PATIENT
NAME: [REDACTED] SAMPLE
AGE: 67 years
SEX: Female
PERFORMANCE STATUS: ECOG 1

DIAGNOSIS
CANCER TYPE: Pancreatic Adenocarcinoma
STAGE: IV
METASTASES: Liver, Bone, Peritoneal, Pleural

BIOMARKERS
GENOMIC TEST: MSK IMPACT
KRAS: Wild-type
KEY FINDING: PDZRN3::RAF1 fusion

Note: No clinically-significant comorbidities limiting treatment tolerance.

Data Source Statement: *All patient information presented in this report is derived from the patient's Personal Health Record (PHR) and treating-clinician documentation.*

Purpose

The purpose of this report is to present the scientific and clinical evidence supporting the use of selected FDA-approved, off-guideline therapies for a patient with advanced pancreatic adenocarcinoma who has progressed on all standard-of-care treatments recommended by current NCCN Guidelines. This report integrates patient-specific clinical history, results from functional precision oncology testing, and a targeted review of the scientific literature to justify medical necessity for off-guideline treatment selection.

Prior Treatment History

First-line	NALIRIFOX with disease control for approximately 14 months, followed by progression
Second-line	Gemcitabine plus nab-paclitaxel for three cycles, with subsequent radiographic and clinical disease progression, including worsening intra-abdominal and hepatic metastatic burden.

Current Clinical Status

The patient is experiencing rapid disease progression despite receipt of guideline-based systemic therapies. She has developed ascites and progressive metastatic disease. Despite this, she maintains a functional status sufficient to tolerate additional systemic therapy.

Molecular and Biomarker Findings

Comprehensive genomic profiling via MSK IMPACT identified the following biomarkers:

- KRAS wild-type
- PDZRN3::RAF1 fusion

Functional Testing Results

The patient underwent functional precision oncology testing using a live tumor sensitivity assay performed on patient-derived tumor material obtained from malignant effusion specimens. The Travera Rapid Therapy Selection Test evaluates *ex vivo* tumor cell response to a panel of FDA-approved oncology drugs across multiple classes, generating relative sensitivity scores predictive of *in vivo* therapeutic response.

RESPONSE	DRUGS
High sensitivity	**Trametinib**
Low or no sensitivity	Cisplatin, Carboplatin, Gemcitabine, Paclitaxel, Docetaxel, Cobimetinib, Binimetinib, Selumetinib, Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib, Ensartinib, Osimertinib, Gefitinib, Erlotinib, Afatinib, Dacomitinib

Please review the attached Travera report for additional result details.

> **Interpretation:** The test results indicate a strong predicted tumor response to the MEK inhibitor Trametinib. Notably, the assay showed no meaningful sensitivity to gemcitabine, a drug on which the patient had already clinically progressed.

Outlook and Medical Necessity

The patient has exhausted all systemic treatment options reasonably expected to provide benefit under current NCCN Guidelines for metastatic pancreatic adenocarcinoma. She remains otherwise healthy, motivated, and capable of pursuing further therapy. There is a clear medical necessity to pursue patient-specific, biomarker-driven treatment options supported by emerging clinical evidence and biological rationale, outside of standard NCCN-recommended regimens.

Test Review

Test Overview

The Travera Rapid Therapy Selection Test is a live-cell functional assay that uses novel technology developed at MIT to determine tumor cell response to drugs by measuring changes in cellular mass.[1] It is applicable to all carcinomas and hematologic malignancies and evaluates response across a panel of more than 100 FDA-approved oncology drugs. All testing is performed in a CLIA-certified laboratory licensed in all 50 states and located in Medford, Massachusetts. The assay has been commercially available since 2020.

Predictive Accuracy

The Travera Rapid Therapy Selection Test is early in its clinical validation process, with outcome data currently available from 75 patients spanning more than 10 cancer types. Across this diverse cohort, the test has demonstrated both positive and negative predictive accuracy exceeding 75 percent, supporting its potential utility in predicting in vivo treatment response.[2]

Literature Review

Molecular and Pathway Rationale

RAF1 (CRAF) fusions are activating alterations of the MAPK pathway. In RAF1 fusion proteins, the N-terminal autoinhibitory regulatory domain of RAF1 is typically lost, resulting in constitutive kinase activity and persistent downstream signaling through MEK and ERK, independent of normal extracellular growth factor stimulation.[3] This places the oncogenic dependency downstream of RAF1, making MEK inhibition a rational therapeutic strategy.

The MAPK/ERK (RAS–RAF–MEK–ERK) pathway is a central signaling cascade regulating cell proliferation, survival, angiogenesis, and metastasis. Aberrant activation of this pathway is a hallmark of many malignancies, including pancreatic cancer.[4] Under physiologic conditions, pathway activation requires ligand-mediated receptor signaling that activates RAS, followed sequentially by RAF, MEK, and ERK. Activated ERK then translocates to the nucleus to drive transcriptional programs supporting cell growth.[5]

Relevance in KRAS Wild-Type Pancreatic Cancer

Approximately 95% of pancreatic ductal adenocarcinomas (PDAC) harbor activating KRAS mutations, which lock KRAS in a GTP-bound active state and cause continuous downstream MAPK signaling.[6] In contrast, KRAS wild-type pancreatic tumors are enriched for alternative oncogenic drivers, including gene fusions that converge on MAPK pathway activation.[7]

In the setting of a KRAS wild-type tumor with a PDZRN3::RAF1 fusion, the fusion protein maintains RAF1 in a constitutively active configuration, sending uninterrupted proliferative signals through MEK and ERK. Although KRAS is not mutated, upstream RAS signaling remains present and may further potentiate RAF1 fusion signaling, reinforcing dependence on the MAPK pathway.[8]

Therapeutic Rationale for MEK Inhibition

Direct RAF inhibition in RAF1 fusion tumors may be suboptimal due to paradoxical ERK activation and signaling complexity. In contrast, MEK inhibitors more reliably suppress downstream pathway output and have demonstrated activity across multiple RAF1 fusion–driven cancers.[3] Trametinib, an FDA-approved MEK1/2 inhibitor, directly targets this signaling bottleneck and has shown clinical activity in tumors driven by RAF1 fusions across histologies.

Clinical Evidence Supporting Trametinib in RAF1 Fusion Tumors

PDZRN3::RAF1–Specific Evidence

A published case report described a patient with a rare PDZRN3::RAF1 fusion sarcoma who experienced an excellent clinical response to trametinib combined with low-dose chemotherapy (doxorubicin) following disease recurrence.[9]

A subsequent case report of PDZRN3::RAF1 fusion sarcoma treated with trametinib plus doxorubicin demonstrated radiographic disease stabilization, further supporting pathway sensitivity.[10]

Broader RAF1 Fusion Experience

Clinical activity of MEK inhibition has been reported across other RAF1 fusion–driven malignancies:

- A contemporary melanoma series demonstrated anti-tumor responses to single-agent MEK inhibition in patients harboring RAF1 fusions, supporting a class effect.[3]
- Sustained clinical benefit from trametinib monotherapy has been reported in a central nervous system tumor selected specifically based on a RAF1 fusion.[11]
- Pediatric solid tumors harboring RAF1 fusions (e.g., MAP4–RAF1) have also demonstrated sensitivity to MEK inhibition.[12]

Pancreatic Cancer–Specific Data

RAF1 rearrangements have been identified in rare pancreatic tumor subtypes, with evidence of MAPK pathway activation (phospho-ERK expression).[13]

A reported case of RAF1 fusion–positive pancreatic acinar carcinoma treated with MEK inhibition showed a partial response.[14]

Conclusion

This patient's tumor harbors a KRAS wild-type, PDZRN3::RAF1 fusion, a rare but well-characterized oncogenic alteration that results in constitutive activation of the MAPK pathway through loss of RAF1 autoinhibition and persistent downstream MEK–ERK signaling.[3,8] This molecular configuration establishes a clear, biologically validated dependency on MEK signaling and provides a strong mechanistic rationale for MEK inhibition.

Importantly, this pathway-based rationale is reinforced by functional precision oncology testing performed on live patient-derived tumor cells. The Travera Rapid Therapy Selection Test demonstrated high predicted sensitivity to trametinib and minimal or no sensitivity to gemcitabine or taxane-based therapy, concordant with the patient's observed clinical resistance to gemcitabine plus nab-paclitaxel. The alignment between genomic findings, functional drug sensitivity, and clinical treatment history provides compelling, patient-specific evidence supporting trametinib as the most rational next-line therapy.

Clinical literature further supports this recommendation. Multiple reports across tumor types demonstrate meaningful clinical responses to MEK inhibition in RAF1 fusion-driven cancers, including PDZRN3::RAF1–positive sarcomas treated with trametinib, as well as melanoma, central nervous system tumors, and pediatric solid tumors harboring RAF1 fusions.[3,9-12] Although data in pancreatic cancer are limited due to the rarity of RAF1 fusions, published cases confirm MAPK pathway activation in RAF1-rearranged pancreatic tumors and document clinical responses to MEK inhibition.[13,14] Collectively, these findings support a class effect of MEK inhibitor sensitivity in RAF1 fusion-driven malignancies, independent of tumor histology.

The patient has exhausted all NCCN-recommended systemic therapies for metastatic pancreatic adenocarcinoma and continues to experience rapid disease progression. She remains functionally fit, motivated for further treatment, and without comorbidities limiting tolerance. In this context, trametinib represents a medically necessary, evidence-supported, precision-guided therapy that directly targets the dominant oncogenic driver identified in this patient's tumor.

Based on the convergence of molecular profiling, functional tumor sensitivity testing, and published clinical evidence, treatment with trametinib is strongly recommended as an off-guideline, patient-specific therapy with the highest likelihood of clinical benefit relative to available alternatives.

References

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Prepared by:

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Date: _____