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Original Research

Chemotherapy-free treatment targeting fusions and driver mutations in *KRAS* wild-type pancreatic ductal adenocarcinoma, a case series

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Abstract

Background: *KRAS* wild-type (WT) pancreatic ductal adenocarcinoma (PDAC) represents a distinct entity with unique biology. The therapeutic impact of matched targeted therapy in these patients in a real-world setting, to date, is less established.

Objectives: The aim of our study was to review our institutional database to identify the prevalence of actionable genomic alterations in patients with *KRAS*-WT tumors and to evaluate the therapeutic impact of matched targeted therapy in these patients.

Design: We reviewed electronic medical records of patients with *KRAS-WT* PDAC and advanced disease ($n = 14$) who underwent clinical-grade tissue ± liquid next-generation sequencing (315–648 genes for tissue) between years 2015 and 2021.

Methods: Demographic and disease characteristics were summarized using descriptive parameters. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method.

Results: Of 236 PDAC patients, 14 had advanced/metastatic disease with *KRAS-WT* tumors. Median age at diagnosis was 66 years. There was a high frequency of potentially actionable genomic alterations, including three (21%) with *BRAF* alterations, two (14%) with fusions [*RET-PCM1* and *FGFR2-POC1B* ($N = 1$ each)]; and one with a druggable *EGFR* (*EGFR* E746_A755delISERD) variant; two other patients had an *STK11* and a *MUTYH* alteration. Five patients were treated with matched targeted therapy, with three having durable benefit: (i) erlotinib for *EGFR*-altered tumor, followed by osimertinib/capmatinib when *MET* amplification emerged (first-line therapy); (ii) pralsetinib for *RET* fusion (fifth line); and (iii) dabrafenib/trametinib for *BRAF* N486_P490del (third line). Duration of time on chemotherapy-free matched targeted therapy for these patients was 17+, 11, and 18+ months, respectively.

Conclusion: Sustained therapeutic benefit can be achieved in a real-world setting in a subset of patients with advanced/metastatic *KRAS-WT* PDAC treated with chemotherapy-free matched targeted agents. Prospective studies are warranted.

Keywords: case series, KRAS protein, molecular targeted therapy, oncogene fusion, pancreatic neoplasms

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) most often presents with extra-pancreatic metastatic disease, and chemotherapy remains the mainstay of therapy.[1–3] Chemotherapy response is usually measured in months, and therefore, there is

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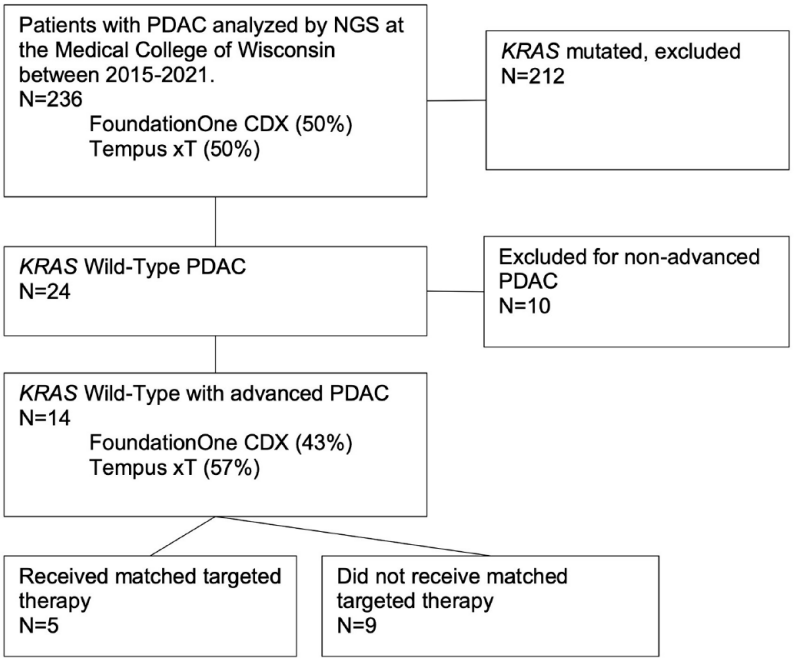


Figure 1. Flow diagram. Foundation Medicine and Tempus are the vendors for the NGS.
NGS, next-generation sequencing; PDAC, pancreatic ductal adenocarcinoma.

intense interest in the development of less toxic targeted therapies as tumor acquisition, and next-generation sequencing (NGS) have become more widely adopted.[1,4]

PDAC is a complex disease with an immunosuppressive microenvironment that supports cancer growth and a unique tumor stroma that hampers drug delivery.[5] Furthermore, this disease is molecularly complex, involving a network of genetic mutations, epigenetic alterations, and chromosomal variants including, but not limited to, mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* genes.[6] The *KRAS* oncogene has been found to be a master driver in PDAC, mutated in over 90% of PDAC tumors.[7,8] The non-negligible remaining 10% of patients with *KRAS* wild-type (WT) PDAC tumors have become an attractive landscape for generating novel therapies. The genomic landscape of *KRAS*-WT PDAC tumors has been characterized previously.[8–11] Recurrent genomic alterations in *BRAF*, *GNAS*, *EGFR*, *FGFR*, *ALK*, *RET*, *NTRK*, *ROS1*, *NRG1*, and *RAF1* are among the most frequent driver alterations in *KRAS*-WT PDAC tumors. The therapeutic impact of matched targeted therapy in these patients in a real-world setting, to date, is less established.

In the current study, we searched our institutional database at the Medical College of Wisconsin (MCW) for patients diagnosed with advanced/metastatic PDAC, further categorizing a subgroup of patients with *KRAS*-WT PDAC. For those patients diagnosed with *KRAS*-WT PDAC, we characterized genomic alterations detected by comprehensive genomic profiling and studied the clinical benefit of matched targeted therapy. Our real-world results demonstrate the high frequency of actionable alterations in patients with *KRAS*-WT PDAC tumors and suggest clinical benefit for matched targeted therapy.

Patients and methods

Patients

Figure 1 represents the flow diagram for selection of patients in this study. We reviewed the electronic medical records of patients with advanced *KRAS*-WT PDAC ($n=14$) who had undergone NGS utilizing clinical-grade tests done by Foundation One[12] (FoundationOne CDx; https://www.foundationmedicine.com/test/foundation-one-cdx) or Tempus[13] (Tempus xT; https://www.tempus.com) between 1 January 2015 to 5 March 2021 at our institution. Cut-off date for outcome

evaluation was 12 October 2022. Notably, since 2019, virtually all patients at our institution with metastatic PDAC have had NGS performed. As genetic testing and genomic profiling are standard of care in PDAC and easily accessible in the USA, these modalities were covered by insurance ± financial assistance from the NGS vendor(s) and did not pose a major financial challenge for the involved patients in this study. None of the involved patients in this study had ampullary or distal bile duct adenocarcinoma as a potential clinical diagnosis. All patients on treatment had regular weekly or biweekly clinical and lab evaluations with available documentation for assessment of adherence and tolerance. All 14 patients had NGS panel DNA sequencing of formalin-fixed, paraffin-embedded tumor samples.[12,13] Three out of 14 (21%) had whole transcriptomic RNA sequencing (RNA-seq) performed, all through Tempus.[13] Source of tissue in seven (50%) patients was primary tumor [surgical samples ($N=4$), fine needle aspiration ($N=2$), bile duct stricture brushing ($N=1$)], and in the other seven patients (50%) was metastatic lesion [liver ($N=5$), peritoneum ($N=1$), peritoneum/ovary ($N=1$)]. Liquid biopsy NGS was done in a subset of patients per treating physicians' discretion, mostly for evaluation of treatment response. As part of institutional standard, all patients were referred to genetic counselor. Nine (64%) had germline profiling done, and 5 (36%) decided against testing (for more details, please refer to the NGS analyses section below and Supplemental Table 1).

NGS analyses

Both FoundationOne CDX and Tempus xT are clinical-grade sequencing; the panel consisted of 324 and 648 genes, respectively. Details of sequencing methodology have been previously published.[12,13] Whole transcriptomic evaluation was performed for tumor tissue with adequate quality and cellularity in 3/14 patients.[13] Liquid biopsy (blood) NGS was done utilizing clinical-grade test done by Guardant Health (Guardant360 CDX; https://guardant360cdx.com/wp-content/uploads/guardant360-cdx-technical-information.pdf) which examined 55 genes; the method has been previously reported in detail.[14–16] Germline sequencing was evaluated by clinical-grade custom multi-gene hereditary cancers panels through Invitae (https://www.invitae.com/en/providers/test-catalog/oncology), which examined 84 genes.

Patient characteristic and outcome analyses

Demographic and disease characteristics were summarized using descriptive parameters. Overall survival (OS) was measured in two ways: (i) from the diagnosis of advanced/metastatic disease and (ii) from the initiation of targeted therapy for advanced metastatic disease to death or last follow-up. Patients still alive at the last follow-up were censored at that time. Progression-free survival (PFS) was measured from the date of initiation of targeted therapy to the date of progression, death, or last follow-up. OS and PFS were estimated using the Kaplan–Meier method. Analyses were performed using R 4.2.2 (R Foundation for Computing, Vienna, Austria). The reporting of this study conforms to the CARE (CAse REport) guideline.[17] The completed checklist from the relevant guideline is submitted as a Supplemental File.

Ethics statement

This study was performed under the master protocol, Profile Related Evidence Determining Individualized Cancer Therapy, MCW PREDICT (NCT05802069), and was carried out in conformity with the regulations of the MCW Institutional Review Board and any experimental interventions for which patients provided consent.

Results

Baseline characteristics

Clinical-grade NGS was performed on the tumors of 236 patients with PDAC; 24 (10%) were *KRAS*-WT, and 14 of these patients had advanced/metastatic disease (Figure 1) and were included in this report. Of these 14 patients, 8 (57%) had metastatic disease at or shortly after diagnosis, and 6 (43%) developed metachronous recurrence after multimodality treatment for localized disease. Median age at diagnosis of advanced disease was 66 years, and 8 (57%) of the 14 patients were female. The two most common metastatic sites were liver ($N=7$, 50%) and lung ($N=4$, 29%). Median carbohydrate antigen 19-9 (CA19-9) at diagnosis of advanced/metastatic disease was 272 U/ml (upper limit of normal ⩽ 35) (Table 1).

Genomic alterations

Supplemental Table 1 represents the genomic alterations in the 14 patients with advanced/

Table 1. Baseline and disease characteristics of patients with *KRAS*-WT advanced PDAC.

Patient and disease characteristics	*KRAS* WT[a], *N* = 14	No matched targeted therapy[a], *N* = 9, %	Matched targeted therapy[a], *N* = 5, %	*p* Value
Sex				>0.99[b]
Male	6 (43%)	4 (44%)	2 (40%)	
Female	8 (57%)	5 (56%)	3 (60%)	
Age at diagnosis, years (range)	66 (52–71)	70 (34–80)	55 (44–65)	0.071[c]
CA19-9 at diagnosis (U/ml)	272 (76–577)	433 (36–2564)	99 (6–310)	0.083[d]
Advanced disease diagnosis year	2019 (2014–2021)	2019 (2014–2021)	2018 (2017–2021)	>0.99[c]
Stage at diagnosis				0.41[b]
Localized	6 (43%)	5 (56%)	1 (20%)	
Locally advanced	3 (21%)	2 (22%)	1 (20%)	
Metastatic	5 (36%)	2 (22%)	3 (60%)	
Tumor cellularity		20 (10–40)[e]	70 (70–70)[e]	0.059[c]
Tumor location				>0.99[b]
Head	10 (71%)	6 (67%)	4 (80%)	
Body	1 (7%)	1 (11%)	0	
Tail	3 (21%)	2 (22%)	1 (20%)	
Organ system/location of metastasis				
Liver	7 (50%)	4 (44%)	3 (60%)	>0.99[b]
Lung	4 (29%)	4 (44%)	0	0.22[b]
Peritoneum	2 (14%)	1 (11%)	1 (20%)	>0.99[b]
Bone	1 (7.1%)	1 (11%)	0	>0.99[b]
Lymph	1 (7.1%)	1 (11%)	0	>0.99[b]
Alterations that may activate the MAPK pathway[f]	5 (36%)	4 (44%)	1 (20%)	>0.58[b]

[a]*N* (%); median (minimum, maximum).
[b]Fisher's exact test.
[c]Wilcoxon rank sum test.
[d]Wilcoxon rank sum exact test.
[e]Cellularity was unknown in six samples (three in each).
[f]Both *SMAD4* and *BRAF* alterations can activate the MAPK pathway[18,19,20]
MAPK, mitogen-activated protein kinase; PDAC, pancreatic ductal adenocarcinoma; WT, wild type.

metastatic *KRAS*-WT PDAC. Two of the patients had no reported tissue alterations. The most common alterations were in the following genes: *TP53* (43%; 6/14), *CDKN2A* (36%; 5/14), *ARID1A* (28%; 4/14), and *SMAD4* (21%; 3/14); all common alterations among patients with PDAC and mutated *KRAS*. Of the potentially actionable genomic alterations, several alterations were of particular interest: three (21%) had *BRAF* alterations [*BRAF* V600E (*N* = 1) and atypical, non-*BRAF* V600E (*N* = 2)]; two (14%) had fusions [*RET-PCM1* and *FGFR2-POC1B* (*N* = 1

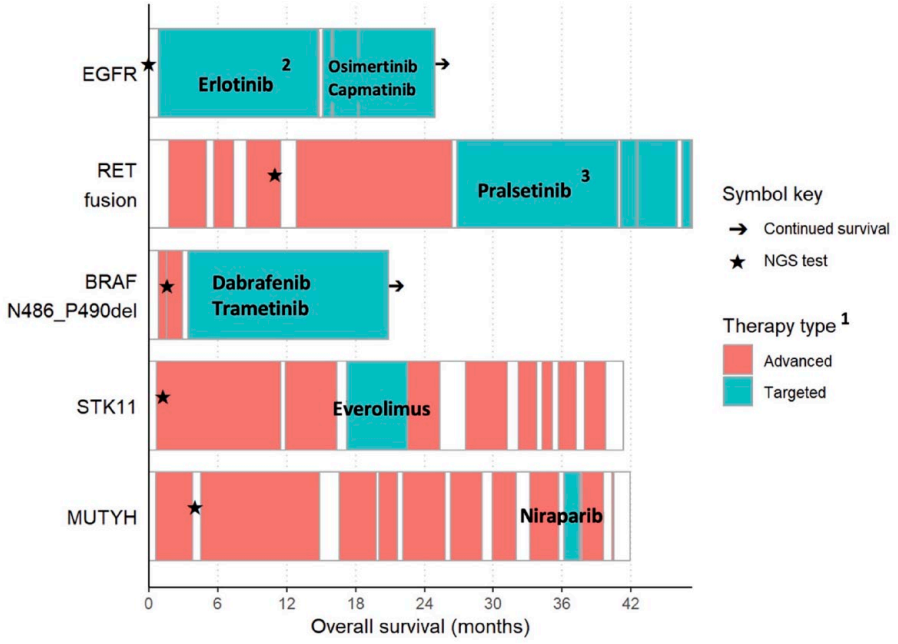


Figure 2. Swimmer plot of survival of five patients treated with matched targeted therapy.
[1]Blue represents treatments, including matched targeted therapy. Red represents treatments for advanced PDAC, not including matched targeted therapy.
[2]For the patient with *EGFR* E746_A755delinsISERD variant, erlotinib was given with gemcitabine for the first 4 months and then switched to erlotinib alone due to emergence of cytopenia for another 7 months. Upon progression, due to emergence of *MET* amplification, osimertinib plus capmatinib was started, and treatment is ongoing (10+ months).
[3]For the patient with *RET* fusion, pralsetinib alone was given for 14 months (progression after 11 months), followed by investigational agent (HSP90 binding molecule to an SN-38 cytotoxic payload) and niraparib (PARP inhibitor) for 4 weeks with fast progression. This was followed by pralsetinib plus cisplatin for 3.5 months.

each)]; and one had an *EGFR* alteration (*EGFR p.*E746_A755delinsISERD). Germline results were available in 9 (64%) of 14 patients; 3 had pathogenic germline alterations [*ATM* ($N=1$), *STK11* ($N=1$), *MUTYH* ($N=1$)].

Treatment course

Overall, 5 (36%) of 14 patients received matched targeted therapy (see Figure 2 for treatment course of these five patients and Table 2 for details of genomic alterations in these five patients. Supplemental Table 2 represents all treatment lines for metastatic/advanced disease for these patients). Somatic alterations and corresponding treatments of particular interest included: *EGFR* exon 19 deletion (*p.*E746_A755delinsISERD variant) treated with erlotinib[21–23] followed by osimertinib[24] together with the MET inhibitor capmatinib therapy[25] (the latter because the patient showed emergence of *MET* amplification on liquid biopsy[26,27]) ($N=1$); *RET* fusion treated with the RET inhibitor pralsetinib[28,29] ($N=1$); and *BRAF* N486_P490del, treated with dabrafenib and trametinib[18,30] ($N=1$). In addition, one patient received everolimus (mammalian target of rapamycin (mTOR) inhibitor) based on the presence of a germline pathogenic *STK11* K84* variant,[31,32] and one patient received niraparib (a Poly (ADP-ribose) polymerase (PARP) inhibitor) based on the presence of germline pathogenic *MUTYH* G396D variant.[33] Three patients with potentially druggable alterations did not receive matched targeted therapy, per treating physicians' choice: *BRAF* V600E variant (two patients) and an *FGFR2* fusion (one patient). 'Detailed clinical course of patients who received matched targeted therapy' is provided in the Supplemental Material.

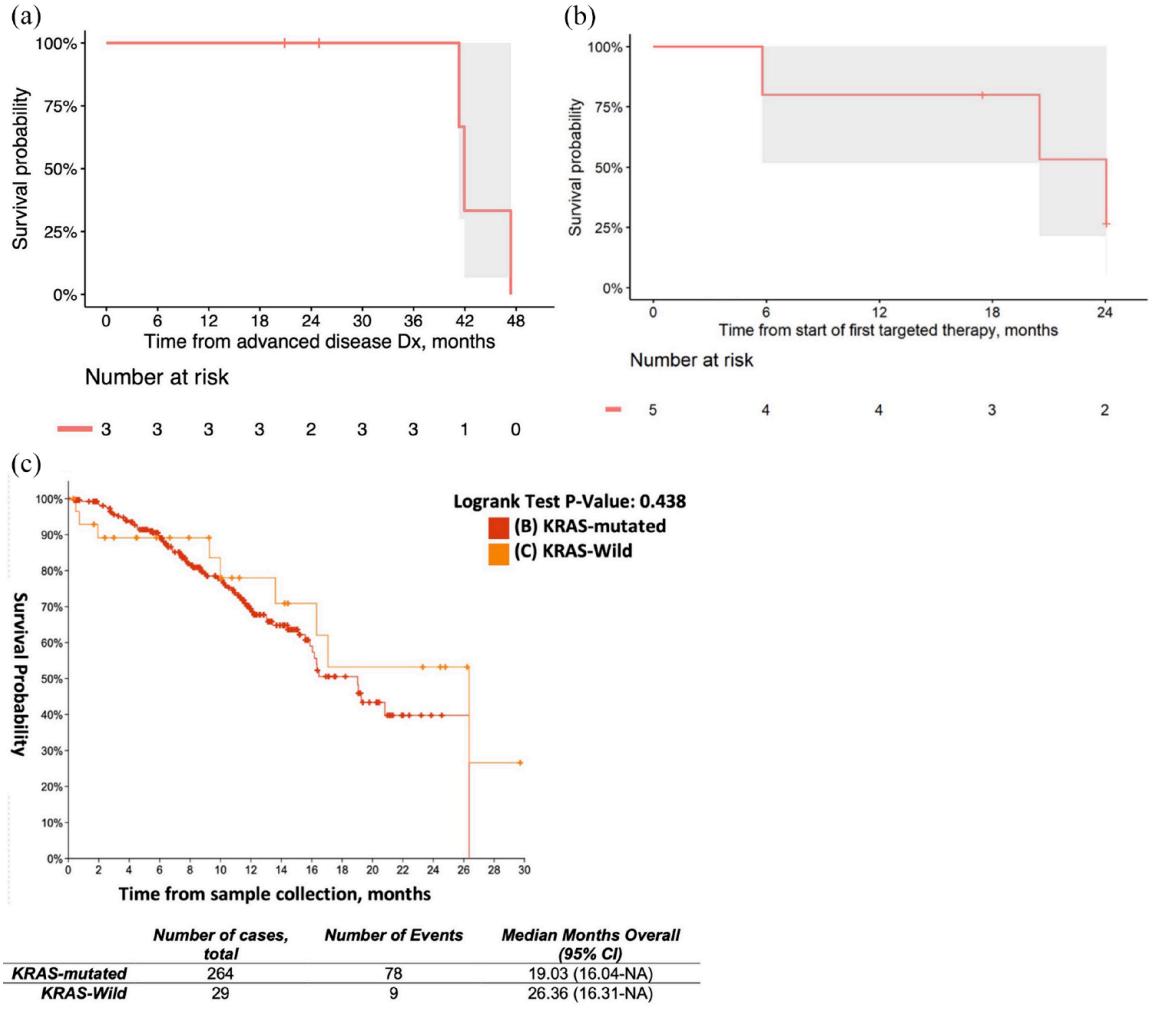
Survival outcome

Among the 14 patients with advanced *KRAS*-WT PDAC, median survival from the date of diagnosis of advanced disease was 28 months. Median OS for the subgroup of patients treated with matched targeted therapy ($n=5$) from diagnoses of advanced/metastatic disease was 42 months

Table 2. Detail of genomic alterations in five patients treated with matched targeted therapy.

Patient ID	Gene	Variant description	VAF (%)	Type consequence	Therapeutic level of evidence[a]	Tissue source	Tumor cellularity
Patient #1 AC14	*ARID1A*	NM_006015.6: c.3219G>A (p.Trp1073*)	21.6	Nonsense LOF	Tier II Level D	Pancreas FNA	70%
	CDKN2A	NM_00077.5: c.47_50delTGGC (p.Leu16fs)	25.6	Frameshift LOF	Tier II Level D		
	EGFR	NM_005228.5: c.2236_2264del insATCTCCGAAAGAGA (p.Glu746_ Ala755delinsIleSerGluArgAsp)	23.3	indel (exon19) GOF	**Tier II Level C**		
	TP53	NM_000546.6: c.584T>C (p.Ile195Thr)	20.5	Missense variant LOF	Tier II Level C		
Patient #2 AC8	*ATM*	NM_000051.4: c.3712_3716del (p.Leu1238fs*6)	NA	Frameshift LOF	Tier II Level C	Liver Core	NA
	RET	PCM1-RET	NA	Fusion	**Tier I[b] Level A**		
	RNF43	NM_017763.6: c.394C>T (p.Arg132*)	NA	Nonsense LOF	NA		
Patient #3 AC13	***BRAF***	NM_004333.6: c.1457_1471del (p.Asn486_Pro490del)	28.2	indel GOF	**Tier II Level C**	Liver Core	70%
	CDKN2A	NM_000077.5: c.56_87del (p.Ala19fs)	30.2	Frameshift LOF	Tier II Level D		
	TP53	NM_000546.6: c.614A>G (p.Tyr205Cys)	56.3	Missense variant LOF	Tier II Level C		
Patient #4 AC9	*ARID1A*	NM_006015.6: c.4153G>T (p.Glu1385*)	NA	Nonsense LOF	Tier II Level D	Peritoneum/ ovary Surgical	NA
	CDKN2A	NM_000077 Rearrangement intron 1	NA	Nonsense LOF	Tier II Level D		
	MDM2	Amplification	NA	CNV	NA		
	STK11[c]	NM_000455.5: c.250A>T (p.Lys84*)	NA	Nonsense LOF	**Tier II Level D**		
Patient #5 AC10	***MUTYH***[c]	NM_012222.3: c.1187G4A (p.Gly396Asp)	NA	Missense variant LOF	**Tier II Level D**	Pancreas FNA	NA
	NOTCH2	NM_024408.4: c.6909_6910insC (p.Ile2304fs*9)	NA	Nonsense LOF	NA		

Genes that were targeted are in bold and underlined.
[a]Therapeutic level of evidence is obtained from OncoKB[34,35] (https://www.oncokb.org), last accessed 4 February 2024; level of evidence is for pancreatic cancer; therapeutic level of evidence is classified per AMP/ASCO/CAP variant categorization[36]; conversion of levels available at (https://www.oncokb.org/therapeutic-levels#version=AAC).
[b]Level of evidence for pralsetinib is level 3B, for selpercatinib is level 1; notably, the indication is with any *RET* fusion and not the specific *RET* fusion in our patient.
[c]Germline classification based on ClinVar (https://www.ncbi.nlm.nih.gov/clinvar), last accessed 2 February 2024; *STK11* p.Lys82* (Exon 3, heterozygous, pathogenic, associated with Peutz–Jeghers syndrome); *MUTYH* p. Gly396Asp (Exon 13, heterozygous, pathogenic, multiple cancers including *MUTYH*-associated polyposis).
ASCO, American society of clinical oncology; AMP, association for molecular pathology; CAP, college of American pathologists; CNV, copy number variation; Core, core needle biopsy; FNA, fine needle aspiration; GOF, gain of function; LOF, loss of function; NA, not available; VAF, variant allele frequency.



	Number of cases, total	Number of Events	Median Months Overall (95% CI)
KRAS-mutated	264	78	19.03 (16.04-NA)
KRAS-Wild	29	9	26.36 (16.31-NA)

Figure 3. OS of five patients treated with matched targeted therapy. (a) OS from the diagnosis of metastatic/advanced disease. For this analysis, patients were left-truncated at the start of targeted therapy. Gray area is the pointwise 95% confidence interval band. (b) OS from the first targeted therapy. Gray area is the pointwise 95% confidence interval band. (c) Survival of PDAC patients in MSK-IMPACT cohort. MSK-IMPACT patient data was retrieved (10,945 patients). Overall, 384 patients with pancreatic adenocarcinoma were selected. Patients were divided by *KRAS* mutation status into two groups (*KRAS*-WT = 29, *KRAS*-mutated = 264). This analysis included all stages (metastatic and non-metastatic) combined. Survival was analyzed. OS was defined as the time between the procedure date when the tumor specimen was collected, and the date of death or last follow-up. While OS is numerically different, the difference was not statistically significant.
MSK-IMPACT, memorial sloan kettering integrated mutation profiling of actionable cancer targets; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

[Figure 3(a)], and 24 months from the initiation of first matched targeted therapy [Figure 3(b)]. Median PFS for first matched targeted therapy was 11 months. Total duration of time on chemotherapy-free matched targeted therapy for the five patients was 17+, 11, 18+, 5.2, and 1.3 months (Figure 2). Figure 3(c) shows cBioPortal data for PDAC patients (metastatic and non-metastatic combined) from MSK-IMPACT cohort (https://www.cbioportal.org, accessed 8 February 2023). Median OS from the time of tissue collection for *KRAS*-mutated PDAC was not significantly different than that for *KRAS*-WT *PDAC* [19 *versus* 26 months ($p = 0.436$)].

Discussion

This report demonstrates the high frequency of potentially actionable genomic alterations among our 14 patients with advanced *KRAS*-WT PDAC: three (21%) with *BRAF* alterations, two (14%) with fusions [*RET-PCM1* and *FGFR2-POC1B*

($N=1$ each)]; and one (7%) with a druggable *EGFR* variant. All 14 patients with *KRAS*-WT advanced PDAC had a median OS of 28 months from diagnosis of advanced disease, and the median OS among the five patients treated with matched targeted therapy was 42 months [Figure 3(a)]. Although not directly comparable, the median survival from the date of tissue collection of *KRAS-WT* PDAC patients in the cBioPortal database was only 26 months [Figure 3(c)]. Median PFS on matched targeted therapy in our five treated patients was 11 months. Of interest, one patient who had an *EGFR* alteration did well on an erlotinib regimen for 11 months; when progression appeared accompanied by evidence of a *MET* amplification on liquid biopsy, the patient was switched to osimertinib and capmatinib (MET inhibitor) and continued to do well 23+ months from start of EGFR inhibitor-based therapy by the data cut-off of October 2022. Moreover, liquid biopsy showed marked decrease in % ctDNA for the *EGFR* alteration [Figure 4(a) and (b)].

Of the 236 patients with tissue NGS performed in our study, 24 patients had *KRAS*-WT tumors (10.1%). This is in line with 12% reported in Singhi *et al.*[8] study, 10.7% in Philip *et al.*,[9] and 9.2% reported by Singh *et al.*[11] Enrichment of *KRAS*-WT tumors with actionable genomic alterations has been previously reported: *BRAF* alterations (11–13%), and kinase fusions (12–17%), are among the most frequently reported actionable altertions.[8–11] Patient #1 received erlotinib with a response lasting roughly 11 months [Figure 4(a)]. A grade 1 rash was the only notable side effect of this treatment. After progression, response was recaptured by introducing osimertinib and capmatinib when *MET* amplification on liquid biopsy and progression on scans appeared [Figure 4(b)]. Response was ongoing by October 2022, 23+ months from initiation of matched targeted therapy. Patient #2 who was found to have a *RET* fusion, received single agent pralsetinib with benefit for 11 months. Side effects were limited to cytopenia in need of treatment interruption, which did not recur later upon re-initiation of the drug at the same dose. Of the three patients with *BRAF* alterations in our cohort, only one was treated with matched therapy (patient #3). She experienced a prolonged response to the combination of trametinib (MEK inhibitor) and dabrafenib (BRAF inhibitor) lasting 18+ months (ongoing by October 2022) with minimal toxicity [Figure 4(c)]. Non-standard (non-V600E) *BRAF* alterations can respond to MEK inhibitors such as trametinib; the role of combined BRAF/MEK inhibitors *versus* MEK inhibitors alone remains unclear.[18,37] These three patients clearly show the potential for durable response with minimal toxicity in patients with *KRAS*-WT PDAC and actionable genomic alterations when treated with matched targeted therapy.

A recent study by Ben-Ammar *et al.*[38] compared genomic alterations and clinical outcomes of patients with *KRAS*-WT PDAC ($N=54$) to that of *KRAS*-mutated PDAC ($N=288$). Nineteen out of 54 (34%) of *KRAS*-WT tumors, and 46/288 (16%) of patients with *KRAS* mutation had potentially actionable alterations. Actionability was defined per ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). Those with ESCAT I–III were considered actionable (I = ready for routine use, II = Investigational, III = Hypothetical target). Twelve patients with *KRAS*-WT PDAC received molecularly matched targeted therapy for actionable alterations. Of these, by the time of study cut-off, 4/12 had PFS >10 months (microsatellite instability high (MSI-H) receiving immunotherapy ($N=1$), *FGFR2* alteration receiving erdafitinib ($N=1$), V-Raf Murine Sarcoma Viral Oncogene Homolog B (*BRAF*) V600E variant receiving BRAF and MEK targeted inhibitors ($N=1$), *NRG-1* alteration for which treatment was not specified ($N=1$)]. Three patients had PFS < 10 months, but ongoing at the time of data cut-off [*FGFR2* alteration receiving erdafitinib ($N=1$), *RET* fusion receiving selpercatinib ($N=1$), *BRAF* V600E receiving BRAF and MEK inhibitors ($N=1$)]. Our results are in line with this study, showing that targeting *BRAF* alterations and RTK fusions can lead to durable clinical responses in patients with *KRAS*-WT PDAC. Notably, while in patients who were not treated with matched targeted therapy, survival was higher in those with *KRAS*-WT tumors ($p=0.00015$), in the subset of patients treated with matched targeted therapy, there was no survival difference based on *KRAS* mutational status.[38]

KRAS-WT tumors with actionable molecular alterations compromise only a minority of PDAC patients (~5%).[38] These patients, however, are not the only subset of patients that would benefit from targeted therapy. While the prognostic value of pathogenic germline alterations in core homologous recombination repair (HRR) genes and

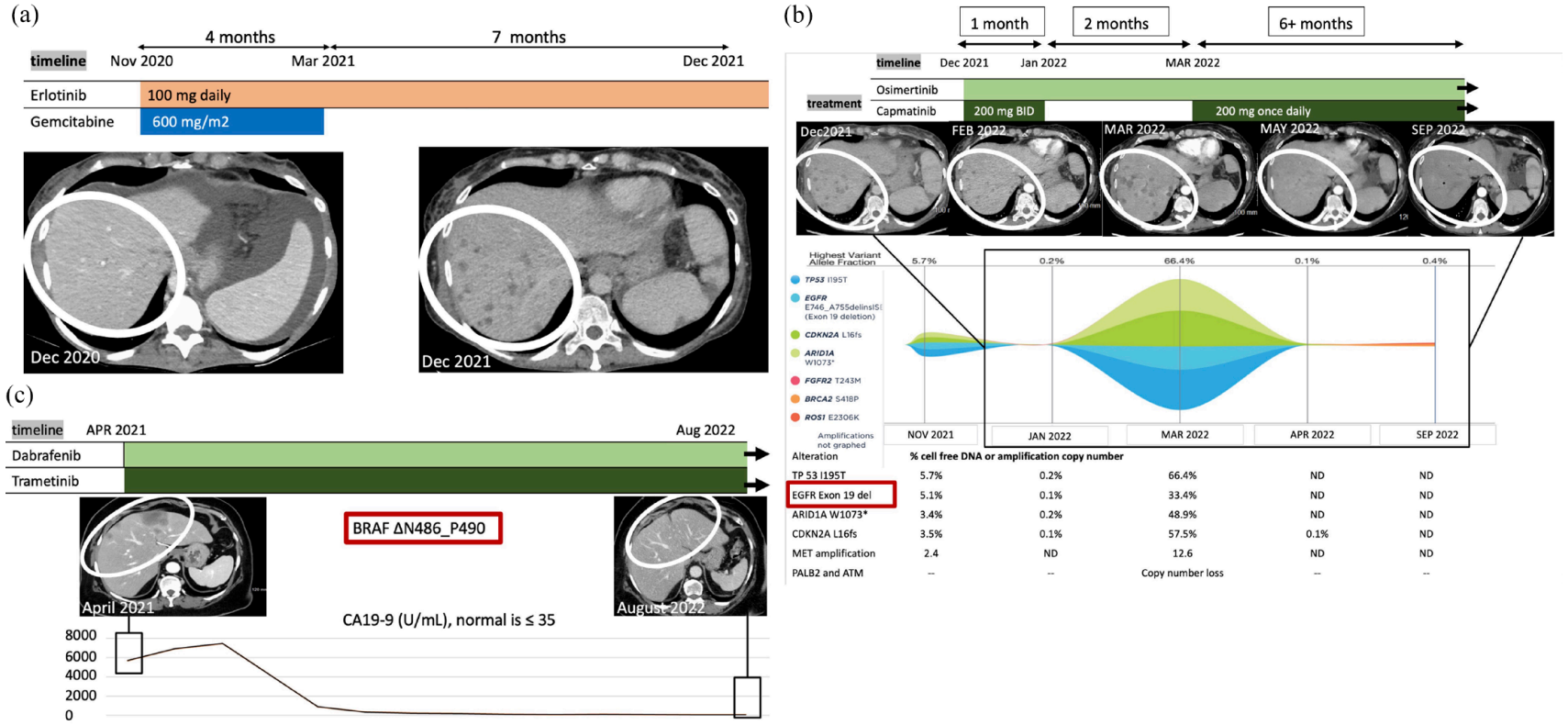


Figure 4. Treatment and outcome represented in patient #1 and patient #3. (a) Forty-six-year-old woman with advanced PDAC with *ARID1A*, *CDKN2A*, *EGFR* E746_A755del insISERD, and *TP53* alterations on tissue NGS (Table 2 and Supplemental Table 1). She was started on gemcitabine plus erlotinib (EGFR inhibitor) with transition to erlotinib alone due to cytopenia; she attained stable disease for 11 months until progression in the liver (Darker spots in the liver, which were absent in December 2020 scan and emerged in December 2021 scan, are metastatic lesions). (b) In December 2021, osimertinib (EGFR inhibitor) and capmatinib (MET inhibitor) were started, the latter due to *MET* amplification on liquid biopsy. Repeat CT scans and ctDNA in January 2022 showed partial response with resolution of *MET* amplification and significant decrease in % cell-free DNA of *EGFR* from 5.1% to 0.1%. Capmatinib was then held from January to March 2022 because of creatinine elevation. Repeat imaging and ctDNA in March 2022 show rapid progression of tumor in the liver [represented by increase in number and size of dark spots (metastatic lesions) in the liver] and rise in ctDNA upon stopping capmatinib, and rapid response with resumption of capmatinib with ongoing response (May and September 2022 scans show disappearance of the metastatic lesions in the liver). Total duration of *EGFR*-based targeted therapy is 23+ months at time of data cut-off; total duration of chemotherapy-free *EGFR*-based targeted therapy is 19+ months. (c) Sixty-four-year-old woman with PDAC and liver metastasis treated with dabrafenib/trametinib in third line due to *BRAF* ΔN486_P490 in-frame deletion. She has continued partial response at ~18+ months after initiation of matched targeted therapy. Imaging at baseline and last follow-up, along with serial CA19-9, shows the prolonged and deep response.

CT, computed tomography; EFGR, epidermal growth factor receptor; MET, MET proto-oncogene, receptor tyrosine kinase; NGS, next-generation sequencing; PDAC, pancreatic ductal adenocarcinoma.

mismatch repair (MMR) genes in patients with PDAC is debated, their role in prediction of response to matched therapy is established.[39] The value of PARP-inhibition is established in patients with PDAC with pathogenic germline variants in core HRR genes such as *BRCA1/2* and *PALB2* (comprising nearly 10% of PDAC cases).[40] Immunotherapy is an option for patients with MMR deficient tumors (~1% of PDAC cases, majority carrying pathogenic germline variants in MMR genes).[41,42] These two groups of patients signify the importance of genetic testing, not only for assessment of risk of cancer in family, but also for search for biomarkers of response to targeted therapy and immunotherapy. There are other subsets of patients with PDAC that would also benefit from molecular tumor board-directed matched therapies, specifically if utilized in earlier lines of cancer treatment.[43–46] Furthermore, with the emergence of KRAS-directed targeted therapies, it is expected that increasingly more patients with PDAC can benefit from genomic profiling-directed therapies.[47] We therefore believe that early and universal tumor profiling and genetic testing, followed by discussion in a molecular tumor board, would be the best pathway to assure each patient would receive the best treatment at any given time. Availability of tissue, availability and affordability of NGS testing, access to accredited molecular tumor board, and access to targeted therapies and clinical trials would, however, limit the practicality and applicability of this approach in different treatment settings and different countries.

Our experience with patient #1 demonstrated several additional clinical observations of potential interest. Foremost, there may be value in the continuation of targeted therapy beyond progression with the addition of further therapies directed against emerging resistant clones, as evaluated by serial ctDNA in the case of our patient.[43,45] In patient #1 with a somatic *EGFR* alteration, this is represented by the addition of capmatinib (MET inhibitor) to osimertinib (EGFR inhibitor) upon emergence of *MET* amplification in ctDNA after treatment with erlotinib. This scenario is similar to that observed in lung cancer,[25,27,48] but has not previously been reported, to our knowledge, in PDAC. Second, there seems to be a potential for rapid progression of disease upon abrupt interruption of matched targeted therapy. This was experienced upon stopping capmatinib in patient #1 (as evidenced by increased % ctDNA and increase in liver metastases) and was mitigated by its resumption. The latter observation also demonstrates the need for combination therapy (osimertinib plus capmatinib) rather than osimertinib by itself, consistent with prior reports demonstrating that patients whose tumors harbor more than one driver alteration require therapy that addresses as many drivers as possible for optimized outcomes.[43,45] Lastly, in selected patients, matched targeted therapy was associated with durable response with good tolerance, raising the question of optimal treatment sequencing with respect to cytotoxic chemotherapy. Prior reports suggested that patients with advanced PDAC treated with matched targeted therapies did best in first line.[46] Our patient with the longest response duration received targeted therapy in the first line, yet responses were also seen in heavily pretreated patients as well (including one patient treated in fifth line).

Our current report has limitations. This is a retrospective study at a single center with a small sample size. Patients included in this study underwent genomic profiling utilizing NGS with standard gene panels for tissue, ±liquid biopsy. We did not utilize whole transcriptomic evaluation in 11/14 patients. We, therefore, might have missed fusions in a subset of our patients. Data for our patients who had NGS performed by vendors other than Tempus and Foundation Medicine or did not have NGS performed is not reported. As these patients were excluded from our study, our report is subjected to selection bias. Our study did not compare the genomic profiling or the clinical outcome of patients with *KRAS*-WT PDAC to that of patients with *KRAS*-mutated PDAC. This issue has been previously addressed by other groups.[8,9,38] Our study was mostly focused on characterizing the clinical benefit of chemotherapy-free matched targeted therapy in patients with *KRAS*-WT PDAC. Due to the retrospective nature of our study, we could not share patients' perspectives on treatments they received. The administration of targeted therapy and adjustment of treatment to resistance/tolerance was performed under the guidance of pancreatic cancer oncologists and precision oncology experts. The time and intensity of such patient management may not be reproducible in busy community oncology practices. Finally, our report focused on matched gene-targeted therapies for patients with PDAC. Previous reports have also examined matched immunotherapy based on microsatellite unstable disease or chromatin remodeling gene alterations and have shown benefits; this area also merits further investigation.[38,44]

Conclusion

In conclusion, we report a high frequency of actionable genomic alterations in patients with *KRAS*-WT PDAC and a subset of patients showed durable responses with matched chemotherapy-free targeted therapy. Further prospective studies in patients with *KRAS*-WT PDAC are warranted to address the optimal sequencing of targeted therapy with cytotoxic chemotherapy. Furthermore, the impact of targeted therapy on modulating clonal selection and resistance emergence, and the optimal approach for adjustment of treatment upon emergence of such resistance needs to be explored prospectively.

Declarations

Ethics approval, consent to participate, and consent for publication

This study was conducted according to the World Medical Association Declaration of Helsinki. This manuscript conforms with ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. This study was performed under the master protocol, Profile Related Evidence Determining Individualized Cancer Therapy, MCW PREDICT (NCT05802069), and was carried out in conformity with the regulations of the MCW Institutional Review Board and any experimental interventions for which patients provided consent. Written informed consent was obtained from the legally authorized representative (next of kin) of the deceased patients and from the living patients themselves for the publication of this case series.

Author contributions

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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