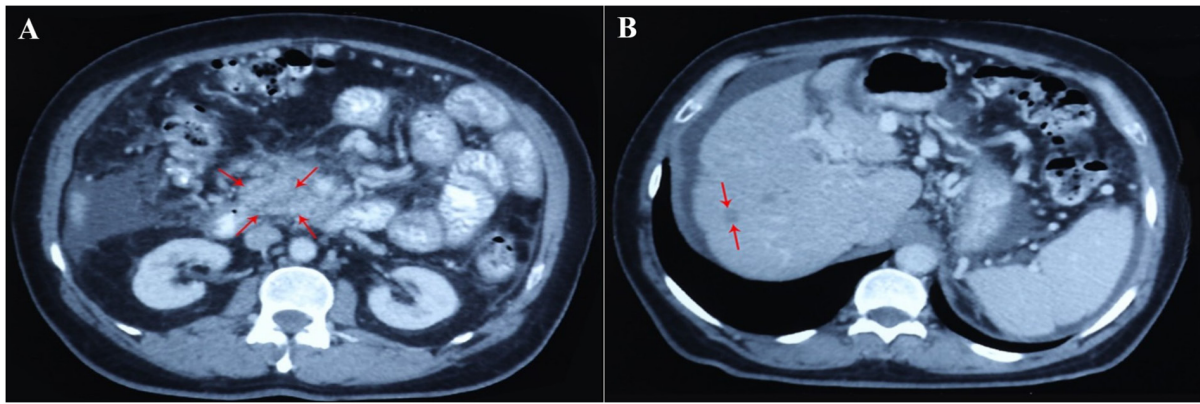


Figure 4. Post-selpercatinib treatment contrast-enhanced computed tomography abdomen axial section (venous phase) showing (A) reduction in the size of the pancreatic primary mass lesion (red arrows) to 3.3 (anteroposterior dimension) x 3.8 (transverse dimension) x 3.0 cm (craniocaudal dimension) along with (B) significant reduction in the number and size of hepatic metastases (red arrows), the largest measuring ~1.3x0.8 cm.

Following the report of NGS, chemotherapy was discontinued and selpercatinib, was started at a dose of 160 mg orally twice daily. In the radiology assessment at 2 months after the start of selpercatinib (baseline), the patient exhibited stable disease. At 5 months from baseline, the CT scan showed a 17% reduction in the SLD of the pancreatic mass, along with a reduction in the size of the lymph node (25% reduction in short-axis diameter) and hepatic metastases (37% reduction in the SLD). This benefit had continued at 15 months, with the CT scan revealing a further reduction in the size of the pancreatic mass (48% reduction in the SLD of the pancreatic mass compared with its pre-selpercatinib treatment SLD) (Fig. 4A), peripancreatic lymphadenopathy (65% reduction in short-axis diameter compared with pre-selpercatinib treatment) and further reduction in the size and number of hepatic metastases (57% reduction in the SLD compared with pre-selpercatinib treatment SLD) (Fig. 4B). Total resolution of left supraclavicular lymphadenopathy was observed. The lungs and mediastinum continued to be free of disease, as shown by the CT scan of the chest. CT scan of the brain did not reveal any metastases and there was no new metastatic site elsewhere in the body.

In addition to the radiological response, there was a biochemical response with normalisation of CA19.9 to 18.12 U/ml and further fall of AFP to 129.50 ng/ml. During this period, there was significant clinical improvement, with the patient becoming largely symptom-free. Selpercatinib was well-tolerated. Bilirubin, ALP and AST, which were elevated at the time of diagnosis, remained near the normal range. The patient required increased doses of anti-hypertensive medication to control hypertension; this was probably due to selpercatinib. There was intermittent grade 2 leukopenia and grade 2 thrombocytopenia, starting 1 month after the start of selpercatinib, but these did not require a dose reduction. A total of 17 months after the start of selpercatinib, as of last follow-up in March 2026, the patient continues to remain in partial remission, still on selpercatinib, without any significant symptoms associated with pancreatic cancer.

## Discussion

Novel targeted cancer therapies have emerged as a rapidly growing field of research, promising effective and tolerable

cancer treatments. These medications block biological transduction pathways and/or cancer-related proteins, leading to cancer cell death by apoptosis and/or the activation of immune response (7). Identifying and targeting various RET fusions is crucial, as it signals a specific vulnerability to targeted treatment, which can be potentially more effective than broader treatments, such as immunotherapy, for cancer patients (7). The RET proto-oncogene is located on the long arm of chromosome 10 (10q11.21) (Fig. 3). Somatic RET gene alterations act as pathogenic drivers in ~2% of various types of solid tumor (8). Thyroid papillary carcinoma and lung adenocarcinoma account for the highest number of RET fusions, with a prevalence rate of 9.09 and 1.14% respectively (8). These RET fusions are also found in colorectal and breast cancer, and in cholangiocarcinoma, but at lower frequencies (8). In pancreatic cancer, various RET fusions have been reported in a small fraction of cases, with an incidence of 0.6% (2). However, the HOOK3-RET fusion, as seen in the present case, has not yet been reported in pancreatic cancer in the medical literature. HOOK3-RET fusion results in ligand-independent signaling and oncogenesis, leading to the production of chimeric proteins with constitutively active RET kinase domains (6,7).

AFP-producing pancreatic carcinomas secrete AFP glycoprotein (9). Elevated AFP levels are associated with tumor progression, angiogenesis, immune evasion and drug resistance (10). These are known to have high malignant potential with early multiorgan metastatic spread, particularly liver and lymph node metastasis, at the time of diagnosis, resulting in poor prognosis (9). The present case had very high AFP levels, extensive metastatic spread at diagnosis with diffuse liver parenchymal involvement and widespread lymph node spread. Due to extensive liver parenchymal metastasis, the patient presented with jaundice at diagnosis. Gemcitabine-based combination chemotherapy was started while awaiting the results of NGS. However, the repeat imaging performed 10 weeks later showed progressive disease, despite clinical improvement marked by the resolution of jaundice. This primary resistance to chemotherapy may be linked to a high baseline AFP level.

In the present case, the high levels of AFP may have had a compounding negative prognostic effect on the already adverse prognosis linked to patients with pancreatic cancer.

This was reflected in the present patient, who presented with widespread metastatic disease and jaundice due to diffuse hepatic parenchymal involvement at diagnosis. In addition, primary resistance to gemcitabine and cisplatin-based combination chemotherapy was observed.

Genome-driven precision oncology has become the cornerstone of personalized treatment in patients with cancer. RET proto-oncogene fusions lead to loss of the transmembrane domain and trigger a cascade of oncogenic signals in the cytoplasm by activating the RET kinase domain (11). This results in the activation of the PI3K/Akt and RAS/RAF/MEK/ERK kinase pathways, which promote the proliferation and survival of cancer cells (12). Earlier multi-kinase RET inhibitors, such as cabozantinib and lenvatinib, exhibited only a modest clinical effect with significant toxicity due to their off-target activity (8). Selpercatinib and pralsetinib are a new class of highly selective RET tyrosine kinase inhibitors with a more potent activity and significantly less toxicity (8). Selpercatinib was engineered to block RET kinase activity specifically by binding to its adenosine triphosphate-binding site, thus preventing the kinase from phosphorylating substrates and halting oncogenic signaling (12). It produced a durable response that lasted over a year and 3 months in the present chemo-refractory HOOK3-RET fusion-positive patient with pancreatic cancer with widespread metastatic disease to the lymph nodes and liver. At the time of writing, the patient continues to be in partial remission, according to the CT scans and serum tumor markers, 15 months after the start of selpercatinib.

Selpercatinib has high efficacy rates and patients can achieve sustained remission, which is rare with systemic chemotherapy in pancreatic carcinoma. Furthermore, it has a manageable toxicity profile, and thus, it spares patients from the additional toxicity associated with systemic chemotherapy (2). The most common grade 3 adverse events of selpercatinib are AST/ALT elevation and hypertension (2). While the efficacy of RET-fusion targeted therapy is marked, the estimated incidence of RET fusions in pancreatic adenocarcinoma is low, with a reported incidence of 0.6% (6). With otherwise limited therapeutic options for pancreatic cancer, the use of selpercatinib in RET fusion cases enhances the range of available therapies in pancreatic cancer (6). Other targeted therapies are available for patients with pancreatic cancer who are MMR-deficient, positive for neurotrophic tyrosine receptor kinase fusions, have a high tumor mutational burden, are positive for the BRAF V600E mutation or carry germline breast cancer antigen 1/2 mutations (2).

In conclusion, the present case highlights the efficacy of selpercatinib in HOOK3-RET fusion-positive pancreatic cancer. Durable clinical improvements and radiological response exemplified the drug's potent therapeutic activity. It also underscored the importance of a comprehensive genomic analysis in treating pancreatic cancer.

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#### Availability of data and materials

The NGS data generated in the present study may be found in the National Center for Biotechnology Information (NCBI) Sequence Read Archive (SRA) database under accession no. PRJNA1427561 and at the following URL: <https://www.ncbi.nlm.nih.gov/sra/PRJNA1427561>. The remaining data may be requested from the corresponding author.

#### Authors' contributions

HSS analyzed and interpreted the patient data, drafted the manuscript and critically revised the manuscript. SJ treated the patient, and was involved in conception and design of study. AN performed the molecular tests and was involved in the literature search. HSS, SJ and AN confirm the authenticity of all raw data, and have read and approved the final manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Patient consent for publication

Informed consent was obtained from the patient for publication of this case, including publication of data and images.

#### Competing interests

The authors declare that they have no competing interests.

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#### References

1. International Agency for Research on Cancer: Global Cancer Observatory. World Health Organization: Pancreas. Geneva, 2025. <https://gco.iarc.who.int/media/globocan/factsheets/cancers/13-pancreas-fact-sheet.pdf>. Accessed November 6, 2025.
2. Bhamidipati D, Yedururi S, Huse J, Chinapuvvula SV, Wu J and Subbiah V: Exceptional responses to selpercatinib in RET Fusion-driven metastatic pancreatic cancer. *JCO Precis Oncol* 7: e2300252, 2023.
3. Sorensen JB, Klee M, Palshof T and Hansen HH: Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer* 67: 773-775, 1993.
4. Ouyang G, Liu Z, Huang S, Li Q, Xiong L, Miao X and Wen Y: Gemcitabine plus cisplatin versus gemcitabine alone in the treatment of pancreatic cancer: A meta-analysis. *World J Surg Oncol* 14: 59, 2016.
5. Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
6. Subbiah V, Wolf J, Konda B, Kang H, Spira A, Weiss J, Takeda M, Ohe Y, Khan S, Ohashi K, *et al*: Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): A phase 1/2, open-label, basket trial. *Lancet Oncol* 23: 1261-1273, 2022.
7. McKinley BJ, Coston TW and Starr JS: Primary resistance to RET inhibition in a RET Fusion-positive pancreatic neuroendocrine carcinoma. *Oncologist* 30: oyae034, 2025.

8. Parimi V, Tolba K, Danziger N, Kuang Z, Sun D, Lin DI, Hiemenz MC, Schrock AB, Ross JS, Oxnard GR, *et al*: Genomic landscape of 891 RET fusions detected across diverse solid tumor types. *NJP Precis Oncol* 7: 10, 2023.
9. Gvajaia A, Imeh M and Raza A: An interesting case of Alpha-fetoprotein (AFP)-Producing pancreaticoduodenal tumor. *Cureus* 16: e59384, 2024.
10. Kim H, Jang M and Kim E: Exploring the multifunctional role of Alpha-fetoprotein in cancer progression: Implications for targeted therapy in hepatocellular carcinoma and beyond. *Int J Mol Sci* 26: 4863, 2025.
11. Subbiah V, Cassier PA, Siena S, Garralda E, Paz-Ares L, Garrido P, Nadal E, Vuky J, Lopes G, Kalemkerian GP, *et al*: Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med* 28: 1640-1645, 2022.
12. Deschler-Baier B, Krebs M, Kroiss M, Chatterjee M, Gundel D, Kestler C, Kerscher A, Kunzmann V, Appenzeller S, Maurus K, *et al*: Rapid response to selpercatinib in RET fusion positive pancreatic neuroendocrine carcinoma confirmed by smartwatch. *NJP Precis Oncol* 8: 167, 2024.



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