Despite advances in cancer therapeutics, pancreatic ductal adenocarcinoma (PDAC) remains among the deadliest malignancies, with a poor prognosis at time of diagnosis, reflecting a 5-year survival rate of approximately 10% across all stages and 2% in patients with metastatic (stage IV) disease. Research in PDAC has suggested that adaptive signaling in the tumor microenvironment may promote tumor proliferation and survival. Several FGFR fusion genes—specifically FGFR2—are involved with the creation and progression of cancer. These mutations are found in a variety of cancer types. This report presents a unique case of a young patient with stage IV PDAC with a known FGFR2 fusion. This molecular alteration afforded a remarkable response to FGFR inhibitor therapy, erdafitinib, after the patient experienced disease progression on multiple chemotherapy regimens.

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FGFR2 mutations have also been found in other cancers, such as gallbladder, breast, thyroid, and prostate, but at a lower rate. In pancreas cancer, FGFR mutations exist in approximately 5% of cases, and fusions are even more rare. Although these genetic variations are carcinogenic, they are certainly more rare than other mutations, such as KRAS mutations, which occur in nearly 90% of PDAC cases. Multiple nationwide clinical trials currently explore therapies that selectively target FGFR signaling, yet only 2 have acquired FDA approval. Erdafitinib, a small molecule inhibitor of FGFR1–4, was approved in 2019 for patients with locally advanced or metastatic FGFR2- or FGFR3-mutated...
urothelial carcinoma that has progressed on or after chemotherapy. Shortly after in 2020, pemigatinib, a small molecule inhibitor of FGFR1-3, was approved for patients with pre-treated locally advanced unresectable or metastatic cholangiocarcinoma and a FGFR2 fusion or rearrangement.12–13

This report presents a unique case of a young patient with stage IV PDAC with a known FGFR2 fusion. This molecular alteration afforded a remarkable response to FGFR inhibitor therapy, erdafitinib, after the patient experienced disease progression on multiple chemotherapy regimens. Previous studies report rare FGFR2 fusions in patients with pancreatic cancer.14–16 As such, we present one of the few documented cases in which a patient with advanced PDAC harboring a FGFR fusion experienced a durable response to FGFR inhibitor therapy.

Case Report
A 28-year-old Hispanic male presented with epigastric pain. Investigation with cross-sectional imaging found a pancreatic neck mass as well as innumerable liver lesions and scattered lung lesions suspicious for metastases. An upper endoscopic ultrasound revealed a 4 × 3.8-cm hypoechoic, well-defined mass lesion with central irregular anechoic cystic component in the neck of the pancreas. A core needle biopsy of the pancreatic mass was obtained, confirming diagnosis of poorly differentiated adenocarcinoma. Ultrasound-guided biopsies of the liver confirmed poorly differentiated adenocarcinoma, consistent with metastasis from pancreaticobiliary tract origin. Tumor histology revealed a poorly differentiated adenocarcinoma, consistent with metastasis from pancreaticobiliary tract origin. Tumor histology was unremarkable, with positive Cam5.1, SMAD4, and Ki67 (Table 1). The patient was promptly started on FOLFOXIRI treatment, in- interval CT imaging of the chest, abdomen, and pelvis showed disease progression. At this time the patient enrolled in the Dual-Afinity Targeting Trial and received 2 cycles of MGD009-01, a bispecific antibody-based molecule targeting B7H3 and CD-3 expressing tumor cells (ClinicalTrials.gov identifier: NCT02628535). However, his disease quickly progressed after 2 cycles, especially in the many lung metastases.

At that time, CT scans revealed that the patient had increased ascites, a new left pleural effusion, a perihepatic nodule, and multiple mildly increased pulmonary and hepatic lesions. As a result, the patient began FGFR2 inhibitor therapy, erdafitinib, and has experienced an excellent response to this therapy. Compared with his previous CT scan, the scans performed after initiation of erdafitinib therapy showed a significant decrease in pulmonary lesions (Figure 1). Previous physical examinations showed PDAC-related weight loss, ascites, and hypercalcemia, but following FGFR2 inhibitor therapy, the patient’s weight improved, and the latter issues had resolved. In addition, his CA 19-9 level, which was used as the tumor marker in this pancreas cancer case, decreased after initiation of erdafitinib therapy (Table 2). At the time of writing, the patient has been continuing this treatment for >12 months with an excellent response (Figure 2).

Discussion
Our case is notable because it examines the approach to treatment and clinical outcomes of an extremely rare patient population within pancreatic cancer. Our patient had been diagnosed with PDAC at a relatively young age. According to SEER data collected from 2013 to 2017, the average age of diagnosis of PDAC is 70 years; only 0.6% of diagnoses represent individuals aged 20 to 34 years, with those aged ≥80 years at nearly 100 times greater risk to be diagnosed with PDAC than those aged <39 years.17,18 FGFR abnormalities are also rarely found in patients with PDAC. In a 2016 study, only 4% to 6% of the patients with pancreatic exocrine carcinoma had tumors with an FGFR aberration.5 In addition, FGFR2 fusions are rarely noted, with only 15 previous cases reported to our knowledge.

Table 1. Initial Histology Results of Pancreas Tumor at Diagnosis

<table>
<thead>
<tr>
<th>Histology/Antibody</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cam5.2</td>
<td>Positive</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Negative</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Negative</td>
</tr>
<tr>
<td>CD56</td>
<td>Negative</td>
</tr>
<tr>
<td>Trypsin</td>
<td>Negative</td>
</tr>
<tr>
<td>Glypican</td>
<td>Negative</td>
</tr>
<tr>
<td>Beta-catenin</td>
<td>Negative</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Positive</td>
</tr>
<tr>
<td>Sall4</td>
<td>Negative</td>
</tr>
<tr>
<td>Ki67</td>
<td>Positive (20%–30% proliferation index)</td>
</tr>
<tr>
<td>HER2</td>
<td>Negative</td>
</tr>
</tbody>
</table>

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Finally, the patient was noted to be KRAS WT, and in pancreas cancer KRAS mutations affect the overwhelming majority.\(^{11,15}\) Patients with KRAS WT disease make up approximately 12.4% of PDAC cases, and these patients have been found to have improved clinical outcomes and harbor targetable alterations including FGFR fusions.\(^{11,20}\)

Our case supports the hypothesis that patients with PDAC—especially those diagnosed at a young age (<50 years) with KRAS WT PDAC—are more likely to have fusion abnormalities. One 2020 study reported that 22% of patients with KRAS WT disease were found to have targetable fusions, such as FGFR2, ALK, ROS1, RET, and NOTCH1. A later study in 2021 confirmed this trend, reporting that 31% of patients with PDAC found to have KRAS WT tumors also had targetable fusions, including FGFR2, MET, NRG1, and RAF1.\(^{15,21}\)

Similarly, another study found that 11% of KRAS WT PDACs were found to have a fusion abnormality, and approximately 23% of those fusions involved FGFR2.\(^{15}\) In addition, a study that identified 5 patients with PDAC harboring ALK fusions, ranging in age from 32 to 46 years, found that their genomic profiles showed KRAS WT.\(^{22}\) Researchers concluded that ALK fusions in patients with PDAC are characterized by young age at presentation along with the absence of a KRAS mutation. Our case reinforces the idea that alternative mutations may drive PDAC in young patients, and further research into this field is warranted to uncover pathogenesis of disease and/or targetable mutations.\(^{20}\)

The patient’s excellent response to erdafitinib demonstrates that FGFR2 fusions may be a therapeutic target in patients with PDAC. Erdafitinib is a small molecule, pan-FGFR inhibitor, which is orally administered.\(^{23}\) The treatment was approved by the FDA in 2019 and is intended for use in patients who have locally advanced or metastatic urothelial carcinoma with FGFR2 or FGFR3 alterations.\(^{24}\)

Previous studies have shown the efficacy and clinical impact of erdafitinib in patients with urothelial cancer and cholangiocarcinoma. A phase II, second-line, randomized study including patients with an FGFR3 mutation or an FGFR2/3 fusion in unresectable locally advanced or metastatic urothelial cancer showed a confirmed response rate of 40% to erdafitinib therapy, which led to its FDA approval.\(^{12}\) Another study investigating erdafitinib reported an overall response rate of 50% for patients with advanced cholangiocarcinoma and an FGFR gene alteration.\(^{25}\)

Although not currently FDA-approved for patients with PDAC, erdafitinib therapy in this specific case exhibits the possibility of expanded usage of this drug while supporting exploration of other FGFR inhibitors. Early in vitro data showed that erdafitinib inhibits phosphorylation and signaling of FGFR and decreased cell viability in lines with FGFR alterations including fusions, making it an effective therapy for patients with FGFR alterations.\(^{24}\)

In another report in 2021, a 68-year-old patient with PDAC was also identified with an FGFR2 fusion and KRAS WT status.\(^{19}\) This patient received erdafitinib therapy and had an extremely positive response, similar to our patient. The exceptional response to this therapy in this rare patient population supports the recommendation that all patients should undergo sequencing early to identify targetable mutations as new therapies are developed.

**Conclusions**

Our report presents one of the few, rare cases in which a patient with PDAC was found to have an FGFR2 fusion. Given the exceptional response of this patient specifically, further exploration into the biology of FGFR mutations and their role in carcinogenesis can help identify at-risk populations while exploring therapeutic options. Our case bolsters the notion that young patients with KRAS WT PDAC should be sequenced early to identify targetable mutations, such as fusion abnormalities, and to facilitate early initiation of appropriate treatment options.
treatment strategies. As new targetable mutations are uncovered and precision therapies are developed to treat those with specific mutations, this case supports more generally that all patients with PDAC—especially young patients with KRAS WT tumors—should undergo sequencing specifically to identify fusion mutations in order to determine optimal care.

Figure 2. Timeline of therapy and disease. Abbreviation: FOLFOXIRI, folinic acid/fluorouracil/oxaliplatin/irinotecan.

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