Dear Dr Sample,

The following is your Perthera Patient Brief for Patient #: P-XXXXXXX. This Report is intended to provide you with a concise, comprehensive perspective of your patient's treatment options by aggregating and curating relevant information needed to help support your treatment decisions.

Our rules-based algorithmically generated ranking of therapy options is informed by the most current published literature and guidelines, your patient's medical history and molecular test results (if available), and an expert opinion from our team of medical and multiomics specialists through our virtual molecular tumor board.

Perthera has sponsored or co-authored over 50 publications highlighting the benefits of precisely matched, ranked therapies in treatment decision-making, including one in The Lancet Oncology. The Perthera Patient Brief has become a trusted resource and been used by over 1,500 oncologists in more than 600 cancer centers around the world.

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Patient Name: ***** *****
Date Of Birth: **/**/****
Sex: *****
Location: *****
MRN: *****
Specimen Date: **/**/****
Specimen Location: *****

Physician: ***** *****
Institution: *****

MEDICAL HISTORY

This is a XX-year-old XXX who first reported abdominal pain on XX-XX-XX. A colonoscopy in XX-XX-XX revealed an obstructive mass in the proximal ascending colon, confirmed by a CT scan and some liver masses. In XX-XX-XX, the patient underwent a right hemicolectomy, which identified a T4bN2cM1 colon adenocarcinoma with 5 out of 20 lymph nodes affected. An MRI further confirmed multiple liver lesions in both lobes. The patient started treatment with FOLFIRINOX combined with bevacizumab from XX-XX-XX to XX-XX-XX, followed by maintenance 5FU with Bevacizumab from XX-XX-XX to XX-XX-XX, which was switched to Capecitabine and Bevacizumab from XX-XX-XX to XX-XX-XX. The Patient received radiotherapy to the abdominal wall nodule on XX-XX-XX, XX-XX-XX, and XX-XX-XX. Maintenance therapy continued with 5-FU and Bevacizumab from XX-XX-XX to XX-XX-XX, followed by a single dose of FOLFIRI with Bevacizumab on XX-XX-XX. A liver biopsy on XX-XX-XX confirmed adenocarcinoma. The patient then participated in a KymweKT-253 trial involving an MDM2 inhibitor from XX-XX-XX to XX-XX-XX, but the disease progressed. He began treatment with Trifluridine/Tipiracil and Bevacizumab on XX-XX-XX, with further disease progression noted in XX-XX-XX. The patient received radiation therapy to the lesions in the umbilical/abdominal wall on XX-XX-XX and the left inguinal/lower abdominal wall from XX-XX-XX to XX-XX-XX. The patient initiated FOLFIRI on XX-XX-XX.

MULTI-OMIC RESULTS

Genomic Findings

Gene	Result
MSI	Stable
TMB	Low (5.8 Muts/Mb)
AMER1	R601*
APC	R213*
APC	T1556fs

Gene	Result
HRD	negative
KRAS	G13D
PIK3CA	Q546K
PTEN	R233*
SAMD3	R368*

Protein Findings

Protein	Result
MLH1	Positive
MSH2	Positive
MSH6	Positive
PMS2	Positive

Considerations & Pertinent Negatives

- A complete proteomic profile was not available

SUMMARY RECOMMENDATIONS

- Participation in clinical trials is always encouraged. Contacting each clinical trial site is recommended to evaluate eligibility and slot availability.

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.

Rank Score Therapy Option & Rationale — **Standard Option** **Clinical Trial** **Expanded Access**

1	6	A KRAS directed therapy on a clinical trial e.g. NCT05786924 or NCT05163028 or NCT05578092	
	2	MOLECULAR	**Positive Predictors:** KRAS G13D
	2	DISEASE	KRAS-directed therapies have shown to be promising [1]
	2	PATIENT	The patient has not had this class of agents
2	6	Alpelisib/capivasertib off label or preferably a PIK3CA inhibitor on a clinical trial e.g. NCT05216432 or NCT05683418 or NCT04589845	
	2	MOLECULAR	**Positive Predictors:** PIK3CA mut
	2	DISEASE	PIK3CA inhibitors are approved in combination with endocrine therapy for PIK3CA-mutated hormone-positive breast cancer[mPFS:11.0v5.7m,HR=0.65;p=0.00065] but have not demonstrated activity as single agents
	2	PATIENT	Patient has not had this type of therapy
3	6	Regorafenib	
	0	MOLECULAR	No implicated markers
	4	DISEASE	Regorafenib is a standard agent in this disease
	2	PATIENT	The patient has not had this class of agents
4	6	Fruquintinib or a next-generation antiangiogenic agent on a clinical trial	
	0	MOLECULAR	No implicated markers
	4	DISEASE	Fruquintinib was approved in 2023 for colorectal cancer in the setting after either TAS-102 or regorafenib
	2	PATIENT	bevacizumab
5	5	A MEK or ERK inhibitor in combination on a clinical trial e.g. NCT05585320 or NCT06270082	
	1	MOLECULAR	**Positive Predictors:** KRAS G13D
	2	DISEASE	MEK inhibitors have shown limited activity as single agents in KRAS-mutated tumors
	2	PATIENT	Patient has not had this type of therapy
6	5	A Wnt inhibitor on a clinical trial e.g. NCT05919264	
	2	MOLECULAR	**Positive Predictors:** AMER1 mut, APC mut
	1	DISEASE	This class of agents has limited clinical evidence
	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. NCT02817633 or NCT05293496 or NCT04446351	
	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

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Rank Score Therapy Option & Rationale — Standard Option | Clinical Trial | Expanded Access

8	4	A KRAS vaccine on a clinical trial e.g. NCT04117087
1	MOLECULAR	**Positive Predictors:** KRAS G13D
1	DISEASE	Targeting KRAS isoforms through immune activation is a promising approach [2]
2	PATIENT	The patient has not had this class of agents
9	3	CAR T-cell immunotherapy on a clinical trial e.g. NCT03412877
0	MOLECULAR	**Negative Predictors:** PTEN mut
1	DISEASE	Re-engineering T-cells is a promising approach described as the 'advance of the year' by ASCO in 2018
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 XX/XX/XXXX we have identified the following appropriate clinical trials that are active and recruiting patients (unless otherwise noted).

Therapies	Clinical Trial	Location & Contact Details
1	NCT05786924	
A Study of BDTX-4933 in Patients With KRAS, BRAF and Select RAS/MAPK Mutation-Positive Cancers		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
1	NCT05163028	
A Dose Escalation Study of SHP2 Inhibitor in Patients With Solid Tumors Harboring KRAS of EGFR Mutations		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
1	NCT05578092	
A Phase 1/2 Study of MRTX0902 in Solid Tumors With Mutations in the KRAS MAPK Pathway		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
2	NCT05216432	
First-in-Human Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, as a Single Agent in Advanced Solid Tumor Patients and in Combination With Fulvestrant in Patients With Advanced Breast Cancer		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
2	NCT05683418	
A Study to Evaluate the Safety and Tolerability of TOS-358 in Adults With Select Solid Tumors		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
2	NCT04589845	
Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
5	NCT05585320	
A Phase 1/2a, Open-Label, Multicenter, Nonrandomized, Safety and Anti-tumor Activity Study of IMM-1-104, a Novel Oral Dual MEK1/2 Inhibitor in Participants With Previously Treated RAS-Mutated Advanced or Metastatic Solid Tumors		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
5	NCT06270082	
Study of IK-595 in RAS- or RAF-altered Advanced Tumors		(XXX) Miles from patient; trial organization's name, city & state Contact name, email address and phone number for trial as listed in resources

Therapies	Clinical Trial	Location & Contact Details
6	NCT05919264	
FOG-001 in Locally Advanced or Metastatic Solid Tumors		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
7	NCT02817633	
A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Patients With Advanced Solid Tumors (AMBER)		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
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		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
7	NCT04446351	
A Phase 1 First-Time-in-Human, Open-Label Study of GSK6097608 Administered as Monotherapy and in Combination With Anticancer Agents in Participants With Advanced Solid Tumors		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
8	NCT04117087	
Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Resected MMR-p Colorectal and Pancreatic Cancer		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources
9	NCT03412877	
A Phase II Study Using the Administration of Autologous T-Cells Genetically Engineered to Express T-Cell Receptors Reactive Against Neoantigens in Patients With Metastatic Cancer		(XXX) Miles from patient; trial organization's name, city & state Contact name, email & phone number for trial as listed in resources

SIGNED BY:

This report has been approved and signed by:

Chief Medical Officer
Perthera, Inc.

Appendix

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THERAPEUTIC ASSOCIATIONS

Immunotherapy:

- Mismatch repair (MMR) protein expression was intact by IHC

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 [3] and single agent MEK inhibitors have had limited clinical success in randomized trials despite promising results from earlier phase studies ([4], [5], [6], [7], [8], [9], [10]). It is likely that multi-pronged strategies including a MEK/ERK inhibitor plus a CDK4/6 inhibitor ([11], [12]), a PI3K/AKT/mTOR inhibitor ([13], [14], [15], [16], [17], [18]), a pan-RAF inhibitor ([19], [20]), a multi-targeted TKI ([21], [22]), EGFR/HER2 inhibitors [23], an Hsp90 inhibitor [24], an HDAC inhibitor [25], or immunotherapy will be necessary to overcome resistance to single agents in KRAS mutated malignancies.

PI3K Pathway:

- PIK3CA activating mutation was present. PIK3CA encodes the catalytic subunit of PI3K and is a central component of the PI3K/AKT/mTOR pathway. Activating mutations can be germline (rare immunodeficiency syndrome) or somatic. These mutations have been associated experimentally with sensitivity to PI3K inhibitors and downstream inhibitors of AKT and mTOR. ([26], [27]). As single agents, all of these inhibitors face rapidly acquired resistance mechanisms through crosstalk with RAS/MEK/ERK and NF-kB pathways. ([28], [17]). There is also data from cervical cancer that PI3K activation is a factor in platinum resistance and tumors can regain sensitivity with PI3K inhibition [29]. There are many combinations in trials that include PIK3CA targeting agents that could be considered.
- PTEN inactivating alteration was seen. PTEN encodes a phosphatase and tumor suppressor that negatively regulates PI3K-mediated activation of AKT via PDK1 ([30], [31], [32]). Experimentally, PTEN inactivating alterations sensitize tumor cells to PI3K/AKT/mTOR inhibitors, particularly in the context of other PI3K pathway alterations. As an upstream regulator of the DNA damage response (DDR) pathway, PTEN inactivating mutations have also been shown to sensitize cancer cells to PARP inhibitors in a variety of contexts ([33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43]). A clinical trial of a PI3K/AKT/mTOR inhibitor could be considered. Recent studies also suggest that PTEN inactivation may be associated with resistance to immunotherapies ([44], [45]) but this has not yet been prospectively validated.

WNT Pathway:

- APC inactivating mutation was noted. The APC gene product acts as a tumor suppressor and is most commonly germline mutated in familial adenomatous polyposis (FAP) and its resulting colon adenocarcinoma. Somatic mutations are well known in other cancers like breast, pancreatic, and lung. APC mutations usually result in a truncated form of the protein resulting in loss of function. Mutations in APC have been identified in early stages of cancer progression making it a therapeutic target. APC is best known for its role as a negative regulator of the WNT/beta-catenin pathway. However, APC also mediates several other normal cell functions independently of WNT/beta-catenin signaling such as apical-basal polarity, microtubule networks, cell cycle, DNA replication, DNA repair, apoptosis, and cell migration. Inactivating mutations in APC have also been described as a contributor to chemotherapeutic resistance [46]. A clinical trial including a WNT inhibitor could be considered.

Other Pathways:

- AMER1 (also called WTX or FAM123B) mutation was seen. AMER1 encodes a negative regulator of the WNT signaling pathway that stabilizes beta-catenin [47]. Low levels of AMER1 in tumor cells has been associated with increased activity of the WNT/beta-catenin pathway [48].

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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

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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