ORDER DETAILS

Name:	****, ****
Date of Birth:	**/**/****
Sex:	****
MRN:	****
Location:	****
Specimen Date:	**/**/****
Site:	****
Provider:	****
Institution:	****

MEDICAL HISTORY

- This is a **-year-old **** who developed pancreatitis in **/****. An MRI revealed a mass in the pancreatic head, and an EUS/biopsy in **** confirmed pancreatic adenocarcinoma. The CEA levels were elevated, slightly increasing in CA 19-9.
- Family History: paternal aunt with bladder cancer

MULTI-OMIC RESULTS

Genomic Findings

Gene	Result
MSI	Stable
TMB	Low (1 Muts/Mb)
HRD	Negative
ACVR1B	V14fs*72

Gene	Result
KRAS	G12D
NF1	splice site 2325+1G>A
TP53	R175H

Considerations & Pertinent Negatives

- No significant genomic findings suggesting microsatellite instability (MMR status unavailable)
- A complete proteomic profile was not available

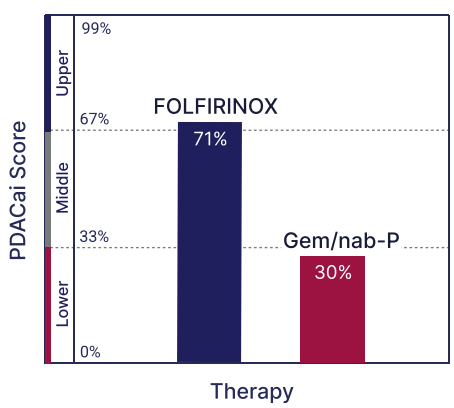
SUMMARY RECOMMENDATIONS

Molecular Tumor Board Recommendations:

- The molecular profile showed a KRAS G12D mutation. The compound MRTX1133, which targets the KRAS-G12D mutation, demonstrated notable preclinical effectiveness against tumor cells harboring KRAS-G12D, including in cases of pancreatic ductal adenocarcinoma. [1]. Our therapy options have included clinical trials directed toward KRAS G12D.
- If a new tissue biopsy is obtained, the determination of Claudin18.2 by IHC is recommended since clinical studies targeting Claudin-18.2 for pancreatic cancer have been of interest [2].
- Participation in clinical trials is always encouraged. Contacting each clinical trial site is recommended to evaluate eligibility and slot availability.

PDACai Highlights:

a. **FOLFIRINOX 71%:** Your percentile for FOLFIRINOX based on PDACai was 71% which correlates with potentially increased benefit based on real-world outcomes from patients with similar genomic profiles.
b. **Gem/nab-P 30%:** Your percentile for Gem/nab-P based on PDACai was 30% which correlates with potentially decreased benefit based on real-world outcomes from patients with similar genomic profiles.



PDACai Response groups:
Lower (0-33%) Middle (34-66%) Upper (67-99%)

For more details on PDACai recommendations please refer to the Appendix.

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RANKED THERAPY OPTIONS

The ranking given to each therapy option is intended to highlight how strongly that option aligns with the molecular findings, the available scientific, clinical evidence, and patient's medical and cancer history, but is NOT meant to indicate or imply that any one option has a known greater chance of clinical success.

Standard Option | Clinical Trial | Expanded Access

Rank	Score	Therapy option & rationale	
1	7	**FOLFIRINOX, NALIRIFOX, FOLFOX, FOLFIRI, or 5FU/nal-IRI e.g. NCT03597581 or NCT04753879**	
	1	PDACai Score:	Your percentile for FOLFIRINOX correlates with potentially increased benefit
	0	MOLECULAR:	No implicated markers
	4	DISEASE:	NALIRIFOX was recently approved in pancreatic cancer but has not been evaluated head-to-head against FOLFIRINOX
	2	PATIENT:	FOLFIRINOX is planned
2	5	**Gemcitabine plus nab-paclitaxel e.g. NCT04098081 or NCT05630183 or NCT06119217**	
	-1	PDACai Score:	Your percentile for Gem/nab-Paclitaxel correlates with potentially decreased benefit
	0	MOLECULAR:	No implicated markers
	4	DISEASE:	This is a standard combination
	2	PATIENT:	The patient has not had this class of agents
3	5	**A KRAS G12D-targeting agent on a clinical trial e.g. NCT05737706 or NCT06040541 or NCT05382559**	
	2	MOLECULAR:	**Positive Predictors:** KRAS G12D
	1	DISEASE:	KRAS-directed therapies have shown to be promising [3]
	2	PATIENT:	The patient has not had this class of agents
4	5	**A MEK or ERK inhibitor in combination on a clinical trial e.g. NCT05585320 or NCT06194877 or NCT06270082**	
	2	MOLECULAR:	**Positive Predictors:** NF1 mut, KRAS G12D
	1	DISEASE:	MEK inhibitors have shown limited activity as single agents in KRAS-mutated tumors
	2	PATIENT:	Patient has not had this type of therapy
5	4	**A KRAS-directed therapy on a clinical trial e.g. NCT05379985 or NCT05578092 or NCT05585320**	
	1	MOLECULAR:	**Positive Predictors:** KRAS G12D
	1	DISEASE:	This class of agents has limited clinical evidence
	2	PATIENT:	The patient has not had this class of agents
6	4	**A KRAS vaccine on a clinical trial e.g. NCT06253520 or NCT06015724 or NCT05846516**	
	1	MOLECULAR:	**Positive Predictors:** KRAS G12D
	1	DISEASE:	Targeting KRAS isoforms through immune activation is a promising approach [4]
	2	PATIENT:	The patient has not had this class of agents
7	4	**An immunotherapy doublet containing a PD-1/PD-L1 inhibitor on a clinical trial e.g. NCT05293496 or NCT04104672 or NCT03821935**	
	0	MOLECULAR:	No implicated markers
	2	DISEASE:	Checkpoint inhibitor combinations are being explored extensively in clinical trials
	2	PATIENT:	The patient has not had this class of agents

For targeted therapy trials and closest location details, see next section Clinical Trials by Ranked Therapy Options.
For more information regarding biological and clinical significance, see the Therapeutic Associations in the report Appendix.
Please refer to appendix for explanation of Perthera's Algorithmically-Ranked Therapy Option scoring system.

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CLINICAL TRIALS BY RANKED THERAPY OPTIONS

IMPORTANT: While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continuously updated and should be investigated by the physician or research staff. This is not meant to be a complete list of available trials.

As of 14 May 2023 we have identified the following appropriate clinical trials that are active and recruiting patients (unless otherwise noted).

Therapies	Clinical Trial	Location & Contact details
1	NCT03597581	
A Study to Investigate BGB-3245 (Brimarafenib) With Panitumumab in Participants With Advanced or Metastatic RAS Mutant Colorectal and Pancreatic Ductal Cancers		(*** Miles), USOR - Virginia Cancer Specialists - Fairfax Office, Fairfax, Virginia, United States MapKure, clinicaltrials@mapkure.com, 1-877-828-5568
1	NCT04753879	
Multi-agent Low Dose Chemotherapy (Gemcitabine, Nabpaclitaxel, Capecitabine, Cisplatin, Irinotecan) Followed by Maintenance Olaparib and Pembrolizumab in Untreated Metastatic Pancreatic Ductal Adenocarcinoma.		(*** Miles), Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States Trish Brothers, RN, 410-614-3644, GIClinicaltrials@jhmi.edu
2	NCT04098081	
1911GCCC: Galeterone or Galeterone With Gemcitabine for Patients With Metastatic Pancreatic Adenocarcinoma		(*** Miles), University of Maryland Medical Center, Baltimore, Maryland, United States Aaron Ciner, MD, 410-328-6505
2	NCT05630183	
A Study of Botensilimab in Participants With Metastatic Pancreatic Cancer		(*** Miles), Medical Oncology Hematology Consultants (MOHC) - Helen F. Graham Cancer Center, Newark, Delaware, United States Jamal Misleh
2	NCT06119217	
Phase 2 Study of TTX-030 and Chemotherapy With or Without Budigalimab for 1L mPDAC Patients		(*** Miles), Investigative Site, Columbia, Maryland, United States Trishula Therapeutics, Inc., clinicaltrials@trishulatx.com, +1 888-480-0554
3	NCT05737706	
A Phase 1/2 Multiple Expansion Cohort Trial of MRTX1133 in Patients With Advanced Solid Tumors Harboring a KRAS G12D Mutation		(*** Miles), John Hopkins Medicine - Hematology/oncology, Baltimore, Maryland, United States Nilofer Azad, Site 306, 410-502-2995
3	NCT06040541	
A Study of ASP3082 in Adults With Previously Treated Solid Tumors		(*** Miles), Johns Hopkins University, Baltimore, Maryland, United States Revolution Medicines, Inc., CT-inquiries@RevMed.com, (650) 779-2300
3	NCT05382559	
A Study of ASP3082 in Adults With Previously Treated Solid Tumors		(*** Miles), NEXT Oncology - Virginia Cancer Specialists, Fairfax, Virginia, United States Astellas Pharma Inc., astellas.registration@astellas.com, 800-888-7704
4, 5	NCT05585320	
A Phase 1/2a Study of IMM-1-104 in Participants With Previously Treated, RAS-Mutant, Advanced or Metastatic Solid Tumors		(*** Miles), NEXT Oncology, Fairfax, Virginia, United States Alex Spira, MD, PhD

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CLINICAL TRIALS BY RANKED THERAPY OPTIONS

Therapies	Clinical Trial	Location & Contact details
4	NCT06194877	
A Trial of RSC-1255 for Treatment of Patients With Advanced Malignancies		(*** Miles), UC Davis Comprehensive Cancer Center, Sacramento, California, United States Bonnie Wettersten, MS, clinicaltrials@rascaltherapeutics.com, (847) 644- 9818
4	NCT06270082	
Study of IK-595 in RAS- or RAF-altered Advanced Tumors		(*** Miles), Next Oncology- Virginia Cancer Specialists, Fairfax, Virginia, United States Blake Paterson, mpoole@nextoncology.com, 703-783-4505
5	NCT05379985	
Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS		(*** Miles), Johns Hopkins University, Baltimore, Maryland, United States Revolution Medicines, Inc., rmc-6236_ct-inquiry@revmed.com, (650) 779- 2300
5	NCT05578092	
A Phase 1/2 Study of MRTX0902 in Solid Tumors With Mutations in the KRAS MAPK Pathway		(*** Miles), Johns Hopkins University, Baltimore, Maryland, United States Nilofer Azad, Site 001-103, 410-502-2995
6	NCT06253520	
Autologous T-cells Genetically Engineered to Express Receptors Reactive Against KRAS Mutations in Conjunction With a Vaccine Directed Against These Antigens in Participants With Metastatic Cancer		(*** Miles), National Institutes of Health Clinical Center, Bethesda, Maryland, United States NCI/Surgery Branch Recruitment Center, irc@nih.gov, 866-820-4505
6	NCT06015724	
Anti-CD38 Antibody With KRAS Vaccine and Anti-PD-1 Antibody in Subjects With Pancreatic Ductal Adenocarcinoma and Refractory Non-Small Cell Lung Cancer		(*** Miles), Georgetown Lombardi Comprehensive Cancer Center, Washington, District of Columbia, United States Jennifer Mont, jem257@georgetown.edu, 202-687-8974
6	NCT05846516	
A Phase 1b Study to Evaluate the Safety, Tolerability and Preliminary Efficacy of ATP150/ATP152, VSV-GP154 and Ezabenlimab (BI 754091) in Patients With KRAS G12D/G12V Mutated Pancreatic Ductal Adenocarcinoma (KISIMA-02)		(*** Miles), , Virginia Cancer Specialists, Fairfax, Virginia, United States Carrie Friedman, RN, Carrie.Friedman@usoncology.com
7	NCT05293496	
A Phase 1/1b Dose Escalation and Cohort Expansion Study of MGC018 in Combination With Checkpoint Inhibitor in Participants With Advanced Solid Tumors		(*** Miles), Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States Eugene Shenderov
7	NCT04104672	
A Study to Evaluate the Safety and Tolerability of AB680 in Participants With Gastrointestinal Malignancies		(*** Miles), University of Pennsylvania, Philadelphia, Pennsylvania, US Medical Director, ClinicalTrialInquiry@arcusbio.com, +1-510-462-3330
7	NCT03821935	
Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of Livmoniplimab (ABBV151) as a Single Agent and in Combination With Budigalimab (ABBV-181) in Participants With Locally Advanced or Metastatic Solid Tumors		(*** Miles), NYU Langone Medical Center /ID# 209822, New York, NY, US ABBVIE CALL CENTER, abbvieclinicaltrials@abbvie.com, 844-663-3742

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SIGNED BY:

This report has been approved and signed by:

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Chief Medical Officer
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Appendix THERAPEUTIC ASSOCIATIONS

KRAS PATHWAY:

- **KRAS** had an activating mutation. Constitutively activating KRAS mutations promote tumor growth through sustained signaling to RAF/MEK/ERK and PI3K/AKT/mTOR signaling cascades. Targeting RAS directly has been unsuccessful to date [5] and single agent MEK inhibitors have had limited clinical success in randomized trials despite promising results from earlier phase studies ([6], [7], [8], [9], [10], [11], [12]). It is likely that multi-pronged strategies including a MEK/ERK inhibitor plus a CDK4/6 inhibitor ([13], [14]), a PI3K/AKT/mTOR inhibitor ([15], [16], [17], [18], [19], [20]), a pan-RAF inhibitor ([21], [22]), a multi-targeted TKI ([23], [24]), EGFR/HER2 inhibitors [25], an Hsp90 inhibitor [26], an HDAC inhibitor [27], or immunotherapy will be necessary to overcome resistance to single agents in KRAS mutated malignancies.

MAPK PATHWAY:

- **NF1** inactivating mutation was found. NF1 encodes the Ras-GAP, neurofibromin, which acts as a tumor suppressor by negatively regulating Ras signaling activity ([28], [29]). Germline mutations are associated with neurofibromatosis type I. Inactivating NF1 mutations have been associated with increased sensitivity to MEK inhibitors ([30], [31], [32]). Thus, a clinical trial including a MEK inhibitor could be considered.

REGULATORY NETWORK:

- **TP53** (p53) inactivating mutation was present. The p53 system acts as a tumor suppressor by normally controlling cellular fate after DNA damaging exposures. Dysregulation of p53 confers tumor resistance to programmed cell death despite DNA damage. p53 is dysregulated in the majority of cancers, and there are currently no clinically successful agents directly reversing p53 dysregulation. Experimentally, p53-deficient tumors may be selectively sensitive to Wee1 inhibitors ([33], [34], [35], [36]), CHK1 inhibitors [33], or p53-directed vaccine therapies.

OTHER PATHWAYS:

- **ACVR1B** mutation was seen. ACVR1B encodes the activin receptor type 1B that is a receptor tyrosine kinase. Activin is the ligand and ACVR1B cooperates with other activin receptors in a complex that binds SMAD3 and SMAD4. Mutations in ACVRB1 thus dysregulate TGF-beta signaling. These mutations have been described in pancreatic cancer [37]. Loss of ACVR1B has been shown to accelerate growth of mutant KRAS-indluced pancreatic IPMNs in mice via NOTCH4 and loss of p16 [38]. ACVR1B loss has also been correlated with an aggressive clinical phenotype in pancreatic cancer [39]. No therapy is known to directly target this mutation.

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Appendix PERTHERA'S ALGORITHMICALLY-RANKED THERAPY OPTION REPORT

Perthera utilizes a patent-protected[1] rules-based algorithms to generate patient specific match scores that rank available monotherapies and drug combinations according to their ability to target the patient's specific cancer biomarkers. The algorithmic treatment ranking in the Perthera Report is determined using a unique combination of scoring models established by a coalition of medical oncology experts from the United States who participate on Perthera's Virtual Molecular Tumor Board platform[2]. This patient-specific, assistive, rules-based algorithm for ranking pharmaco-oncologic treatment options is based on the patient's tumor-specific cancer marker information (e.g. tissue-based or blood-based NGS testing results) obtained from prior molecular pathology, immunohistochemical, or other pathology results which have been previously interpreted and reported separately. Perthera's ranking system was shown to correlate with clinical benefit in previous publications where patients who received the top ranked therapy had a 2X increase in overall survival and 4X progression -free survival compared to a similar cohort of patients who did not receive the top ranked therapeutic option[3].

[1] US 11,475,992 B2 Integration of Muti-omic Data into a Single Scoring Model of Input into a Treatment Recommendation Ranking; US-11574718-B2 Outcome driven persona-typing for precision oncology; US-20190355478-A1 Systems an Methods for an Expert System for Precision Oncology.

[2] Pishvaian MJ, Blais EM, Bender RJ, Rao S, Boca SM, Chung V, Hendifar AE, Mikhail S, Sohal DPS, Pohlmann PR, Moore KN, He K, Monk BJ, Coleman RL, Herzog TJ, Halverson DD, DeArbeloa P, Petricoin EF 3rd, Madhavan S. A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology to physicians and their patients. JAMIA Open. 2019 Oct 7;2(4):505-515

[3] Pishvaian MJ, Blais EM, Brody JR, Lyons E, DeArbeloa P, Hendifar A, Mikhail S, Chung V, Sahai V, Sohal DPS, Bellakbira S, Thach D, Rahib L, Madhavan S, Matrisian LM, Petricoin EF 3rd. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial. Lancet Oncol. 2020 Apr;21(4):508-518.

Perthera Scoring Model

PDACai Score (-1 to 1)

-1) Decreased benefit from this standard option
0) Typical benefit from this standard option
1) Increased benefit from this standard option

Molecular Score (0 to 3)

0) Neutrally predictive biomarker profile
1) Weakly predictive biomarker profile
2) Moderately predictive biomarker profile
3) Strongly predictive biomarker profile

Disease Score (0 to 4)

0) Unsupportive evidence of clinical activity
1) Limited clinical evidence/activity
2) Emerging evidence or modest activity
3) Promising evidence or moderate activity
4) Strong clinical evidence/activity

Patient Score (0 to 2)

0) Re-challenge is a major concern
1) Re-challenge is a minor concern
2) Treatment history is not a concern

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Appendix ENHANCED CLINICAL DECISION SUPPORT POWERED BY PDACai

Enhanced clinical decision support within standard of care powered by PDACai and Real-World Evidence from Perthera

PDACai provides physicians with patient-specific insights into how well the two standard chemotherapy options in pancreatic adenocarcinoma (PDAC) helped other patients with similar patterns of tumor mutations.

- **PDACai inputs** a patient's genomic testing results from any major commercial NGS laboratory
- **PDACai outputs** two scores (each 0-99%) as percentiles normalized to the PDACai population

More about the two options

FOLFIRINOX (5-Fluorouracil + Irinotecan + Oxaliplatin) & Gem/nab-P (Gemcitabine + nab-Paclitaxel) are the most common 1st line chemotherapy regimens given to patients with metastatic PDAC

- 50% get 1st line FOLFIRINOX (to be followed by Gem/nab-P) vs 1st line Gem/nab-P
- 50% with metastatic PDAC never get a chance to receive a 2nd line of therapy

PDACai Validation Studies

PDACai was validated in cohorts of patients who were diagnosed with metastatic pancreatic adenocarcinoma (PDAC) and received either of the two most common frontline therapy options.[1, 2] PDACai is intended for patients who have not yet exhausted these standard of care chemotherapy options for PDAC. PDACai has not been validated in the perioperative/neoadjuvant/adjuvant setting nor in the second line setting. Efforts are ongoing to validate whether PDACai predictions correlate with outcomes in these scenarios where similar regimens are used. Clinical correlation of other important factors (e.g. DPYD status, possible allergies, patient comorbidities, previous exposures to similar agents, tolerability concerns, drug labels) is always advised when interpreting PDACai results within its intended use case (insights into frontline options for metastatic PDAC).

PDACai Results and Guidance

The flowchart and examples below illustrate how to interpret PDACai results

PDACai Scenario		PDACai Guidance
FOLFIRINOX Upper Score (>66%)?	Yes →	1st line FOLFIRINOX (vs Gem/nab-P)
↓ No		
Gem/nab-P Lower Score (<33%)	Yes →	1st line FOLFIRINOX or similar for tolerance
↓ No		
Gem/nab-P Score much higher than **FOLFIRINOX** Score	Yes →	1st line Gem/nab-P (vs FOLFIRINOX)
↓ No		
Standard Guidance	Yes →	Clinical trials are always encouraged, especially when both scores are low

Examples

FOLFIRINOX: Upper	80%	• 1st Line FOLFIRINOX (or FOLFOX or Gem/Cis) • 2nd Line Gem/nab-P (+/- New Trial Agent) • 3rd Line Clinical Trial (see Perthera Report)
Gem/nab-P: Middle	40%	
FOLFIRINOX: Middle	50%	• 1st Line FOLFIRINOX (or FOLFIRI or FOLFOX) • 2nd Line Clinical Trial (see Perthera Report) • 3rd Line Gemcitabine (+/- nab-Paclitaxel)
Gem/nab-P: Lower	20%	
FOLFIRINOX: Lower	30%	• 1st Line Gem/nab-P (+/- New Trial Agent) • 2nd Line FOLFIRI (FOLFOX or FOLFIRINOX) • 3rd Line Clinical Trial (see Perthera Report)
Gem/nab-P: Upper	70%	

A Perthera Report's ranked therapy options may differ from these examples based on a patient's

- multi-omic actionability for certain therapies
- eligibility for nearby/accessible clinical trials,
- previous clinical/treatment history

[1] Validation of PDACai v2.0 in predicting relative benefit from frontline FOLFIRINOX and gemcitabine with nab-paclitaxel for patients with metastatic pancreatic cancer Pishvaian et al. ASCO GI. Jan 2025; DOI: 10.1200/JCO.2025.43.4_suppl.776

[2] Validation of the PDACai Signature in Predicting Relative Benefit from Frontline FOLFIRINOX and Gemcitabine/nab-Paclitaxel for Patients with Metastatic Pancreatic Cancer. Pishvaian et al. ASCO. Jun 2023; DOI: 10.1200/JCO.2023.41.16_suppl.4149

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