original reports

Identification of Targetable Gene Fusions and Structural Rearrangements to Foster Precision Medicine in *KRAS* Wild-Type Pancreatic Cancer

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abstract

PURPOSE It has recently been described that alternative oncogenic drivers may be found in *KRAS* wild-type (*KRAS*^{WT}) pancreatic cancers. This study aimed to determine the incidence of targetable gene fusions present in *KRAS*^{WT} pancreatic adenocarcinoma and response to targeted therapy.

METHODS One hundred consecutive patients with pancreatic adenocarcinoma who underwent targeted next-generation sequencing using DNA sequencing with RNA sequencing (n = 47) or without RNA sequencing (n = 53) at a single institution were included in the study. The frequency and landscape of targetable fusions in *KRAS*^{WT} pancreatic adenocarcinoma was characterized and compared with the frequency of fusions in *KRAS*-mutated (*KRAS*^{MUT}) pancreatic adenocarcinoma. Results were validated in two independent cohorts using data from AACR GENIE (n = 1,252) and TCGA (n = 150). The clinical history of fusion-positive patients who received targeted treatment is described.

RESULTS Pancreatic cancers from 13 of 100 patients (13%) were found to be *KRAS*^{WT}. Targetable fusions were identified in 4/13 (31%) *KRAS*^{WT} tumors compared with 0/87 (0%) *KRAS*^{MUT} pancreatic adenocarcinomas (P = .0002). One patient with a novel *MET* fusion had a complete response to targeted therapy with crizotinib that is ongoing at 12+ months of treatment. In the validation cohorts, gene fusions were identified in 18/97 (19%) and 2/10 (20%) *KRAS*^{WT} tumors reported in the AACR GENIE and TCGA cohorts, respectively.

CONCLUSION Oncogene fusions are present in *KRAS*^{WT} pancreatic adenocarcinomas at an increased frequency when compared with *KRAS*^{MUT} pancreatic adenocarcinomas. As these fusions may be susceptible to targeted therapy, molecular analyses for the detection of fusions in *KRAS*^{WT} pancreatic adenocarcinomas may warrant increased consideration.

JCO Precis Oncol 5:65-74. © 2021 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States with 57,600 new cases and 47,050 deaths projected in 2020.[1] Clinical studies have established the antitumor activity of polychemotherapy approaches including FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) and gemcitabine combined with nab-paclitaxel for advanced or metastatic pancreatic cancer.[2,3] Despite the activity of polychemotherapy, the majority of patients with advanced or metastatic pancreatic cancer develop disease progression within 6 months, and thus more effective therapies are needed.[2,3]

In recent years, enthusiasm for targeted therapy in pancreatic cancer has grown with the approval of the PARP-inhibitor olaparib for the treatment of patients with *BRCA*-mutated disease and the identification of alternative oncogenic drivers in *KRAS* wild-type (*KRAS*^{WT}) tumors.[4-6] Further advances have included the identification of *NRG1* fusions in *KRAS*^{WT} pancreatic adenocarcinoma and case reports describing exceptional responders to targeted therapy in pancreatic cancers harboring a variety of oncogene fusions, all identified in *KRAS*^{WT} tumors.[7-10]

Although *KRAS*^{WT} tumors represent a minority of pancreatic cancer cases, they may possess potentially targetable alterations, making their identification a therapeutic opportunity.[5,6] This study sought to characterize the landscape of targetable oncogene fusions detected in *KRAS*^{WT} pancreatic adenocarcinoma through a retrospective analysis of 100 pancreatic adenocarcinoma cases sequenced at a single institution. Results were validated through two other pancreatic adenocarcinoma studies. Finally, we report the clinical course of a series of fusion-positive cases treated with matched targeted therapy.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 4, 2020 and published at ascopubs.org/journal/po on January 11, 2021: DOI https://doi.org/10.1200/PO.20.00265

CONTEXT

Key Objective

To describe the landscape targetable gene fusions in *KRAS* wild-type (*KRAS*^{WT}) pancreatic cancer including a cohort of patients treated with matched targeted therapy.

Knowledge Generated

Targetable gene fusions are detected in *KRAS*^{WT} pancreatic cancers at an increased rate (approximately one out of five) compared with *KRAS*-mutated pancreatic adenocarcinomas. Some patients treated with targeted therapy directed at these fusions can achieve meaningful clinical benefit.

Relevance

The increased frequency of oncogene fusions in *KRAS*^{WT} pancreatic adenocarcinoma suggests that *KRAS* status may be used as a method to identify patients who are more likely to harbor targetable fusions. The identification of *MET* fusions in the setting of *KRAS*^{WT} pancreatic cancer suggests a novel target in *KRAS*^{WT} cases that should be interrogated with assays capable of detecting *MET* fusions with both known and novel partners.

METHODS

Patient Selection and Data Collection

This study was conducted in accordance with an institutional review board–approved protocol. The protocol was approved by Moffitt Cancer Center (MCC) in accordance with the Declaration of Helsinki and the 21st Century Cures Act. A cohort comprising 100 consecutive patients (MCC 100) was identified from a Moffitt database that discretely annotates all genomic results from targeted next-generation sequencing (NGS) panels.[11] Cases were required to have a pathologically confirmed diagnosis of pancreatic adenocarcinoma and had targeted NGS performed using FoundationOne, FoundationOne CDx, or Moffitt STAR assays between March 1, 2013, and August 30, 2019, as part of clinical care. Targetable gene fusions were defined as those with clinical evidence supporting the use of targeted therapy as follows: *ALK, BRAF, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK2, NTRK3, RAF1, RET*, and *ROS1* (Data Supplement, online only).

Assays Used

Moffitt STAR. The Illumina TruSight Tumor 170 gene (TST170) platform is a NGS platform designed to detect genetic alterations in 170 genes. The assay uses an enrichment-based hybrid capture targeted panel that simultaneously analyzes DNA for single-nucleotide variants, multi-nucleotide variants, and indels, and RNA for fusions and splice variants (55 genes).[12]

FoundationOne. This assay has been described in depth previously.[13] The assay uses hybridization-based capture of 4,557 exons of 287 cancer-related genes and 47 introns of 19 genes frequently rearranged in solid tumors.

FoundationOne CDx. This assay has been described in depth previously.[14] The assay uses hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one noncoding (ncRNA), and select intronic regions from 34 commonly rearranged genes.[14] A list of genes included in each of these assays is available in the Data Supplement.

Validation Using Two Independent Cohorts

As a validation cohort, the AACR GENIE and TCGA Pancreatic Adenocarcinoma data sets were analyzed. For the AACR Genie data set, only pancreatic adenocarcinoma cases were included from sites within the AACR GENIE consortium that contributed data on both structural rearrangements (ie, fusions) and mutation data (Memorial Sloan Kettering Cancer Center [MSK] and Vanderbilt-Ingram Cancer Center [VICC]).[15] Sites reporting structural and mutation data included 1,252 of 2,048 unique patients within the AACR GENIE data set. Molecular profiling assays and associated bioinformatics pipeline used by AACR GENIE consortium sites has been previously described.[15] Samples identified in the AACR GENIE database without any mutations or copy number alterations identified were excluded to avoid failed genotyping samples. A complete list of included cases is available in the Data Supplement.

As a second validation cohort, the TCGA Pancreatic Adenocarcinoma data set was obtained through cBioportal.[16,17] The 150 cases from TCGA were included as these cases had a pathologic confirmation of a diagnosis of pancreatic adenocarcinoma along with sufficient tumor cellularity for sequencing.[18] Detailed methods for the sequencing and bioinformatics pipeline has been described elsewhere.[18] A complete list of cases included is available in the Data Supplement.

Statistical Analysis

Fisher's exact test (two-tailed) was performed to test for differences in the incidence of fusions in *KRAS*^{WT} versus

TABLE 1. Characteristics of the Moffitt Cancer Center (MCC100) Cohort

Characteristic	Entire Cohort (N = 100)	*KRAS* Mutant (n = 87)	*KRAS* Wild-Type (n = 13)
Median age (years) at the time of tumor sequencing (range)	67 (40-88)	68 (40-88)	61 (46-81)
Sex			
Male	65% (n = 65)	67% (n = 58)	54% (n = 7)
Female	35% (n = 35)	33% (n = 29)	46% (n = 6)
Stage at tumor sequencing			
Stage I or II	6% (n = 6)	7% (n = 6)	0
Stage III	6% (n = 6)	6% (n = 5)	8% (n = 1)
Stage IV	88% (n = 88)	87% (n = 76)	92% (n = 12)
NGS assay used			
FoundationOne™	29% (n = 29)	30% (n = 26)	23% (n = 3)
FoundationOne CDx™	24% (n = 24)	25% (n = 22)	15% (n = 2)
Moffitt STAR™	47% (n = 47)	45% (n = 39)	62% (n = 8)

Abbreviation: NGS, next-generation sequencing.

KRAS-mutated (*KRAS*^{MUT}) patients in each of the three cohorts (MCC100, AACR GENIE, and TCGA).

RESULTS

Patient Cohort and Molecular Characteristics

A cohort comprising 100 patients (MCC100) diagnosed with pancreatic adenocarcinoma who underwent somatic molecular sequencing with one of the three clinical NGS assays (FoundationOne, FoundationOne CDx, or Moffitt STAR) is included (Table 1). The median age for MCC100 at the time of NGS was 67 years (range, 40-88 years) with a male predominance (65%). The majority of patients (88%) had stage IV disease. Thirteen (13%) patients had *KRAS*^{WT} pancreatic adenocarcinoma and 87 (87%) had *KRAS*^{MUT} pancreatic adenocarcinoma, with *KRAS* (p.Gly12Asp) as the most commonly observed *KRAS* alteration (n = 42). Targetable oncogene fusions were identified in 31% (4 of 13) of *KRAS*^{WT} and 0% (0 of 87) of *KRAS*^{MUT} pancreatic adenocarcinomas (P = .0002) (Fig 1).

Targetable Oncogene Fusions Identified in *KRAS*^{WT} Pancreatic Adenocarcinoma

The fusion events in MCC100 involved four targetable genes. The first was an *FGFR2-PAWR* rearrangement (number of supporting reads not reported) in which exons

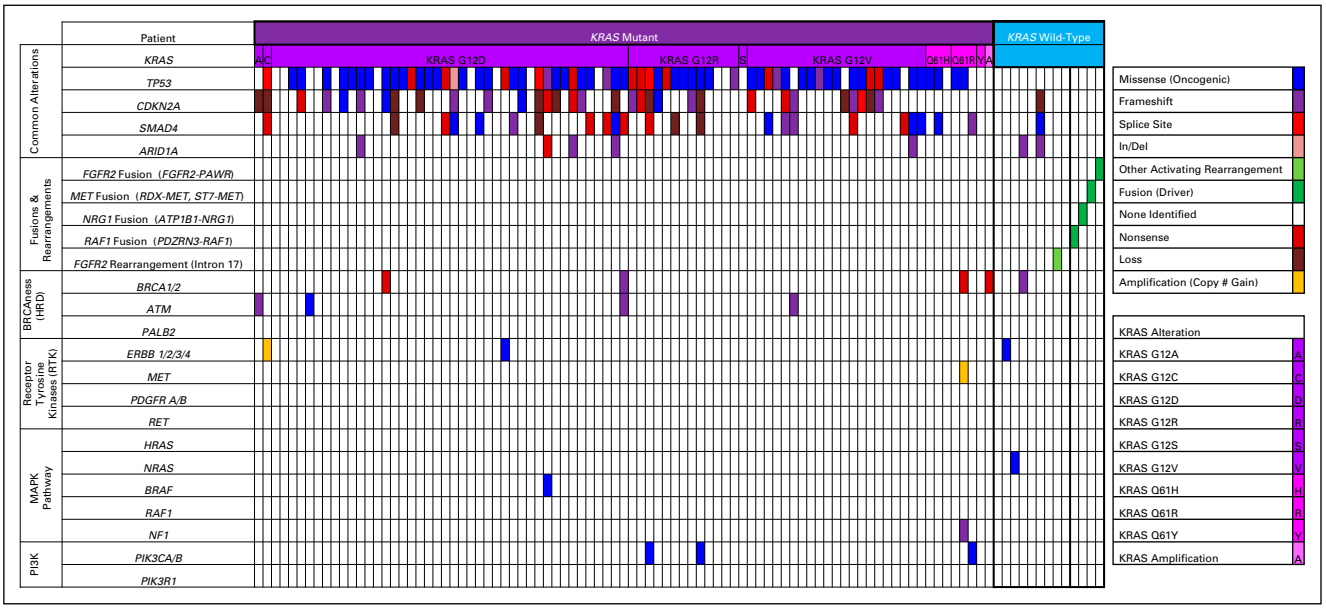

FIG 1. Enrichment for oncogene fusions in *KRAS*^{WT} pancreatic adenocarcinoma. Targetable fusions were identified in 4 of 13 *KRAS*^{WT} patients with no alternative driver oncogenes identified. Additionally, a *FGFR2* rearrangement was identified that was predicted to be activating.

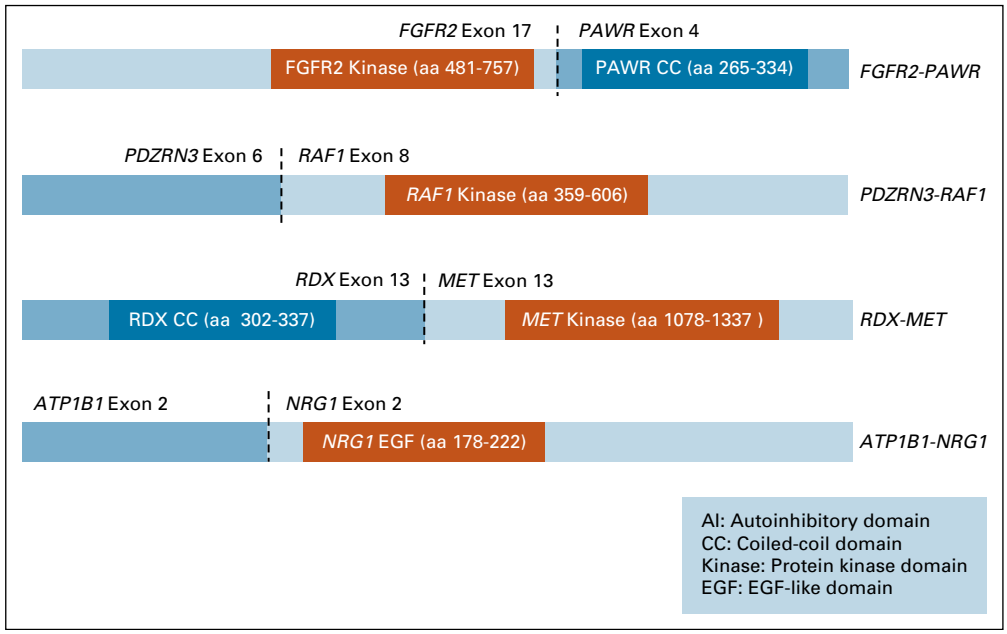

FIG 2. Targetable fusions identified in the MCC100 cohort. Schematic representation of the predicted products of the four fusions identified among 13 *KRAS*^{WT} patients. Fusions were predicted to be activating based upon the known mechanism of activation, observed breakpoints, and relevant functional domains retained or lost in the chimeric fusion transcript.

1-17 of *FGFR2* are fused with exons 4-7 of *PAWR* (Fig 2). This fusion was consistent with other known activating *FGFR2* fusions, which frequently occur with a breakpoint after exon 17 at the 3′ end of *FGFR2* with a 3′ partner that typically contributes a coiled-coil domain or other domain capable of oligomerization.[19-23]

The second fusion was a *PDZRN3-RAF1* rearrangement (543 supporting reads) with the chimeric transcript involving exons 1-2 of *PDZRN3* fused with the 5′ end of exon 8 of *RAF1* (Fig 2). This fusion was consistent with previously observed *RAF1* fusions, which frequently have an exon 8 breakpoint leading to loss of an N-terminal autoinhibitory region (amino acids, 1-147) of *RAF1* and constitutive activation.[24-27]

A third fusion was an *ATP1B1-NRG1* rearrangement (652 supporting reads) with the chimeric transcript involving exons 1-2 of *ATP1B1* fused with the 5′ end of exon 2 of *NRG1* (Fig 2). Across studies, the 5′ partner of *NRG1* has been variable. All activating *NRG1* fusions retain the *EGF*-like domain (exons 6 and 7) of *NRG1*,[6,8] enabling ligand binding of the *EGF*-like domain of NRG1 to ERBB3, which activates ERBB2/ERBB3 heterodimerization and downstream proliferative signaling.[7,8,28] The identified fusion was consistent with this known mechanism, with the *EGF*-like domain predicted to be retained in the chimeric protein.

The fourth identified fusion was a novel *RDX-MET* fusion (142 supporting reads) that has not been previously reported. The fusion involves exons 1-13 of the *RDX* gene fused with the 5′ end of *MET* exon 13 (Fig 2). The fusion was found to be consistent with previously described activating *MET* gene fusions, involving the intracellular domain of *MET* (with an intact kinase domain) fused at its amino terminus with a dimerization motif such as a coiled-coil domain.[29-31] In the described case, the chimeric transcript retains an intact *MET* kinase domain and *RDX* contributes a coiled-coil domain capable of oligomerization. A second *MET* fusion was also detected in the same patient. This fusion involved exons 1-11 of *MET* as the 5′ partner of the chimeric transcript fused to the 5′ end of exon 4 of the *ST7* gene. This second fusion does not retain the *MET* kinase domain, and thus, may be a reciprocal fusion with the first fusion, *RDX-MET*, serving as the oncogenic driver.

Among the *KRAS*^{WT} subset of MCC100, there was also a rearrangement of *FGFR2* at intron 17 that was not categorized as a fusion but was predicted to be activating as a result of loss of the 3′ untranslated region (UTR) of *FGFR2*.[21,32,33]

Validation in Independent Data Sets

Among the AACR GENIE cohort of 1,252 patients with unique pancreatic adenocarcinoma, 92% (n = 1,155) were *KRAS*^{MUT}. Targetable oncogene fusions were identified in 19% (n = 18) of *KRAS*^{WT} cancers (Fig 3) compared with < 1% (n = 4) of *KRAS*^{MUT} cancers ($P < .0001$). One of the four *KRAS*^{MUT} cancers with fusions identified harbored an atypical *KRAS* alteration (KRAS [p. Ile118Leu]) that has not been characterized as activating. Among *KRAS*^{WT} cancers, the identified fusion was the lone mitogenic driver in 89% (16/18) of fusion-positive samples, supporting consideration of these fusions as oncogenic drivers of cellular proliferation. One notable exception was a sample harboring both a *BRAF* fusion and a BRAF V600E mutation.

In the TCGA cohort, *KRAS* mutations were identified in 93% (140/150) of pancreatic adenocarcinoma samples. Targetable oncogene fusions were identified in 20% (n = 2) of *KRAS*^{WT} cancers (Fig 3) compared with < 1% (n = 1) of

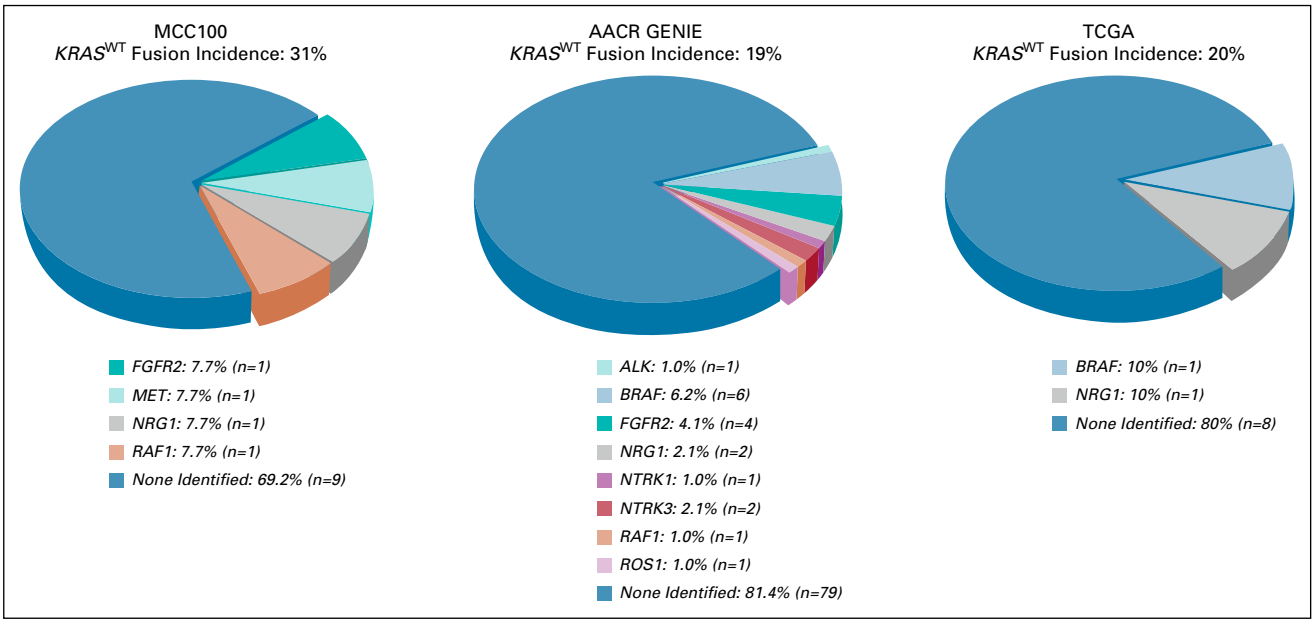

FIG 3. Targetable oncogene fusions identified in *KRAS*^{WT} pancreatic adenocarcinoma in the Moffitt Cancer Center (MCC100) and independent cohorts (AACR GENIE and TCGA). Targetable fusions were reported across all three cohorts at an incidence of at least 19% among *KRAS*^{WT} pancreatic adenocarcinoma patients.

KRAS^{MUT} cancers (P = .0116). Among *KRAS*^{WT} cancers, the identified fusion was the lone mitogenic driver in both of the fusion-positive samples.

Targeted Treatment for Oncogene Fusions in *KRAS*^{WT} Pancreatic Adenocarcinoma

Four cases of *KRAS*^{WT} pancreatic adenocarcinomas with targetable gene fusions (n = 3) or structural rearrangements (n = 1) in MCC100 received targeted treatment on the basis of the recommendations of the molecular tumor board at MCC.[11]

Patient Case #34: *PDZRN3-RAF1*

An 81-year-old male with pancreatic adenocarcinoma presented with a pancreatic head mass and multiple liver metastases. He was treated with gemcitabine plus nab-paclitaxel for 11 months. At progression, targeted NGS (Moffitt STAR) was performed, which identified a *PDZRN3-RAF1* fusion. Treatment with fluorouracil and leucovorin was initiated as second-line therapy, but after 5 months cancer antigen (CA) 19-9 continued to rise and chemotherapy was stopped. On the basis of prior case reports describing responses to MEK inhibition (MEKi) in *RAF1* fusion-positive patients,[26,34,35] targeted therapy with trametinib (MEKi) was initiated at a dose of 2 mg daily. Treatment with trametinib was discontinued after 3 weeks as a result of the development of a left gluteal hematoma after a fall. Comparison of pre- and post-trametinib computed tomography (CT) scans revealed a decrease in the size of the primary mass in the pancreatic head (decreasing from 2.9 × 5.2 cm to 2.4 × 3.9 cm). However, an increase in the size of upper abdominal nodes and liver lesions were observed, including a right hepatic lobe lesion that increased from 3.6 cm to 4.2 cm. The patient's condition continued to decline, and 2 weeks later he was transitioned to hospice care.

Patient Case #82: *ATP1B1-NRG1*

A 56-year-old female, who was initially diagnosed at 50 years of age, presented with recurrent metastatic pancreatic adenocarcinoma. She previously underwent four resections and five lines of chemotherapy, including most recently HIPEC with mitomycin-C. Following debulking and HIPEC, CA 19-9 continued to rise with imaging suspicious for recurrence. Targeted NGS (Moffitt STAR) was performed, with an *ATP1B1-NRG1* fusion identified. On the basis of the described clinical benefit of afatinib in prior case series of *NRG1* fusion-positive cases,[7,8] the patient was started on treatment with afatinib 40 mg daily. She received treatment for approximately 2 weeks before the medication was temporarily held as a result of the development of an acneiform rash that resolved with clindamycin gel and a break from treatment. Her subsequent CT scans showed stable disease and the decision was made to restart afatinib at a reduced dose of 30 mg daily, which she tolerated well. Unfortunately, at her follow-up scans 4 months after initiating treatment with afatinib, she had progressed with new liver lesions.

Patient Case #73: *RDX-MET*

An 80-year-old male with pancreatic adenocarcinoma was diagnosed at 77 years of age. He underwent a partial pancreatectomy and completed 6 months of adjuvant gemcitabine plus capecitabine. Four months later, a peritoneal metastasis was found and treated with gemcitabine plus nab-paclitaxel. CT scans 2 months later showed

progressive disease and rising CA 19-9. At this time, NGS (Moffitt STAR) identified a novel *RDX-MET* fusion. Subsequent CT scans showed further progression with CA 19-9 continuing to rise to a zenith of 17,406 U/mL, and treatment was initiated with the c-MET inhibitor, crizotinib, on the basis of the identified *MET* fusion. After 2 weeks of the targeted therapy, CA 19-9 had decreased to 7,752 U/mL. CT scans after 2 months of treatment with crizotinib demonstrated resolution of peritoneal disease in parallel to continued decline in CA 19-9 down to 123 U/mL. At approximately 7 months of treatment, a complete response was demonstrated on positron emission tomography and CT with normalization of CA 19-9 down to 32.7 U/mL. The response is ongoing now at > 12 months of treatment with crizotinib (Fig 4).

Patient Case #53: *FGFR2* Rearrangement (Intron 17)

A 48-year-old female with metastatic pancreatic adenocarcinoma was diagnosed after work-up for severe abdominal pain and new-onset jaundice identified a mass in the pancreatic head. She was initially treated with FOLFIRINOX (5FU, leucovorin, irinotecan, and oxaliplatin), but treatment was switched to maintenance FOLFIRI (5FU, leucovorin, and irinotecan) as a result of toxicity after 6 months. Subsequent CT scans showed disease progression with enlargement of liver lesions and pancreatic lesion. On the basis of her NGS results (FoundationOne CDx), which identified an *FGFR2* rearrangement, treatment with erdafitinib was initiated. Follow-up CT scans at 2 months demonstrated a partial response and she has continued on treatment (Fig 5).

DISCUSSION

It has been previously reported that alternative oncogenic drivers may be present in pancreatic cancers lacking a *KRAS* oncogene mutation; data from the three cohorts described here (MCC100, AACR GENIE, and TCGA) corroborate this finding. Among MCC100, targetable oncogene fusions were identified in 31% of *KRAS*^{WT} pancreatic adenocarcinomas and this enrichment for targetable fusions among *KRAS*^{WT} cases was validated through the independent AACR GENIE and TCGA cohorts. The lowest incidence of targetable fusions identified was 19% among any of the three analyzed cohorts. Across the three cohorts, fusions were identified in *ALK, BRAF, FGFR2, MET, NRG1, NTRK1, NTRK3, RAF1*, and *ROS1* in the setting of *KRAS*^{WT} pancreatic adenocarcinoma. Other studies have also described fusions in *EGFR*, *ERBB4*, *FGFR3*, and *RET*.[36] Recent studies incorporating RNA sequencing (RNA-seq) provide additional confirmation of our finding of targetable gene fusions in approximately one of five *KRAS*^{WT} pancreatic cancers.[37] This enrichment for targetable fusions in *KRAS*^{WT} cases suggests that the identification of *KRAS*^{WT} status should trigger a dedicated search for

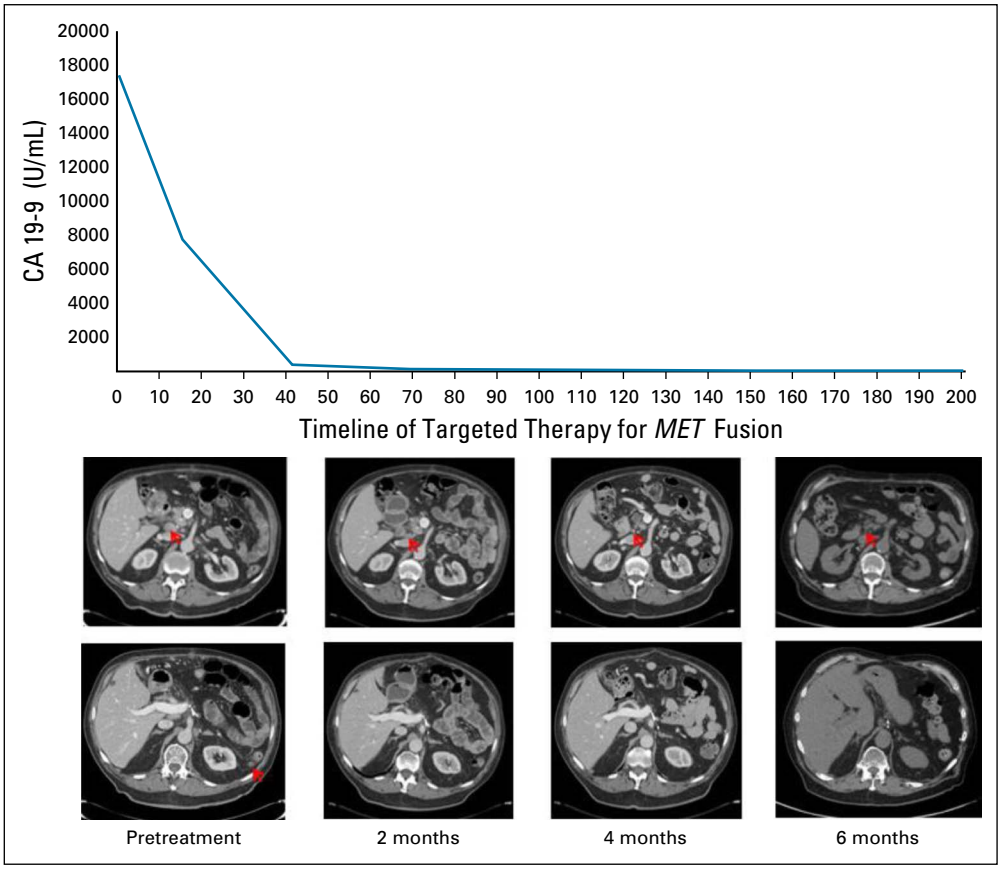

FIG 4. Response to MET-targeted treatment with crizotinib in *KRAS*^{WT} pancreatic adenocarcinoma. Top: scans demonstrating the resolution of peritoneal disease in the *RDX-MET* fusion patient treated with crizotinib. Bottom: schematic of the patient's CA 19-9 decline from a zenith of 17,406 U/mL down to 33 U/mL.

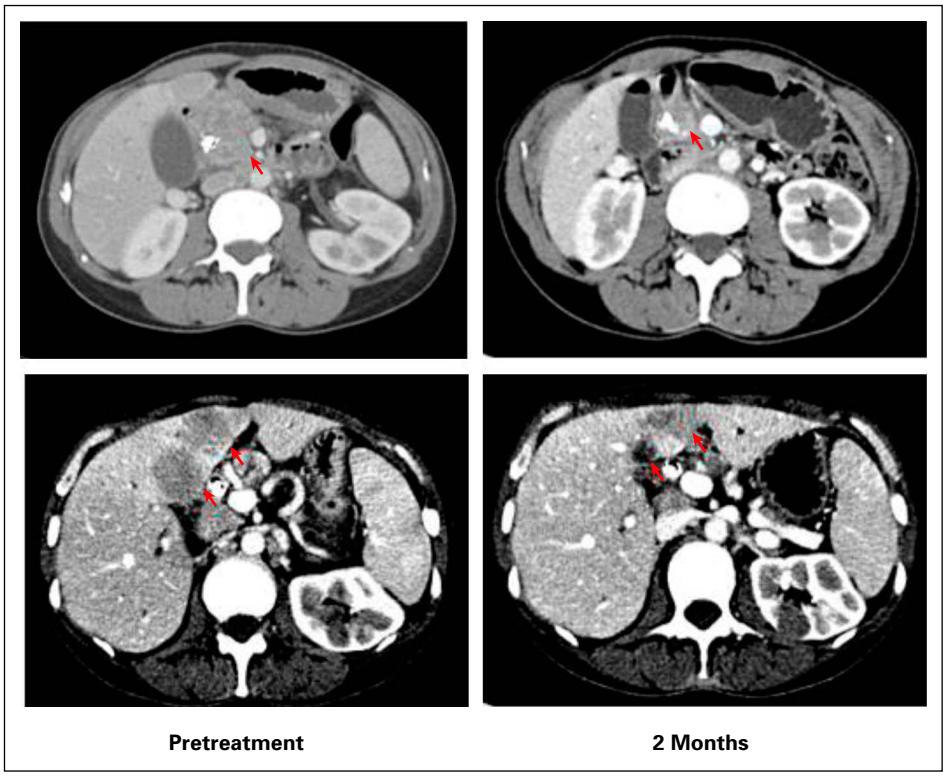

FIG 5. Partial response observed at 2 months in an *FGFR2*-rearranged case treated with FGFR-targeted treatment with erdafitinib.

targetable fusions or rearrangements in patients who would be candidates for such targeted therapies.

In this study, clinical correlation of response to targeted therapy is described. Notable among these is a novel *RDX-MET* fusion in which treatment with crizotinib resulted in an ongoing complete response. *MET* oncogene fusions responsive to targeted therapy have been identified in NSCLC and primary brain tumors.[29,30,38,39] Durable responses to targeted treatment with crizotinib have been described previously in the setting of *MET* fusion-positive NSCLC, with responses ranging from 8 months to ongoing at over a year of targeted treatment.[29,30,38] To the best of our knowledge, this is the first report of a *MET* fusion-positive pancreatic adenocarcinoma that has been treated with *MET*-targeted therapy. Additionally, a second *MET* fusion-positive pancreatic cancer was identified recently in another cohort, suggesting that this may be a rare, but recurrent, feature of $KRAS^{WT}$ pancreatic cancers.[37] The incidence of *MET* fusions in pancreatic adenocarcinoma remains unknown, but improved fusion detection with RNA-seq may reveal additional cases with targetable *MET* fusions.[40-42]

To provide meaningful treatment advances, prospective studies are needed to identify the optimal method of targeted treatment for each of oncogene fusions in $KRAS^{WT}$ pancreatic adenocarcinoma. With the growing knowledge of the gene fusions present, it may become more feasible to open umbrella trials with targeted therapy specific for each of the oncogene fusions known to be present in $KRAS^{WT}$ pancreatic adenocarcinoma. This would allow for more patients to receive treatment and a more robust assessment of response to targeted treatment.

In the MCC cohort, two fusions were identified with RNA-seq (*NRG1* and *MET*) that would not have been detected by many DNA sequencing (DNA-seq) assays as a result of technical limitations. DNA-seq is capable of identifying fusions that occur at recurrent breakpoints with high sensitivity,[41] but is limited in interrogating fusions in genes with large introns (eg, *NRG1*) or those occur outside a common intronic breakpoint (eg, *RDX-MET*).[40,41,43] These inherent limitations of DNA-seq can be overcome with RNA-seq, as only the coding exons are targeted with the introns already spliced out.[40-42]

This study has limitations. Multiple assays were used, including some that used only DNA for fusion detection. Consequently, we are able to confidently report that targetable fusions are present in $\geq$ 19% of $KRAS^{WT}$ cases, but additional studies using RNA-seq for all $KRAS^{WT}$ cases would be warranted to confirm the respective incidence of each of the targetable fusions identified. A second limitation is that *FGFR2* fusions are well described in other pancreaticobiliary malignancies such as intrahepatic cholangiocarcinoma, suggesting that patients with altered *FGFR2* in our cohort may instead be cholangiocarcinoma.[32,44] However, *FGFR2* fusions have been reported in other large pancreatic cancer studies,[36,37] and an additional pathology and radiology review validated the diagnosis.[36,37]

The clinical utility of NGS for pancreatic cancer has advanced over the last 5 years, and the National

Comprehensive Cancer Network guidelines now recommend tumor or somatic gene profiling for patients with locally advanced or metastatic disease who are candidates for anticancer therapy.[45] Platinum-based chemotherapy or PARP inhibitors can provide meaningful clinical benefit for patients with germline or somatic alterations in homologous recombination repair genes such as *BRCA1*, *BRCA2*, and *PALB2*.[46,47] Microsatellite instability is relatively rare in pancreatic cancer (< 1%), but these rare cases can experience durable responses with immune checkpoint blockade.[48] *ERBB2* (HER2) amplification has been identified in approximately 3% of pancreatic cancers and has been identified in both *KRAS*^{WT} and *KRAS*^{MUT} tumors (approximately 3% and approximately 2%, respectively).[36] HER2-targeted approaches have not been successful thus far in pancreatic cancer,[49] but assessment of *KRAS* status may be important for future clinical trials (as has been seen in colon cancer).[50] The development of novel HER2-targeted agents may also assist with the realization of clinical benefit in this population.[51,52] In the setting of *KRAS*^{WT} tumors, there is an enrichment for *BRAF* mutations (V600E: approximately 3% and in-frame insertions or deletions: approximately 3%) with responses to targeted treatment described[6,36,37,53] and a diverse group of oncogenic fusions including *ALK, BRAF, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK3, RAF1*, *RET,* and *ROS1* (approximately 20%). Expanded access to somatic testing in appropriate patients will help optimize the treatment of each of these molecular subsets in pancreatic cancer and will accelerate the development of new treatments for patients with advanced or metastatic disease.

This report and others have shown that some patients with pancreatic adenocarcinoma treated on the basis of identified fusions can derive substantial clinical benefit.[7-10,54-56] This is an important finding in a disease where clinical outcomes in the advanced stages remain poor. Additionally, the incidence of *MET* fusions in pancreatic adenocarcinoma remains unknown as a result of limitations of many assays and future studies may consider incorporating RNA-based testing for *KRAS*^{WT} cancers with inclusion of coverage of the *MET* oncogene. Future clinical investigations may reveal the optimal method for targeting each of the fusions reported among *KRAS*^{WT} pancreatic adenocarcinoma to offer more effective therapeutic options for patients in need.

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SUPPORT

Supported in part by the Biostatistics and Bioinformatics Shared Resource at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30-CA076292); a State of Florida Endowed Chair in Cancer Research; and by funds provided by Moffitt Cancer Center in pursuit of its mission "To contribute to the prevention and cure of cancer." T.C. Knepper is supported by the NCI of the NIH under an LRP award.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Stock and Other Ownership Interests: Ions Pharmaceuticals
Honoraria: Illumina, Excel CME
Research Funding: Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb, Excel CME, Illumina

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Patents, Royalties, Other Intellectual Property: Patent application: Large Data Set Negative Information Storage Model.

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Stock and Other Ownership Interests: Cancer Genetics, Interpares Biomedicine, Clariifi, Pharmazam
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Patents, Royalties, Other Intellectual Property: U.S. Application No. 15/780,799, based on International Application No. PCT/US2016/065763, titled "Polymeric Drug Delivery Systems For Treatment of Disease," by Chun Li et al.; in the Name of Board of Regents, The University of Texas System

No other potential conflicts of interest were reported.

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ACKNOWLEDGMENT

This work has been supported in part by the Biostatistics and Bioinformatics Shared Resource at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30-CA076292). T.C. Knepper is supported by the NCI of the NIH under an LRP award.

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