BIOLOGY AND MOLECULAR MEDICINE

Case Report

Durable Remission in BRCA2-Mutated, PD-L1–Overexpressing Pancreatic Cancer with Multimodal Precision Therapy: A Case Report

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with a 5-year survival rate of only 13.3%. New effective strategies are needed for PDAC, including those with actionable mutations that may confer sensitivity to targeted therapies.

Patient Presentation: We describe a 60-year-old man (never-smoker, no significant alcohol use) with a strong family cancer history who presented with acute pancreatitis. Workup revealed PDAC in the distal pancreas and germline testing identified a pathogenic BRCA2 mutation. The patient had borderline resectable disease and enrolled in a phase II clinical trial of modified FOLFIRINOX plus losartan with stereotactic body radiation therapy (SBRT) and nivolumab (anti–PD-1) prior to surgery. He then underwent distal pancreatectomy and splenectomy, achieving a complete resection. Pathology showed near-complete response (only a single 1 mm residual tumor focus in one lymph node, ypT0N1). One month postoperatively, surveillance MRI detected a new solitary liver lesion. Biopsy confirmed metastatic PDAC with PD-L1 combined positive score (CPS) = 100. The liver metastasis was treated with percutaneous microwave ablation. Shortly thereafter, the patient was started on maintenance therapy with a PARP inhibitor (olaparib) and PD-1 inhibitor (pembrolizumab).

Outcome: The patient remains in clinical remission, now over five years since the detection of the liver metastasis. He has no evidence of disease on serial MRI and PET/CT imaging and continues on maintenance olaparib and pembrolizumab.

Statement of Significance: This case illustrates an exceptional and durable response in advanced PDAC through a genomically guided, multimodal treatment strategy. The integration of platinum-based chemotherapy, targeted radiation, immunotherapy, and maintenance PARP inhibition was informed by the tumor's unique BRCA2 mutation and high PD-L1 expression. Our findings support early molecular testing to identify PDAC patients suited for precision oncology approaches, which may contribute to more favorable outcomes.

Keywords: Pancreatic ductal adenocarcinoma, Pancreatic Cancer, Immunotherapy, Precision Therapy, PD-L1, PD-1 Therapy, BRCA2 Mutation, Homologous Recombination Deficiency

Abbreviations: Pancreatic ductal adenocarcinoma (PDAC), stereotactic body radiation therapy (SBRT), magnetic resonance imaging (MRI), combined positive score (CPS), homologous recombination deficiency (HRD), tumor mutational burden (TMB)

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and remains one of the most lethal solid tumors [1]. Despite advances in therapy, the overall 5-year survival for PDAC is approximately 13.3% [1]. Traditional cytotoxic chemotherapy regimens have modestly improved outcomes [2]. PDAC's abundant desmoplastic stroma and immunosuppressive tumor microenvironment render it largely resistant to immune checkpoint inhibitors [2]. Only extremely rare biologic subsets, such as those with mismatch repair deficiency, have shown meaningful responses to immunotherapy in PDAC. There is growing recognition that comprehensive molecular profiling can identify actionable subsets of PDAC that might benefit from targeted or immune-based therapies [2]. This case report describes a patient with advanced PDAC harboring a germline BRCA2 mutation and exceptionally high PD-L1 expression, combined positive score (CPS) = 100, who achieved a durable remission through a personalized, multimodal treatment approach. By integrating immune checkpoint inhibition and maintenance combination therapy (PARP inhibition plus PD-1 blockade), we highlight the potential of precision oncology in PDAC. This case emphasizes how understanding a tumor's molecular underpinnings can inform the use of emerging targeted and immunotherapies, ultimately aiming to improve outcomes in a cancer considered treatment-refractory.

2. Case Presentation

2.1. Patient Information and Clinical Course

A 60-year-old male with no history of smoking and no significant alcohol use presented with acute pancreatitis. He had a notable family history of cancer (including a brother with pancreatic cancer). Imaging and workup revealed an adenocarcinoma in the distal pancreas. The primary tumor was deemed borderline resectable due to local vascular encasement, but at diagnosis there was no evidence of distant metastasis. The patient underwent germline genetic testing given his family history; this revealed a pathogenic BRCA2 mutation. Notably, this same BRCA2 mutation had been identified in his brother's pancreatic tumor, though the brother had not disclosed this result to the family until after our patient's diagnosis. The patient was enrolled in a randomized phase II clinical trial investigating a neoadjuvant multimodal regimen for localized PDAC. Treatment included modified FOLFIRINOX chemotherapy combined with losartan (an angiotensin receptor blocker hypothesized to modulate stroma), followed by stereotactic body radiotherapy (SBRT) and an initial dose of the anti–PD-1 checkpoint inhibitor nivolumab. The patient completed eight cycles of induction mFOLFIRINOX with excellent tolerance and clinical improvement in symptoms. He then received SBRT to the pancreatic tumor and one dose of nivolumab as per trial protocol. Subsequently, the patient underwent a distal pancreatectomy with splenectomy, which achieved an R0 resection. Surgical pathology demonstrated a near-complete treatment response, with only a single minute 1 mm focus of residual viable adenocarcinoma in one lymph node out of 12 lymph nodes (ypT0N1) and no viable tumor in the pancreas. The single positive lymph node had a PD-L1 CPS of 50. All margins were clear. Approximately one month after surgery, routine surveillance imaging (MRI) detected a new liver lesion. A core-needle biopsy of the liver lesion confirmed metastatic PDAC. Remarkably, IHC of the liver metastasis showed a PD-L1 combined positive score (CPS) of 100, the maximum possible score, indicating that essentially all tumor and associated immune cells expressed PD-L1. Given the solitary nature of this metastasis, the patient was treated with percutaneous microwave ablation of the liver lesion. At the time, a clinical trial investigating PARP inhibitor plus PD-1 blockade was available for patients with stage IV pancreatic cancer, but the pancreatic cohort had already closed. Given the patient's molecular profile, he was initiated on off-label maintenance therapy within a month of ablation, consisting of olaparib 200 mg twice a day (to target his germline BRCA2 mutation) in combination with pembrolizumab, 400 mg every 6 weeks (to leverage the tumor's exceptionally high PD-L1 expression). This regimen was selected on the basis of the tumor's homologous recombination deficiency (HRD) and strong immunogenic features, with the aim of reducing recurrence risk and achieving durable disease control. Since initiating olaparib plus pembrolizumab, the patient has remained clinically well and cancer-free for five years. He elects to continue therapy, although discontinuation has been discussed. Serial imaging (MRI and PET/CT) shows no evidence of active disease, and the patient's performance status remains excellent (fully active, ECOG 0). He has returned to normal daily activities and reports only grade 1 fatigue as an ongoing side effect.

2.2. Molecular and Genomic Data

Histologic evaluation and immunoprofiling confirmed a pancreaticobiliary origin, with tumor cells positive for CK7, and CDX2 (weak and patchy), consistent with an upper gastrointestinal/pancreatic phenotype. P63 was negative, helping to exclude a squamous tumor component or a different primary tumor. Immunohistochemistry for DNA mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) showed intact nuclear expression of all four, indicating the tumor was microsatellite stable. On initial biopsy, there was no PD-L1 stain performed, as this was not considered standard of care. Importantly, both the residual lymph node after resection and liver metastasis displayed an exceptionally high level of PD-L1 expression. The liver metastasis

had a PD-L1 CPS of 100, representing the maximum score. This suggested a highly inflamed tumor microenvironment and provided a strong rationale for incorporating immune checkpoint blockade. Germline next-generation sequencing confirmed a pathogenic BRCA2 mutation, indicative of an underlying HRD. Tumor sequencing revealed a low tumor mutational burden (TMB) and multiple somatic alterations, including mutations in BRCA2, FGFR2, CDKN2A, CDKN2B, KRAS (G12V), TP53, KDM5A, MTAP, PRKCI, and TERC. The patient's tumor exhibited a genomically complex profile with canonical driver mutations (KRAS, TP53) as well as a BRCA2 mutation highlighting potential vulnerabilities related to DNA damage repair deficiency and cell-cycle regulation. Although somatic alterations involving FGFR2 and CDKN2A/B were identified, these were not considered actionable driver mutations and did not influence clinical management. Low TMB is common in PDAC, but the combination of BRCA2 mutation with exceptionally high PD-L1 CPS is extremely rare and suggests a unique, atypical molecular phenotype which provided strong biological rationale to continue PD-1 blockade in combination with maintenance PARP inhibition.

3. Discussion

PDAC remains an aggressive malignancy with poor outcomes, but increasing knowledge of its molecular heterogeneity may open new avenues for precision therapy [2]. PDAC is projected to become the second-leading cause of cancer-related mortality in the United States by 2030 [3], underscoring the urgency for novel interventions.

3.1. HRD/BRCA2 and PARP Therapy

On a molecular level, nearly all PDAC harbor KRAS mutations, along with frequent inactivation of tumor suppressors such as TP53, CDKN2A, and SMAD4 [4]. Beyond these common somatic events, a subset of patients, estimated at 7%, carry germline mutations in cancer-predisposition genes [4]. Notable inherited contributors in PDAC include BRCA2 (as seen in this patient), as well as BRCA1, CDKN2A, ATM, PALB2, and others. These germline variants not only confer an elevated risk of developing pancreatic cancer, but importantly, they can also inform targeted treatment strategies (for example, DNA repair defects predicting sensitivity to platinum chemotherapy and PARP inhibitors)[5, 6]. Increasing adoption of broad multigene testing for patients with PDAC has revealed clinically actionable mutations even in those without overt family history [6, 7]. In our patient, early germline testing identified a BRCA2 mutation, which influenced therapy decisions (prompting use of platinum and PARP inhibitor). This case exemplifies how upfront molecular profiling can unmask therapeutic vulnerabilities in PDAC that might otherwise remain unrecognized.

3.2. PD-L1 and Immunotherapy

Another distinctive feature of this case was the tumor's PD-L1 CPS of 100, indicating an exceptionally immunogenic tumor microenvironment for PDAC. Typical PDACs are considered "cold" tumors with dense stroma and few T cells, and single-agent immune checkpoint inhibitors have historically shown negligible activity in unselected PDAC. Our patient's tumor, however, by virtue of its high PD-L1 expression (and possibly induced by the clinical trial regimen with SBRT and losartan), may have been rendered more susceptible to immunotherapy. This unusual PD-L1–high status provided a strong rationale for incorporating PD-1 checkpoint blockade alongside PARP inhibition as systemic therapy. The durable remission observed suggests a synergistic benefit: the PARP inhibitor may attenuate tumor growth, while combination therapy with PD-1 blockade potentially primes the immune response, leading to increased T-cell activity, a hypothesis supported by emerging preclinical and early clinical evidence [8].

3.3. Synthesis and Practice Implications

Therapeutically, this case aligns with and extends lessons from recent trials. The POLO trial was a pivotal phase III study that demonstrated significantly improved progression-free survival (7.4 months vs 3.8 months) with maintenance olaparib in metastatic PDAC patients with germline BRCA mutations who had not progressed on platinum chemotherapy (hazard ratio 0.53, P = 0.004)[9]. While the POLO study's initial overall survival analysis showed no significant difference between olaparib and placebo (approximately 19 months in both arms)[9], it led to the 2019 FDA approval of olaparib for this population. Our patient derived prolonged disease control on maintenance PARP inhibition, consistent with the benefit observed in POLO. However, his remission now far exceeds the medians reported, highlighting the potential impact of additional therapies (surgery, ablation, immunotherapy) in select cases. Combining PARP inhibitors with immune checkpoint inhibitors is an area of active investigation in PDAC. Clinical data are beginning to emerge: for example, the PARPVAX trial (a randomized phase 1b/2 study) evaluated maintenance niraparib with either ipilimumab (CTLA-4 inhibitor) or nivolumab (PD-1 inhibitor) in platinum-responsive advanced PDAC [10]. Notably, the niraparib with ipilimumab arm achieved a significantly higher 6-month progression-free survival rate (59.6%) compared to the niraparib with nivolumab arm (20.6%)[10]. This suggests that CTLA-4 blockade might augment immune activity in PDAC more than PD-1 blockade alone, although further confirmation is needed. Several ongoing trials are now exploring similar combinations – for instance, the POLAR trial (NCT04666740) is testing olaparib with pembrolizumab

(anti–PD-1) in HR-deficient or platinum-sensitive PDAC, which will further inform this approach. In addition to olaparib, other PARP inhibitors are being investigated and utilized in pancreatic cancer. The RUCAPANC2 study was a phase II trial of rucaparib as maintenance therapy in patients with BRCA1/2 or PALB2 mutant PDAC who responded to platinum. RUCAPANC2 reported a median PFS of 13.1 months and median OS of 23.5 months on rucaparib maintenance, demonstrating substantial disease control akin to olaparib [11]. Based on accumulating evidence, current NCCN guidelines include olaparib as the preferred maintenance option for patients with metastatic PDAC who harbor a germline BRCA1/2 mutation and have not progressed after at least 16 weeks of first-line platinum-based chemotherapy [12].

3.4. Limitations

While this case illustrates a durable response to combined PARP inhibitor and PD-1 blockade in a patient with BRCA2-mutated, PD-L1-high PDAC, causal relationships between the therapy and the outcome cannot be established from a single case study. The observed outcome may reflect intrinsic disease heterogeneity, unmeasured biological confounders, or therapeutic activity attributable to either agent alone. Prospective studies with larger cohorts are needed to validate this treatment strategy, clarify whether combination therapy offers incremental benefit over monotherapy, and identify predictive biomarkers that distinguish exceptional responders among patients with BRCA2-mutated, PD-L1–high disease.

4. Conclusion

This case highlights a broader paradigm shift in PDAC management – moving from a one-size-fits-all, empiric chemotherapy approach toward personalized, genomically guided strategies. We advocate that all patients with PDAC, even those with apparently resectable disease, undergo early germline and molecular testing. Identifying biomarkers such as DNA repair deficiencies or high immune checkpoint expression may significantly alter the therapeutic roadmap. In summary, the durable remission in our patient was achieved by leveraging both targeted therapy and immunotherapy guided by his tumor's molecular profile. While PDAC historically portends a dismal prognosis, this case demonstrates that long-term control – even in metastatic disease – is attainable when cutting-edge treatments are tailored to the tumor's genomic and immunologic vulnerabilities. Ongoing research and clinical trials will continue to expand the toolkit of precision oncology in PDAC. Integrating these advances early in a patient's treatment course offers a tangible hope of improving survival in a cancer that is refractory to treatment.

To complement the clinical narrative, the patient shares his perspective below.

5. Patient Perspective

Being told that I had cancer—any type of cancer—felt like a slap in the face. Learning it was pancreatic cancer made it even worse. This diagnosis gave me a new perspective on life and made me appreciate every day. I was no longer the same person after the diagnosis, treatments, and medications. It feels like walking a fine line—balancing the effects of everything I have been through with the consequences of how I have confronted it. Emotionally, it has been a roller coaster: the "up" of being healed and the "down" of facing the side effects of treatments. I remind myself that these pains and limitations are due to treatments that saved my life. Learning that I qualified for a clinical trial gave me a new lease on life. It not only gave me hope that it might work, but also the satisfaction of knowing that I was contributing to something bigger than myself—something that could help others facing this disease in the future. I wholeheartedly advocate for clinical trial participation. I believe that anyone given the opportunity to participate should take advantage of it. This experience made me realize that one can be in the best shape of their life and still have everything change in an instant. Today, I take extra care of myself, with the support of my wife and son, because I feel I have been given another chance at a long, healthy life. While the journey is tough, it is just a speed bump in life—and one well worth overcoming.

Afterword: Blackburn Foundation Message

Wanting to pay forward the love and support I received during my diagnosis, treatment, and recovery, my wife Linda, my son Shane, and I decided to start The Blackburn Family Cancer Foundation: Coaching for a Cure. The Foundation aims to support patients battling cancer and their families while working with doctors to improve patient outcomes. Its goals include funding pancreatic cancer research and helping patients facing financial hardships caused by their ongoing fight against cancer. More information is available at: https://blackburncancerfoundation.com/

See **Figure 1** for a photograph accompanying the patient narrative and community message.

Figure 1. Pictured left to right: Linda Blackburn, Edward Blackburn, Dr. Despina Siolas, and Shane Blackburn, in support of the Blackburn Family Cancer Foundation. Photograph included with permission as part of the patient narrative; not a clinical image.

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Search Strategy and Selection Criteria: Information for this case report was identified through a review of peer-reviewed articles, and clinical guidelines. Searches were performed in PubMed and Google Scholar using combinations of relevant terms, including "pancreatic ductal adenocarcinoma," "BRCA2," "homologous recombination deficiency," "PARP inhibitor," and "PD-1 blockade." Priority was given to publications from the last 10 years, as well as pivotal earlier studies and referenced clinical guidelines directly relevant to the patient's diagnosis and management. No formal systematic review was performed. The literature review was last updated in November 2025.

Author Contributions: D.S. conceived the study, conducted literature reviews, and wrote, edited, and finalized the manuscript. A.K. conducted literature reviews, wrote, and edited the manuscript. C.B. conducted literature reviews, wrote, and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: In accordance with institutional policy, this retrospective single-patient case report did not meet criteria for human subjects research and therefore did not require Institutional Review Board review or approval.

Informed Consent Statement: Written informed consent was obtained from the patient during participation in the clinical trial, including permission to publish this case report and potentially identifying clinical information and accompanying images.

Data Availability Statement: No supporting data are associated with this article.

Conflicts of Interest: Dr. Siolas serves on a colorectal cancer advisory panel for Bristol Myers Squibb and is part of a Clinical Expert panel for Natera, Inc.

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