

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Colon adenocarcinoma (CRC)
NAME Tsai, Yu-Tsen
DATE OF BIRTH 16 March 1969
SEX Female
MEDICAL RECORD # 25617316

PHYSICIAN

ORDERING PHYSICIAN Jiang, Jeng-Kai
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Liver
SPECIMEN ID S110-61563 A (PF21022)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 06 May 2021
SPECIMEN RECEIVED 01 October 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

KRAS G12C
NRAS wildtype
PIK3CA Q546K
APC E1322*
SOX9 Q369*
SPEN R1470*
TP53 C135F

2 Disease relevant genes with no reportable alterations: **BRAF**, **NRAS**

1 Therapies with Clinical Benefit

18 Clinical Trials

2 Therapies with Resistance

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 1 Muts/Mb

GENOMIC FINDINGS

KRAS - G12C

10 Trials *see p. 11*

NRAS - wildtype

0 Trials





PIK3CA - Q546K


10 Trials *see p. 13*

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Cetuximab 	Sotorasib
Panitumumab 	
Cetuximab 	none
Panitumumab 	
none	none

 Extensive evidence showing variant(s) in this sample may confer resistance to this therapy

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

APC - E1322* p. 6 **SPEN** - R1470* p. 7
SOX9 - Q369* p. 7 **TP53** - C135F p. 8

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

ORDERED TEST # ORD-1201781-01

BIOMARKER FINDINGS

BIOMARKER

Microsatellite status

RESULT

MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors¹⁻³, including approved therapies nivolumab and pembrolizumab⁴. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, $p=0.001$)⁵. For patients with chemotherapy-refractory metastatic colorectal cancer, 92% of which were MSS or MSI-Intermediate, a Phase 3 trial reported

no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00); atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)⁶.

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX⁷⁻⁸ and FOLFIRI⁹⁻¹⁰. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy¹¹⁻¹² but less likely to benefit from irinotecan chemotherapy¹³.

FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases^{3,14-18}. MSS colorectal cancers are molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or

chromosomal instability¹⁸. Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors^{14,19-25}.

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor¹⁶. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2^{16,26-27}. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers^{15,28-29}. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{15-16,27,29}.

ORDERED TEST # ORD-1201781-01

BIOMARKER FINDINGS

BIOMARKER

Tumor Mutational Burden

 RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1³⁰⁻³², anti-PD-1 therapies³⁰⁻³³, and combination nivolumab and ipilimumab³⁴⁻³⁹. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors^{30-33,40}. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors³⁰. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥ 16 -20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy⁴¹ or those with lower TMB treated with PD-1 or PD-L1-targeting agents³¹. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with

TMB ≥ 10 Muts/Mb (based on this assay or others) compared to those with TMB < 10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials^{33,40}. Together, these studies suggest that patients with TMB ≥ 10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB ≥ 9.8 Muts/Mb compared with those with tumors with TMB < 9.8 Muts/Mb (~ equivalency < 12 Muts/Mb as measured by this assay)³⁰. Another retrospective study reported that a TMB ≥ 12 Muts/Mb cutoff identifies $> 99\%$ of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors⁴².

FREQUENCY & PROGNOSIS

Elevated TMB has been reported in 8-25% of colorectal cancer (CRC) samples^{17,43-45}. Multiple studies have reported that the majority (up to 90%) of hypermutant CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)^{17,45}. Increased TMB is significantly associated with MSI-H and MMR-D, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and, conversely, that 100% of tumors with low TMB harbor intact MMR⁴³⁻⁴⁵. A subset of CRCs that harbor increased TMB but not MSI-H are driven

by mutations in POLE, which lead to an "ultramutated" phenotype with especially high TMB^{17,45}. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB^{17,45}, whereas TMB-low tumors more frequently harbor mutations in TP53 and APC¹⁷. In a study for 61 patients with metastatic, microsatellite stable (MSS) CRC treated with best standard of care, plasma TMB scores ≥ 28 muts/Mb (approximately 14 muts/Mb as measured by this assay) were associated with reduced OS as compared with plasma TMB scores < 28 muts/Mb (3.0 vs. 5.3 months, HR 0.76, $p=0.007$), whereas tissue TMB was not found to be prognostic in this population⁴⁶.

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma⁴⁷⁻⁴⁸ and cigarette smoke in lung cancer⁴⁹⁻⁵⁰, treatment with temozolomide-based chemotherapy in glioma⁵¹⁻⁵², mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes^{17,53-56}, and microsatellite instability (MSI)^{17,53,56}. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents^{30,40,42}.

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ORDERED TEST # ORD-1201781-01

GENOMIC FINDINGS

GENE

KRAS

ALTERATION

G12C

TRANSCRIPT ID

NM_004985

CODING SEQUENCE EFFECT

34G>T

VARIANT ALLELE FREQUENCY (% VAF)

83.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

KRAS G12C may predict sensitivity to G12C-targeted inhibitors such as sotorasib⁵⁷⁻⁵⁹ and adagrasib⁶⁰. The Phase 1 CodeBreak 100 trial of sotorasib in G12C-mutated solid tumors observed clinical benefit for patients with non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), with additional responses observed in several other tumor types⁵⁹; patients with CRC achieved a relatively low ORR (7.1% [3/42]) but demonstrated a high DCR of 74% (31/42) with mPFS of 4 months⁵⁹. In the Phase 1/2 KRYSTAL-1 trial, treatment with single-agent adagrasib elicited a 45% (23/51) ORR and a 96% (49/51) DCR for patients with G12C-mutated NSCLC⁶¹. Responses to single-agent adagrasib were also reported for patients with other types of G12C-mutated tumors, including colorectal carcinoma with an ORR of 17% (3/18) and individual responses reported for patients with endometrial cancer, pancreatic cancer, ovarian cancer, and cholangiocarcinoma⁶². Preclinical and clinical data

suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors⁶³⁻⁶⁴. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations⁶⁵. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer⁶⁶. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib⁶⁷⁻⁷². However, multiple clinical trials have reported lack of efficacy of trametinib and other MEK inhibitors when used as monotherapy for treatment of patients with KRAS-mutant CRC⁷³⁻⁷⁷. Both clinical⁷⁸⁻⁷⁹ and preclinical⁸⁰⁻⁸¹ studies suggest that combinatorial approaches including MEK inhibitors are likely to be more effective for the treatment of CRC, including strategies such as combination of MEK inhibitors with PI3K inhibitors⁷⁹, RAF inhibitors⁸⁰, pan-ERBB inhibitors⁸¹, or chemotherapeutic agents⁷⁸. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors⁸². A Phase 1b/2 study of PLK1 inhibitor onvansertib in combination with FOLFIRI and bevacizumab for patients with KRAS-mutated metastatic CRC previously treated with chemotherapy reported an 87.5% (7/8; 3 PR, 4 SD) clinical benefit rate, with 1 patient going on to successful curative surgery⁸³.

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from

cetuximab⁸⁴⁻⁸⁷ or panitumumab⁸⁸⁻⁹⁰ for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v.3.2021).

FREQUENCY & PROGNOSIS

KRAS G12C mutations have been identified in 3.2% of colorectal cancers⁹¹. Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)⁹²⁻¹⁰⁰. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC^{94-97,101-102}.

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation^{68,103}. Clinical benefit has been reported for patients with KRAS G12C-mutated solid tumors following treatment with G12C inhibitors such as sotorasib⁵⁷⁻⁵⁹ or adagrasib⁶⁰. However, clinical and preclinical resistance to G12C inhibitors, either by emergence of additional alterations in KRAS or other genes in the RTK/MAPK/PI3K pathway, have also been observed¹⁰⁴⁻¹⁰⁷. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, and K117N have been characterized as activating and oncogenic^{68,108-129}.

GENE

NRAS

ALTERATION

wildtype

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-

targeting antibodies cetuximab⁸⁴⁻⁸⁷ or panitumumab⁸⁸⁻⁹⁰ for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v2.2021).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations^{17100,130-135}. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis¹⁰⁰ and longer

survival¹³⁵⁻¹³⁶ of patients with CRC.

FINDING SUMMARY

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways⁶⁸. No alterations in NRAS were identified in this case.

ORDERED TEST # ORD-1201781-01

GENOMIC FINDINGS

GENE

PIK3CA

ALTERATION

Q546K

TRANSCRIPT ID

NM_006218

CODING SEQUENCE EFFECT

1636C>A

VARIANT ALLELE FREQUENCY (% VAF)

43.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K¹³⁷⁻¹³⁹, AKT¹⁴⁰⁻¹⁴¹, or mTOR¹⁴²⁻¹⁴⁹. Emerging evidence suggests that the glutaminase inhibitor telaglenastat has clinical activity in PIK3CA-

mutated colorectal cancer (CRC). A Phase 1 trial of telaglenastat and capecitabine for patients with CRC who progressed on fluoropyrimidine chemotherapy observed numerically increased median PFS for patients with PIK3CA mutation compared with patients with wildtype PIK3CA status (24.8 vs. 16 weeks, n=7 vs. n=4), including SD >30 weeks for 3 patients with PIK3CA mutation¹⁵⁰.

— Potential Resistance —

Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat CRC, even for tumors that harbor alterations in PIK3CA or PTEN; data are more limited for alterations in other genes in this pathway^{146,151-152}. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation¹⁵³⁻¹⁵⁷.

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 10–20% of colorectal cancers^{17,93,158-159}. A meta-analysis of 864 patients with colorectal cancer treated with cetuximab- or panitumumab-based therapy showed that PIK3CA mutations, particularly in exon 20 (H1047R), are significantly associated with worse response¹⁶⁰ and shorter progression-free and overall survival¹³³.

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival¹⁶¹⁻¹⁶². PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic¹⁶³⁻¹⁸³.

GENE

APC

ALTERATION

E1322*

TRANSCRIPT ID

NM_000038

CODING SEQUENCE EFFECT

3964G>T

VARIANT ALLELE FREQUENCY (% VAF)

81.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer

synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated¹⁸⁴. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines¹⁸⁵⁻¹⁸⁶. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models¹⁸⁷.

FREQUENCY & PROGNOSIS

APC alterations have been found in 77% of tumors in the Colorectal Adenocarcinoma TCGA dataset¹⁷. Inactivation of APC leads to activation of the Wnt/beta-catenin pathway, which is thought to play a role in the adenoma-carcinoma transition in some cancers, including colorectal cancer (CRC)¹⁸⁸. The prognostic significance of APC mutations in sporadic CRC remains unclear¹⁸⁹. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less

T-cell inflammation in one study¹⁹⁰.

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation¹⁹¹. Alterations such as seen here may disrupt APC function or expression¹⁹²⁻¹⁹⁶.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)¹⁹⁷⁻¹⁹⁹. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth²⁰⁰, and in the appropriate clinical context germline testing of APC is recommended.

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GENOMIC FINDINGS

<p>GENE SOX9</p> <p>ALTERATION Q369*</p> <p>TRANSCRIPT ID NM_000346</p> <p>CODING SEQUENCE EFFECT 1105C>T</p> <p>VARIANT ALLELE FREQUENCY (% VAF) 54.6%</p>	<p>POTENTIAL TREATMENT STRATEGIES — Targeted Therapies —</p> <p>There are no therapies available to directly address genomic alterations in SOX9.</p> <p>FREQUENCY & PROGNOSIS Mutation of SOX9 in cancer is typically rare, but it has been reported in 5-9% of colorectal carcinomas, most of which were truncating or frameshift alterations, and fewer than 4% of other tumor types (cBioPortal, COSMIC, Jan 2021)²⁰¹⁻²⁰³.</p>	<p>Increased expression of SOX9 has been associated with tumor development and/or increased aggressiveness of prostate cancer, pancreatic ductal adenocarcinoma, ovarian cancer, glioma, and esophageal adenocarcinoma²⁰⁴⁻²⁰⁷.</p> <p>FINDING SUMMARY SOX9 encodes a transcription factor important for the development and differentiation of multiple tissues, including cartilage, testis, and prostate²⁰⁸.</p>
<p>GENE SPEN</p> <p>ALTERATION R1470*</p> <p>TRANSCRIPT ID NM_015001</p> <p>CODING SEQUENCE EFFECT 4408C>T</p> <p>VARIANT ALLELE FREQUENCY (% VAF) 17.6%</p>	<p>SPEN inactivating mutations. Although gamma-secretase inhibitors are in clinical development to target NOTCH activation, it is not known if these therapies would be beneficial in the context of SPEN mutation.</p> <p>FREQUENCY & PROGNOSIS SPEN truncating mutations have been reported in adenoid cystic carcinoma (ACC) (21%)²⁰⁹ and splenic marginal zone lymphoma (SMZL) (5%)²¹⁰; NOTCH pathway gene mutations were frequent in both ACC and SMZL and observed in approximately 30% of cases²⁰⁹⁻²¹⁰.</p>	<p>HDAC1 and the SMRT/NcoR corepressors²¹¹⁻²¹². SPEN represses the transcriptional activity of the NOTCH signaling pathway²¹³⁻²¹⁴. Activation of NOTCH signaling results in binding of the transcription factor RBPJ to the NOTCH intracellular domain and consequent activation of the NOTCH transcriptional program²¹⁵. SPEN binding to RBPJ has been shown to repress NOTCH-mediated transcription²¹³⁻²¹⁴. SPEN alterations that result in loss of the RBPJ-interaction domain (aa 2804-2816)²¹³⁻²¹⁴ or the SPOC domain (aa 3498-3664)²¹² are predicted to disrupt binding of SPEN to RBPJ or corepressors and are likely to be inactivating.</p>
<p>POTENTIAL TREATMENT STRATEGIES — Targeted Therapies —</p> <p>There are no targeted therapies available to address</p>	<p>FINDING SUMMARY SPEN (also known as MINT or SHARP) encodes a transcriptional regulator that interacts with</p>	

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GENOMIC FINDINGS

GENE

TP53

ALTERATION

C135F

TRANSCRIPT ID

NM_000546

CODING SEQUENCE EFFECT

404G>T

VARIANT ALLELE FREQUENCY (% VAF)

71.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib²¹⁶⁻²¹⁹, or p53 gene therapy and immunotherapeutics such as SGT-53²²⁰⁻²²⁴ and ALT-801²²⁵. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type²²⁶. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer²²⁷. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer²²⁸. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone²²⁹. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/

or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel²³⁰. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations²³¹. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage²²⁴. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model²³². Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246²³³⁻²³⁵. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR²³⁶. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies²³⁷⁻²³⁸; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies²³⁹⁻²⁴⁰. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 60% of colorectal cancer cases^{17,241-246}. A study reported p53 expression in 49% of analyzed colorectal cancer cases²⁴⁷. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC²⁴⁸.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers²⁴⁹. Alterations such as seen here may disrupt TP53 function or expression²⁵⁰⁻²⁵⁴.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers²⁵⁵⁻²⁵⁷, including sarcomas²⁵⁸⁻²⁵⁹. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000²⁶⁰ to 1:20,000²⁵⁹. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30²⁶¹. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion²⁶²⁻²⁶⁷. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy²⁶²⁻²⁶³. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease²⁶⁸. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{266,269-270}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

ORDERED TEST # ORD-1201781-01

THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

Cetuximab

⊗ Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12C

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity for patients with CRC^{84-87,271-272}; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v2.2021). Activating mutations in either KRAS⁸⁴⁻⁸⁷ or NRAS^{133,246}, which function downstream of EGFR, are associated with lack of benefit of cetuximab for patients with CRC and indicate against the use of cetuximab (NCCN Colon Cancer Guidelines v3.2021).

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wild-type CRC, both as first-line combination therapy with FOLFIRI or

FOLFOX^{84-85,272} and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients^{86-87,271}. A prospective study of first-line cetuximab for patients with KRAS/NRAS/BRAF mutation-negative metastatic CRC resulted in limited efficacy, with 10.5% (2/19) of participants experiencing PRs and 57.9% (11/19) experiencing SDs²⁷³. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wild-type metastatic CRC resulted in an ORR of 79.5% (6 CR and 25 PRs, n=39) and a DCR of 92.3%²⁷⁴. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)²⁷⁵. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)²⁷⁶.

Panitumumab

⊗ Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12C

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity for patients with CRC^{88,275,277}; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v2.2021). Activating mutations in either KRAS⁸⁸⁻⁹⁰ or NRAS^{89,244}, which function downstream of EGFR, are associated with lack of benefit of panitumumab for patients with CRC and indicate against the use of panitumumab (NCCN Colon Cancer Guidelines, v3.2021).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and

ORR for patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFOX⁸⁸ and as monotherapy for chemotherapy-refractory patients^{275,277}. An open-label, randomized Phase 2 trial reported that for patients with unresectable RAS-wild-type colorectal adenocarcinoma treated with first-line panitumumab plus FOLFOX₄, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS 59% vs. 49%)²⁷⁸. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)²⁷⁵. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)²⁷⁶.

ORDERED TEST # ORD-1201781-01

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Sotorasib

Assay findings association
KRAS
G12C

AREAS OF THERAPEUTIC USE

Sotorasib is a KRAS G12C inhibitor that is FDA approved for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sotorasib has been reported to confer clinical benefit for patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC)^{59,279}; limited clinical data suggest sotorasib may also provide benefit in other G12C-mutated solid diseases^{59,280}.

SUPPORTING DATA

The Phase 1/2 CodeBreaK 100 trial of sotorasib for patients with previously treated locally advanced or metastatic G12C-mutated solid tumors observed significant benefit for patients with non-small cell lung cancer (NSCLC), achieving an ORR of 37%, a DCR of 81%, median PFS (mPFS) of 6.8 months, and median OS of 12.5 months^{59,279}. In the same study, patients with colorectal cancer (CRC) achieved a lower ORR of 7% (3/42) but had a high DCR of 74% (31/42) and mPFS of 4.0 months, and individual responses (PRs) were observed for patients with melanoma (1/1), pancreatic (1/11), endometrial (1/2), and appendiceal (1/2) cancers⁵⁹.

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

ORDERED TEST # ORD-1201781-01

CLINICAL TRIALS

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and

should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require

medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see [clinicaltrials.gov](https://www.foundationmedicine.com/genomic-testing#support-services). Or visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

GENE
KRAS
ALTERATION
G12C

RATIONALE
Clinical evidence suggests that patients with the KRAS G12C mutation may be sensitive to KRAS G12C specific inhibitors. KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS mutation may

predict sensitivity to PLK1 inhibitors. Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant colorectal cancer; combination therapies may be more effective.

NCT03600883

PHASE 1/2

A Phase 1/2, Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation.

TARGETS
KRAS

LOCATIONS: Fukuoka-shi (Japan), Matsuyama-shi (Japan), Seoul (Korea, Republic of), Wakayama-shi (Japan), Osaka-shi (Japan), Hirakata-shi (Japan), Nagoya-shi (Japan), Sunto-gun (Japan), Yokohama-shi (Japan), Kawasaki-shi (Japan)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

NCT04185883

PHASE 1/2

AMG 510 Activity in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101)

TARGETS
KRAS

LOCATIONS: Nagoya-shi (Japan), Kashiwa-shi (Japan), Washington, California, Utah

ORDERED TEST # ORD-1201781-01

CLINICAL TRIALS

NCT04303403
PHASE 1

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

TARGETS
JAK2, JAK1, MEK

LOCATIONS: Singapore (Singapore)

NCT04801966
PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK,
PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03905148
PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), Texas

NCT03785249
PHASE 1/2

MRTX849 in Patients With Cancer Having a KRAS G12C Mutation

TARGETS
KRAS

LOCATIONS: Alaska, Washington, Oregon, California, Montana

NCT04111458
PHASE 1

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

TARGETS
KRAS, SOS1, MEK

LOCATIONS: Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, Tennessee, Texas, North Carolina

ORDERED TEST # ORD-1201781-01

CLINICAL TRIALS

GENE
PIK3CA
ALTERATION
Q546K

RATIONALE

PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib. Several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced

significant clinical benefit when used as a monotherapy in patients with colorectal cancer; combination therapies may be required to overcome this lack of response. On the basis of preclinical and limited clinical data, PIK3CA activating mutations may predict sensitivity to glutaminase inhibitors.

NCT04589845
PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS

ALK, ROS1, TRKA, TRKB, TRKC, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

NCT04337463
PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS

mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02688881
PHASE 4

Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors

TARGETS

mTOR

LOCATIONS: Seoul (Korea, Republic of)

NCT04803318
PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS

mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT03772561
PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS

PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

ORDERED TEST # ORD-1201781-01

CLINICAL TRIALS

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK,
PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03439462

PHASE 1/2

ABI-009 (Nab-rapamycin) in Combination With FOLFOX and Bevacizumab as First-line Therapy in Patients With Advanced or Metastatic Colorectal Cancer

TARGETS
mTOR, VEGFA

LOCATIONS: Washington, Nevada, Arizona, Texas, New Jersey, Louisiana

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT03006172

PHASE 1

To Evaluate the Safety, Tolerability, and Pharmacokinetics of GDC-0077 Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer

TARGETS
PI3K-alpha, Aromatase, ER, CDK4,
CDK6

LOCATIONS: London (United Kingdom), Surrey (United Kingdom), Bordeaux (France), Barcelona (Spain), Valencia (Spain), Toronto (Canada), Massachusetts, New York, Tennessee

ORDERED TEST # ORD-1201781-01

APPENDIX
Variants of Unknown Significance

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BCOR
K1137R

BRCA1
R762S

ESR1
W200L

FLT1
R183C

PTCH1
D898N

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APPENDIX
Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	APC
AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2
BTB	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73
CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R
CTCF	CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1
DDR2	DIS3	DNMT3A	DOT1L	EED	EGFR	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FAM46C	FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12
FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3
FGFR4	FH	FLCN	FLT1	FLT3	FOXO2	FUBP1	GABRA6	GATA3
GATA4	GATA6	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDMSA	KDMS5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11A	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKB1A	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	P2RY8	PALB2
PARK2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA
PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI	PTCH1
PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	REL	RET
RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC	SDHD	SETD2
SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOC3
SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3	STK11	SUFU
SYK	TBX3	TEK	TET2	TGFBR2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1	WT1	XPO1
XRCC2	ZNF217	ZNF703						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT**	TPRPS2

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

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APPENDIX

About FoundationOne®CDx

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium.


ABOUT FOUNDATIONONE CDx

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details:
www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture-selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials
Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics

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APPENDIX

About FoundationOne®CDx

- of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
- The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
 - Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
 - Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
 - Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive,

and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in <https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/> report the frequency of *HER2* overexpression as 20% in breast cancer. Based on the F1CDx *HER2* CDx concordance study, approximately 10% of *HER2* amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	%CV*
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

*Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PALB2*, *PMS2*, *POLE*,

RAD51C, *RAD51D*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TSC2*, and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1*, *CBL*, *DNMT3A*, *IDH2*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating

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physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
mut/m	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 5.0.0

The median exon coverage for this sample is 958x

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