# Concurrent EGFR exon 19 deletion-insertion and germline BRCA1 alteration in KRAS-wild-type pancreatic ductal adenocarcinoma: A case report and review of therapeutic implications

SHENG YU WEI, WEI YU and QIAO HUANG

Department of Oncology, The First College of Clinical Medical Science, China Three Gorges University, Yichang Central People's Hospital, Yichang, Hubei 443000, P.R. China

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**Abstract.** Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid malignancies, with a dismal prognosis and a 5-year overall survival rate of 5-10%. Owing to the absence of specific symptoms at early stages, the majority of patients are first diagnosed with already locally advanced or metastatic disease. Consequently, such patients are ineligible for curative surgery, resulting in limited therapeutic options and poor outcomes. With advances in molecular profiling and next-generation sequencing, precision medicine has emerged as an important therapeutic approach for advanced PDAC. Targeted therapies directed against specific molecular alterations, including BRCA1/2, HER2 and KRAS, have demonstrated clinical benefit in selected patient populations. However, current evidence predominantly focuses on single gene alterations. There is a lack of data and consensus regarding the optimal treatment strategies for PDAC harboring concurrent multiple genomic aberrations. In the present report, a rare case of KRAS wild-type PDAC harboring a somatic EGFR exon 19 deletion-insertion mutation, a heterozygous germline BRCA1 splice-site mutation and an additional somatic synonymous TP53 variant identified by molecular testing was documented. The patient developed clinically suspected postoperative recurrence and subsequently achieved durable disease control following individualized exploratory treatment with aumolertinib and olaparib. The present case provides a clinically documented observation of individualized targeted therapy in a rare KRAS wild-type PDAC molecular context and may help inform future hypothesis-driven investigations in selected molecularly defined patients. However, further studies are required to clarify the functional relevance of these molecular alterations and the clinical value of this treatment approach in selected patients with molecularly unique PDAC.

*Correspondence to:* Professor Qiao Huang, Department of Oncology, The First College of Clinical Medical Science, China Three Gorges University, Yichang Central People's Hospital, 183 Yiling Avenue, Yichang, Hubei 443000, P.R. China
E-mail: huqi70@163.com

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies of the digestive system, characterized by an insidious clinical onset, rapid disease progression and limited therapeutic options. Epidemiological data indicate that in Western countries, the incidence and mortality rates of PDAC are nearly equivalent, with a 5-year overall survival rate of only 5-10%, reflecting its dismal prognosis (1). At the molecular level, KRAS represents the most prevalent and pivotal driver gene in PDAC, with activating mutations detected in ~90% patients (2). Constitutive activation of KRAS leads to the persistent activation of downstream signaling through pathways, such as MAPK and PI3K/AKT, thereby promoting tumor cell proliferation, metabolic reprogramming, invasion and metastasis (3,4). Previous studies have further demonstrated that the mutational burden of KRAS is closely associated with clinical outcomes in PDAC, with higher variant allele frequencies associating with worse survival (5). Consequently, KRAS mutations not only serve a central role in PDAC tumorigenesis but also constitute a major barrier to the development of effective targeted therapies.

As well as KRAS, TP53 is another frequently mutated gene in PDAC, with an estimated mutation frequency of ~70% (6). As a key tumor suppressor gene, TP53 serves a central role in maintaining genomic stability, regulating cell cycle progression and coordinating cellular responses to DNA damage. The clinical and prognostic implications of TP53 alterations may vary according to the specific variant type. A genomic study identified diverse TP53 alteration types in PDAC, including missense, truncating, frameshift and splice-site variants (7). In a clinical cohort of patients with PDAC receiving FOLFIRINOX, TP53 mutation status was associated with adverse survival outcomes (8). However, synonymous variants should be interpreted cautiously and should not be assumed

to have the same biological consequences as pathogenic missense, truncating, frameshift or splice-site variants.

Increasing attention has been directed toward the role of BRCA gene mutations in the precision treatment of PDAC over the past decade. A previous review estimated that pathogenic germline mutations in BRCA1 or BRCA2 are present in 5-9% patients with PDAC (9). Tumors harboring BRCA mutations are generally characterized by pronounced genomic instability and are associated with unfavorable clinical outcomes (10). Importantly, loss of BRCA function results in defective homologous recombination repair (HRR), rendering tumor cells highly dependent on alternative, error-prone DNA repair mechanisms. This intrinsic vulnerability confers marked sensitivity to DNA damaging therapeutic strategies, particularly platinum-based chemotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors (11). Consequently, BRCA mutated PDAC represents a biologically and clinically distinct molecular subgroup with well-defined therapeutic relevance.

By contrast, the mutation rate of EGFR in PDAC remains relatively low compared with the high-frequency genomic alterations aforementioned. Based on circulating tumor DNA analyses, the reported incidence of EGFR mutations is ~13.3%. However, EGFR protein overexpression is considerably more prevalent, occurring in 32-68% PDAC cases (12). Unlike non-small cell lung cancer, in which activating kinase domain mutations represent the dominant oncogenic mechanism, EGFR dysregulation in pancreatic cancer predominantly manifests as protein overexpression and/or gene amplification, whereas classic driver mutations within the tyrosine kinase domain are exceedingly rare (13). These fundamental differences suggest that the oncogenic role of EGFR and its associated therapeutic response patterns in PDAC may be distinct from those observed in lung cancer. Notably, to the best of the authors' knowledge, among patients with KRAS wild-type PDAC, clinical reports with tumors harboring potentially actionable EGFR alterations, together with germline BRCA1 mutations, remains limited, particularly when accompanied by additional variants of uncertain or unclear functional significance.

The present report aimed to describe the therapeutic implications of a somatic EGFR exon 19 deletion-insertion alteration and a heterozygous germline BRCA1 splice-site alteration in KRAS wild-type PDAC. By integrating a clinically documented case with the relevant literature, the report discusses the rationale, limitations and unresolved questions associated with individualized treatment using an EGFR tyrosine kinase inhibitor in combination with a PARP inhibitor in this rare molecular context.

## Case report

A 60-year-old female patient presented to Yichang Central Hospital (Yichang, China) in January 2020 with a 2-month history of persistent epigastric pain that had progressively worsened over the preceding 2 weeks. The pain was described as a dull, non-radiating discomfort in the upper abdomen and was occasionally accompanied by dizziness. The patient denied fever, nausea, vomiting or jaundice. On physical examination, the patient was in stable condition. Mild tenderness was noted in the epigastrium without rebound tenderness and no palpable abdominal mass was detected.

Laboratory investigations revealed an elevated carbohydrate antigen 19-9 (CA19-9) level of 95.2 U/ml (reference range, <39 U/ml), whilst carcinoembryonic antigen (CEA) remained within normal limits at 2.52 ng/ml (reference range, <13.6 ng/ml). Routine tests, including complete blood count, liver function tests, serum biochemistry and urinalysis, were unremarkable. These findings raised the suspicion of a pancreatic malignancy in the absence of evident systemic dysfunction.

To further investigate the cause of the symptoms, contrast-enhanced computed tomography (CT) angiography of the abdomen was performed. Imaging revealed a mass-like hypodense lesion located in the body of the pancreas, which was highly suggestive of pancreatic malignancy. The lesion was associated with involvement of the proximal splenic vein and significant luminal narrowing, suggesting potential local vascular compression or invasion. Representative axial CT images are shown in Fig. 1A and B.

Following comprehensive evaluation, which revealed no major organ dysfunction and no radiologically evident abnormalities of the hepatic artery or portal vein that would preclude surgery, the patient underwent laparoscopic distal pancreatectomy combined with splenectomy under general anesthesia on January 8, 2020, within the same month as her initial presentation. During intraoperative exploration, a firm mass located in the pancreatic body was identified. Several enlarged lymph nodes along the superior border of the pancreas were also observed, raising suspicion for regional lymph node involvement. The surgical procedure was successfully completed without major intraoperative complications.

Postoperative histopathological examination confirmed moderately differentiated PDAC involving the pancreatic body and tail. H&E staining revealed irregular glandular structures consisting of atypical tumor cells with enlarged hyperchromatic nuclei and visible mitotic figures within a fibrotic/desmoplastic stroma (Fig. 2A-C). Immunohistochemical staining showed positivity for cytokeratin (CK) 7 and CK19, negativity for CK20 and caudal type homeobox 2 and loss/reduced expression of SMAD4 in tumor cells (Fig. 2D-R). Examination of the surgical specimen found that the pancreatic resection margin, vascular margins, omental tissue and spleen were free of tumor invasion, indicating that complete macroscopic tumor resection had been achieved. However, regional lymph node metastasis was detected, with tumor involvement found in 1/8 peripancreatic lymph nodes and in all 3 examined regional lymph nodes. According to the American Joint Committee on Cancer 8th edition TNM staging system, the postoperative pathological stage was determined to be pT2N2M0 (stage III). The presence of infiltrative glandular structures within the desmoplastic stroma, together with regional lymph node metastases, supported a diagnosis of invasive PDAC rather than a high-grade *in situ* lesion.

Following postoperative recovery, the patient received adjuvant chemotherapy. Specifically, between February and June 2020, the patient underwent five cycles of gemcitabine combined with S-1 (GS regimen), with gemcitabine administered intravenously at 1.6 g on day 1 and 1.4 g on day 8, and

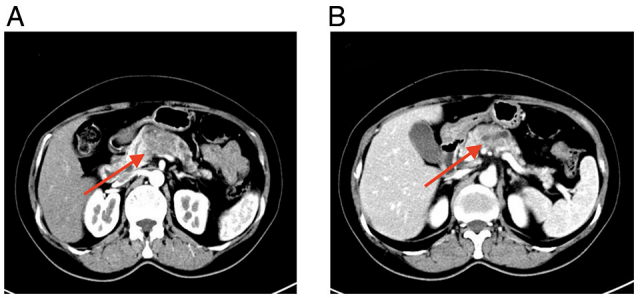


Figure 1. Preoperative contrast-enhanced computed tomography findings of the primary pancreatic lesion. (A) Axial contrast-enhanced CT image showing a hypodense mass-like lesion in the pancreatic body, measuring ~3.1x2.3 cm. The lesion demonstrates lower enhancement than the surrounding pancreatic parenchyma. (B) Axial contrast-enhanced CT image showing atrophy of the distal pancreatic body and tail, accompanied by dilatation of the main pancreatic duct. CT, computed tomography.

S-1 administered orally at a total daily dose of 125 mg in two divided doses on days 1-14. This was followed by two additional cycles of S-1 monotherapy administered between July and August 2020 as maintenance therapy. The patient tolerated the chemotherapy regimen relatively well and completed the planned treatment without severe toxicities. After the completion of adjuvant therapy, she entered a routine surveillance program with periodic imaging examinations and tumor marker monitoring.

The patient remained clinically stable for 4 years and 9 months following surgery. However, during routine follow-up in September 2024, contrast-enhanced abdominal CT revealed a newly developed oval soft-tissue lesion in the portal vein-superior mesenteric artery space, measuring ~1.9 cm in maximal diameter and showing prominent contrast enhancement. Given the prior history of resected PDAC of this patient, the typical locoregional nodal location of the lesion and the concomitant increase in CA19-9 to 216 U/ml, these findings were highly suggestive of clinically suspected locoregional recurrence. Representative CT images of the suspected recurrence are shown in Fig. 3A.

To identify potential therapeutic targets after postoperative recurrence, molecular profiling was performed using archived formalin-fixed paraffin-embedded surgical tumor tissue obtained from the primary pancreatic lesion, with matched peripheral blood used as the germline control. The tumor specimen was initially collected in January 2020 and submitted to 3D Medicines Inc. for molecular testing in September 2024. The estimated tumor cell content was 30%. A probe-based hybrid capture next-generation sequencing assay was used to detect tumor-associated genomic alterations, including clinically relevant somatic variants, germline variants, microsatellite status and DNA damage repair pathway-related alterations. The sequencing quality met the quality control criteria, with an average sequencing depth of 1,989.30x and a Q30 base percentage of 96.04%.

Molecular profiling identified a somatic EGFR exon 19 deletion-insertion mutation (NM_005228.5: c.2237_2256delinsTG; p.E746_S752delinsV; variant allele frequency, 16.43%), a somatic synonymous TP53 variant (NM_000546.6: c.375G>A; p.T125=; variant allele frequency, 10.51%) and a heterozygous germline BRCA1 splice-site mutation (NM_007294.4: c.4485-2A>C). No KRAS mutation was detected by NGS, indicating a KRAS wild-type molecular profile. KRAS status was therefore defined based on molecular testing rather than immunohistochemical staining. The tumor was microsatellite stable. The complete NGS findings, including clinically relevant variants and variants of uncertain significance, are summarized in Table I.

Given the rarity of this molecular profile and the lack of standard targeted treatment options for this clinical scenario, this finding was discussed at a multidisciplinary team (MDT) meeting. Biopsy of the suspected recurrent lesion was considered to obtain histological confirmation and updated molecular profiling. Several potential approaches, including endoscopic ultrasound-guided fine-needle aspiration or biopsy, CT-guided percutaneous biopsy and diagnostic laparoscopy with biopsy, were discussed by the MDT. However, the lesion was located in the portal vein-superior mesenteric artery space and was adjacent to major vascular structures, making tissue acquisition technically challenging and potentially associated with a risk of bleeding or vascular injury depending on the access route. After detailed discussion of the potential benefits and risks of these invasive diagnostic procedures, the patient explicitly declined further biopsy or other invasive tissue sampling. Liquid biopsy was also discussed as a less invasive option for additional molecular reassessment; however, the patient declined further molecular testing after discussion, and the MDT therefore proceeded with non-invasive imaging and tumor marker follow-up. She also refused further cytotoxic chemotherapy and radiotherapy due to concerns regarding treatment-related toxicity. After comprehensive discussion, the MDT recommended an individualized exploratory targeted treatment strategy based on the clinical course of the patient, radiological findings, CA19-9 elevation and the molecular profile of the archived primary tumor tissue.

In October 2024, the patient initiated an individualized exploratory combination regimen consisting of the third-generation EGFR tyrosine kinase inhibitor aumolertinib (110 mg once daily) and the PARP inhibitor olaparib at an initial dose of 300 mg twice daily. After 4 weeks of full-dose olaparib, the patient developed grade 2 nausea/vomiting, grade 3 neutropenia and grade 2 thrombocytopenia according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50). After supportive care, the olaparib dose was reduced to 150 mg twice daily, whilst aumolertinib was maintained at 110 mg once daily. Following dose adjustment, these toxicities were manageable and did not require permanent treatment discontinuation.

After ~3 months of therapy, follow-up imaging demonstrated a reduction in the size of the suspected recurrent lesion, accompanied by a marked decrease in CA19-9 from the pretreatment level of 216 U/ml. With continued therapy, the lesion regressed. By the most recent follow-up in December 2025, after approximately 14 months of treatment, the CA19-9 level gradually returned to the normal range and decreased to 20 U/ml. Serial imaging demonstrated further radiological regression of the suspected lesion, accompanied by durable disease control. Representative follow-up CT images after targeted therapy are shown in Fig. 3B.

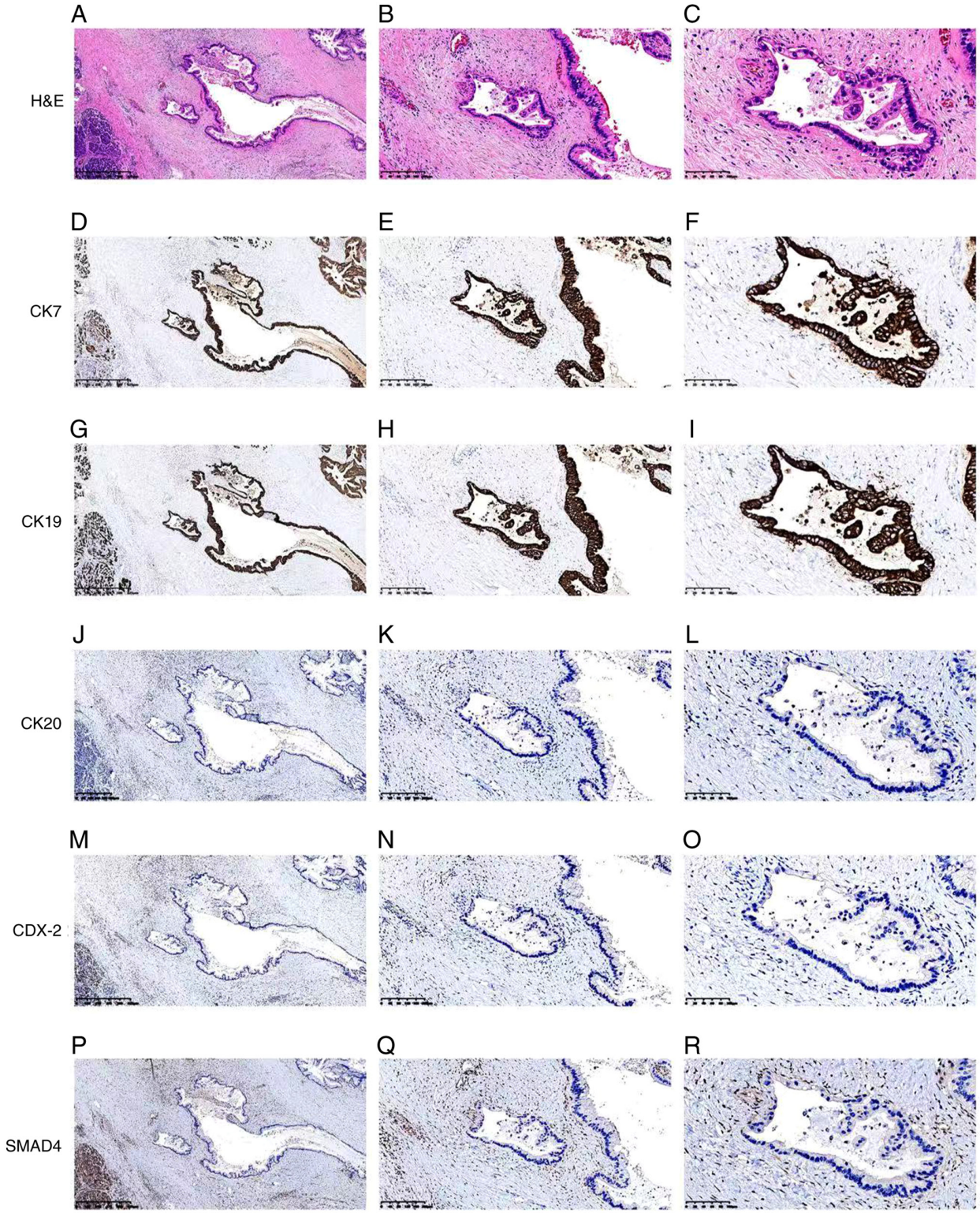


Figure 2. Low- and high-power histopathological and immunohistochemical findings of the resected pancreatic tumor. H&E staining shows irregular glandular structures consisting of atypical tumor cells with enlarged hyperchromatic nuclei and visible mitotic figures within a fibrotic/desmoplastic stroma. (A) Magnification, x40, (B) magnification, x100 and (C) magnification, x200. Immunohistochemical staining shows CK7 positivity (D) magnification, x40, (E) magnification, x100 and (F) magnification, x200. CK19 positivity (G) magnification, x40, (H) magnification, x100 and (I) magnification, x200, CK20 negativity (J) magnification, x40, (K) magnification, x100 and (L) magnification, x200. CDX2 negativity (M) magnification, x40, (N) magnification, x100 and (O) magnification, x200. Loss or markedly reduced SMAD4 expression in tumor cells (P) magnification, x40, (Q) magnification, x100 and (R) magnification, x200. H&E, hematoxylin and eosin; CK, cytokeratin; CDX2, caudal type homeobox 2; SMAD4, SMAD family member 4.

At the most recent follow-up in December 2025, the patient remained on aumolertinib at 110 mg once daily combined with olaparib at the reduced dose of 150 mg twice daily and continued to derive sustained clinical benefit. No evidence of disease progression or distant metastasis had been observed. The patient has achieved a progression-free

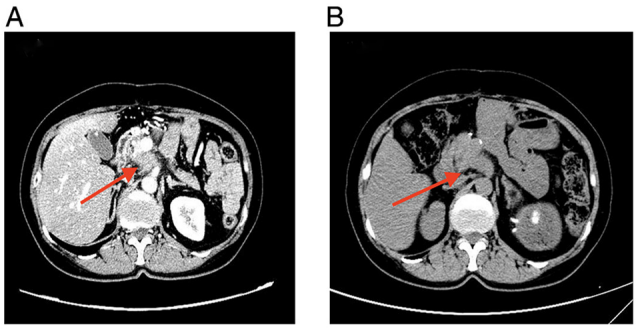


Figure 3. Imaging findings of suspected postoperative recurrence and radiological response to targeted therapy. (A) Contrast-enhanced CT performed in September 2024 revealed an oval soft-tissue lesion located in the portal vein-superior mesenteric artery space, with a maximal diameter of ~1.90 cm and prominent enhancement, suggesting clinically suspected locoregional recurrence. (B) Follow-up CT performed in December 2024 demonstrated a reduction in the size of the lesion at the same site, with the maximal diameter reduced to ~1.63 cm, suggesting radiological regression of the suspected recurrent lesion after targeted therapy. CT, computed tomography.

survival >12 months, with acceptable tolerability following dose modification.

The present case documented a rare KRAS wild-type PDAC molecular context involving a somatic EGFR exon 19 deletion-insertion mutation and a heterozygous germline BRCA1 splice-site mutation, which informed an individualized exploratory treatment strategy with aumolertinib and olaparib. The additional synonymous TP53 variant was reported as part of the molecular profile but was not regarded as a confirmed functional driver or therapeutic determinant.

## Discussion

PDAC is one of the most aggressive malignancies of the digestive system, characterized by profound molecular heterogeneity and an exceptionally poor prognosis. Tumor initiation and progression are typically driven by the stepwise accumulation of multiple genetic alterations involving both oncogenes and tumor suppressor genes. Amongst these, KRAS mutations represent the dominant molecular event in PDAC, occurring in ~90% cases and serving as a central driver of tumorigenesis and disease progression (7,14). These mutations are frequently accompanied by alterations in key tumor suppressor genes, including TP53, CDKN2A and SMAD4 (13), resulting in a highly unstable genomic background. This complex molecular landscape has substantially limited the clinical success of targeted therapies in PDAC.

Importantly, KRAS mutations are not only strongly associated with unfavorable prognosis (15,16), but their long-standing classification as 'undruggable' has represented a major therapeutic bottleneck in PDAC (17). However, 5-10% patients with PDAC harbor KRAS wild-type tumors whose molecular pathogenesis differs fundamentally from that of the classical KRAS-mutant subtype. In a recent large-scale clinicogenomic analysis, Varghese *et al* (5) demonstrated that KRAS wild-type PDAC represents a distinct genomic subgroup associated with specific somatic and germline features, with improved overall survival. Accumulating molecular pathology data suggest that this subgroup is more likely to exhibit defects in DNA damage repair pathways, dysregulation of receptor tyrosine kinase signaling or other potentially actionable driver events, such as BRAF alterations and NRG1 fusions (18). With the increasing clinical adoption of NGS, this distinct molecular subset defined by KRAS wild-type status and the presence of targetable genomic alterations is gaining recognition, opening novel opportunities for individualized treatment in patients with recurrent or treatment-refractory disease.

Among the currently known actionable molecular alterations, mutations involving BRCA and other HRR genes hold particular clinical relevance. BRCA1 and BRCA2 are essential components of the HRR pathway, where their inactivation leads to impaired repair of DNA double-strand breaks, increased genomic instability and tumorigenesis. Germline and somatic BRCA1/2 mutations have both been implicated in PDAC development, with germline carriers exhibiting a markedly elevated lifetime risk of pancreatic cancer (19). In a cohort of 854 patients with apparently sporadic PDAC, deleterious germline BRCA1/2 mutations were identified in 15 patients (1.8%) (19). Although the prevalence of BRCA mutations in PDAC is relatively low, these alterations have established therapeutic implications. Defective HRR constitutes the molecular basis for sensitivity to DNA-damaging therapies. Wang *et al* (20) evaluated preclinical models and a molecularly annotated patient cohort of HRR-deficient PDAC and identified genomic features associated with sensitivity to platinum-based therapy, while also demonstrating heterogeneity in treatment response. Furthermore, the POLO trial confirmed that maintenance therapy with the PARP inhibitor olaparib significantly prolonged progression-free survival in patients with metastatic BRCA-mutant PDAC (median progression-free survival, 7.4 vs. 3.8 months) (21), firmly establishing PARP inhibition as a standard therapeutic strategy now incorporated into CSCO and other international guidelines.

Nevertheless, genomic instability driven by BRCA mutations rarely occurs in isolation and frequently coexists with aberrations in other oncogenic signaling pathways. In KRAS wild-type PDAC, increasing attention has been directed toward dysregulation of receptor tyrosine kinase signaling, particularly the EGFR pathway. Unlike non-small cell lung cancer, activating EGFR kinase-domain mutations are exceedingly rare in PDAC (22). Instead, EGFR abnormalities predominantly manifest as protein overexpression or gene amplification (13). Biologically, EGFR signaling promotes tumor cell proliferation, invasion and survival through the activation of various downstream pathways, such as RAS/RAF/MAPK and PI3K/AKT (13). However, clinical translation of EGFR-targeted therapy in PDAC has been disappointing. Although the addition of erlotinib to gemcitabine demonstrated a statistically significant survival benefit in a previous phase III trial, the magnitude of benefit was modest and clinically limited (23,24). In addition, individual reports have suggested that selected patients with EGFR-mutated pancreatic adenocarcinoma may derive benefit from third-generation EGFR-TKIs (25), although acquired resistance, including EGFR C797S, may subsequently emerge (26).

Table I. Summary of next-generation sequencing findings.

| Category | Gene | Variant/result | Status | VAF/result | Interpretation |
|---|---|---|---|---|---|
| Clinically relevant somatic variant | EGFR | NM_005228.5; exon 19; c.2237_2256delinsTG; p.E746_S752delinsV | Somatic | VAF, 16.43% | EGFR exon 19 deletion-insertion alteration; potentially actionable, although functional relevance in PDAC remains insufficiently characterized. |
| Clinically relevant somatic variant | TP53 | NM_000546.6; exon 4; c.375G>A; p.T125= | Somatic | VAF, 10.51% | Synonymous variant; functional significance uncertain. |
| Clinically relevant germline variant | BRCA1 | NM_007294.4; splice-site region; c.4485-2A>C | Germline | Heterozygous | Germline BRCA1 splice-site mutation; DNA damage repair pathway-related alteration. |
| Driver gene status | KRAS | No mutation detected | - | No mutation detected | KRAS mutation was not detected by NGS. |
| Microsatellite status | MSI | Microsatellite status | - | MSS | Microsatellite stable. |
| Variant of uncertain significance | RHBDF2 | NM_001005498.4; exon 18; c.1988G>A; p.R663H | Not classified in the report | VAF, 8.36% | Variant of uncertain significance. |
| Variant of uncertain significance | SMAD4 | NM_005359.6; exon 3; c.297G>T; p.W99C | Not classified in the report | VAF, 12.35% | Variant of uncertain significance. |
| Variant of uncertain significance | SMARCA4 | NM_003072.5; exon 6; c.1111G>A; p.E371K | Not classified in the report | VAF, 7.99% | Variant of uncertain significance. |

VAF, variant allele frequency; NGS, next-generation sequencing; MSI, microsatellite instability; MSS, microsatellite stable; PDAC, pancreatic ductal adenocarcinoma.

The limited efficacy of EGFR-targeted therapy in PDAC is widely attributed to the high prevalence of downstream KRAS mutations, which enable persistent pathway activation independent of EGFR inhibition. In addition, compensatory activation of paralogous alternative signaling pathways, such as insulin-like growth factor-1 receptors, further contributes to therapeutic resistance (27). In this context, combination treatment strategies have emerged as a rational approach. Notably, EGFR inhibition may be more biologically plausible in selected KRAS wild-type PDAC cases, where downstream signaling may remain at least partially dependent on upstream receptor tyrosine kinase activity. Furthermore, emerging evidence implicating EGFR signaling in early pancreatic carcinogenesis, particularly during acinar-to-ductal metaplasia, provides additional biological rationale for its role as a therapeutic target in selected molecular contexts (13,17).

In the present case, the EGFR alteration was identified as the uncommon exon 19 deletion-insertion variant p.E746_S752delinsV. EGFR exon 19 deletion and deletion-insertion alterations are established sensitizing alterations in non-small cell lung cancer. However, uncommon exon 19 deletion-insertion subtypes may show heterogeneous sensitivity to different EGFR-TKIs (28). The p.E746_S752delinsV variant has been described among the uncommon EGFR exon 19 deletion-insertion alterations in lung cancer, where an isolated clinical report suggested that a tumor harboring this variant may respond to EGFR-TKI treatment (28,29). Nevertheless, these data are largely derived from lung cancer, where the functional relevance and predictive value of this specific EGFR alteration in PDAC remain insufficiently characterized (26,29). No *in vitro* or *in silico* functional validation was performed in the present case. Therefore, aumolertinib was selected as an empirical molecularly guided treatment option in the context of KRAS wild-type PDAC with a potentially actionable EGFR alteration, rather than on the basis of confirmed functional sensitivity of this variant in PDAC.

TP53 alterations are frequent molecular events in PDAC and have been associated with tumor biology and prognosis when pathogenic variants are present (27,30). However, the TP53 alteration identified in the present case was a somatic synonymous variant, rather than a deleterious missense, truncating, frameshift or splice-site mutation. Therefore, this variant was included only as part of the molecular profile and was not used to support the therapeutic rationale for aumolertinib plus olaparib.

To date, to the best of our knowledge therapeutic experience in KRAS wild-type PDAC harboring potentially actionable EGFR alterations together with germline BRCA1 mutations remains limited. The present case was therefore notable because it combines a KRAS wild-type background, a somatic EGFR exon 19 deletion-insertion mutation and a heterozygous germline BRCA1 splice-site mutation. The additional TP53 synonymous variant was included in the molecular profile but was not used as a primary rationale for treatment selection. This molecular context provided a clinical rationale for considering an individualized exploratory targeted approach with aumolertinib and olaparib after multidisciplinary discussion. However, the biological interaction between EGFR inhibition and PARP inhibition in PDAC remains insufficiently defined, where the present case cannot establish a mechanistic synergistic effect between these two agents.

A noteworthy aspect of the present case was the dose adjustment of olaparib during combination targeted therapy. Olaparib was initially administered at 300 mg twice daily. However, the patient developed intolerance during treatment, including grade 2 nausea/vomiting, grade 3 neutropenia and grade 2 thrombocytopenia according to CTCAE v5.0. Therefore, the dose of olaparib was reduced to 150 mg twice daily as an individualized toxicity-management strategy, whilst aumolertinib was continued. This dose reduction reflected real-world tolerability considerations during off-label combination therapy rather than a preplanned low-dose strategy. The observed clinical course cannot determine the independent contribution of aumolertinib, olaparib or their combination. Nevertheless, the durable disease control observed in the present patient, together with the uncommon convergence of KRAS wild-type status, a potentially actionable EGFR alteration and germline BRCA1 mutation, may help define a clinically testable question for future studies evaluating EGFR-TKI and PARP inhibitor-based strategies in selected molecularly defined patients with PDAC.

Several limitations of the present case should be acknowledged. NGS was performed on archived formalin-fixed paraffin-embedded tumor tissue obtained during the initial surgery in 2020, rather than at the time of postoperative recurrence. Although such specimens can generally preserve DNA integrity for extended periods and are widely used in molecular analyses, the use of archival tissue may not fully reflect potential genomic evolution during disease progression. In addition, histological or cytological confirmation of the suspected recurrent lesion was not obtained. The lesion was located in the portal vein-superior mesenteric artery space and was adjacent to major vascular structures. Although several tissue-acquisition approaches, including EUS-guided fine-needle (FN) aspiration/FN biopsy, CT-guided percutaneous biopsy and diagnostic laparoscopy with biopsy, were considered, each would require an invasive procedure and careful assessment of bleeding or vascular injury risk. The patient explicitly declined further invasive diagnostic procedures. Consequently, recurrence was diagnosed clinically based on the prior history of resected PDAC, the appearance of a newly developed enhancing lesion in a typical locoregional nodal region, concomitant CA19-9 elevation and serial radiological follow-up. Although the imaging appearance, typical nodal location, rising CA19-9 level and subsequent radiological regression during targeted therapy supported the clinical diagnosis of recurrence, alternative benign or inflammatory etiologies could not be completely excluded in the absence of histological confirmation. The functional relevance of the EGFR p.E746_S752delinsV alteration and the biological significance of the TP53 synonymous variant in PDAC also remain uncertain. The subsequent dose reduction of olaparib was performed because of CTCAE v5.0-defined treatment-related intolerance during off-label combination therapy, reflecting real-world toxicity

management rather than a predefined dosing strategy. The independent contribution of aumolertinib, olaparib or their combination cannot be determined from a single case.

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**Availability of data and materials**

The next-generation sequencing data generated in the present study have been deposited in the Genome Sequence Archive for Human (GSA-Human) under accession no. HRA020193 (BioProject accession no. PRJCA071184) and are publicly available at https://ngdc.cncb.ac.cn/gsa-human/browse/HRA020193. Additional data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

SYW and WY analyzed the data, and wrote and revised the manuscript. SYW and QH designed the study protocol. QH was the primary care physician of the patient and developed and implemented the treatment plan. SYW, WY and QH performed the literature review and analyzed and interpreted the data in the paper. WY and QH obtained the patient data and performed the histological examination of the tumor. WY and QH reviewed the manuscript. QH was responsible for the analysis and interpretation of the imaging data. SYW, WY and QH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

Written informed consent for the publication of clinical details and images was obtained from the patient.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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