

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)	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE Colon
	NAME Liu, Mei Yuan		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S111-09524K (PF22143)
	DATE OF BIRTH 17 August 1950		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Female		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 08 March 2022
	MEDICAL RECORD # 22888751 PF22143		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 13 December 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

KRAS G12D
NRAS wildtype
KIT W557C
APC P1443fs*30
PIK3CA E545K
TP53 G245S

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

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: Dasatinib (p. 11), Imatinib (p. 11), Nilotinib (p. 12), Ponatinib (p. 12), Sorafenib (p. 12), Sunitinib (p. 13)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: ❌ **Cetuximab** (p. 9), **Panitumumab** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 2 Muts/Mb

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KRAS - G12D	Cetuximab	none
10 Trials see p. 17	Panitumumab	
NRAS - wildtype	Cetuximab	none
0 Trials	Panitumumab	
KIT - W557C	none	Dasatinib
		Imatinib
		Nilotinib
		Ponatinib
		Sorafenib
		Sunitinib
10 Trials see p. 15	none	none
APC - P1443fs*30		
3 Trials see p. 14	none	none
PIK3CA - E545K		
10 Trials see p. 19		

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.

TP53 - G245S 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.

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ORDERED TEST # ORD-1523347-01

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 microsatellite-stable (MSS) metastatic colorectal cancer (CRC), 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. For patients with MSS CRC, a Phase 2 study combining ipilimumab and nivolumab reported an overall DCR of 25% (10/40)⁷. Two Phase 1 studies for patients with MSS CRC treated with regorafenib and nivolumab reported PFSs of 7.9 months⁸ and 5.7 months⁹, and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR¹⁰.

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX¹¹⁻¹² and FOLFIRI¹³⁻¹⁴. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy¹⁵⁻¹⁶ but less likely to benefit from irinotecan chemotherapy¹⁷.

FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases^{3,18-22}. MSS colorectal cancers are

molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability²². Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors^{18,23-29}.

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 tumor²⁰. 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^{20,30-31}. 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^{19,32-33}. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{19-20,31,33}.

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BIOMARKER FINDINGS

BIOMARKER

Tumor Mutational Burden

RESULT

2 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-L1³⁴⁻³⁶, anti-PD-1 therapies³⁴⁻³⁷, and combination nivolumab and ipilimumab³⁸⁻⁴³. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors^{34-37,44-48}. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥ 10 Muts/Mb (as measured by this assay) compared with those with TMB < 10 Muts/Mb in a large cohort that included multiple tumor types⁴⁴; similar findings were observed in the KEYNOTE 028 and 012 trials³⁷. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores < 10 Muts/Mb (HR=0.68)⁴⁸. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples⁴⁹. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR

was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and < 16 Muts/Mb⁴⁷. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as $\geq 16-20$ Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy⁵⁰ or those with lower TMB treated with PD-1 or PD-L1-targeting agents³⁵. 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)³⁴. 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 inhibitors⁵¹.

FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples^{21,52-53}. Multiple studies have reported that up to 90% of hypermutated CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)^{21,52}. 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 MMR⁵². A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which leads to an "ultramutated" phenotype with especially high TMB^{21,52}. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB^{21,52}, whereas TMB-low tumors more frequently harbor mutations in TP53 and APC²¹. The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A

study of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones⁵⁴. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS⁵⁵. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival⁵⁶. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies⁵⁷. In a study for 61 patients with metastatic, 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 compared with plasma TMB scores < 28 Muts/Mb (3.0 vs. 5.3 months, HR=0.76, $p=0.007$), whereas tTMB was not found to be prognostic in this population⁵⁸.

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 melanoma⁵⁹⁻⁶⁰ and cigarette smoke in lung cancer⁶¹⁻⁶², treatment with temozolomide-based chemotherapy in glioma⁶³⁻⁶⁴, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes^{21,65-68}, and microsatellite instability (MSI)^{21,65,68}. 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^{34,44,51}.

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ORDERED TEST # ORD-1523347-01

GENOMIC FINDINGS

GENE
KRAS

ALTERATION
G12D

TRANSCRIPT ID
NM_004985.3

CODING SEQUENCE EFFECT
35G>A

VARIANT CHROMOSOMAL POSITION
chr12:25398284

VARIANT ALLELE FREQUENCY (% VAF)
56.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib⁶⁹⁻⁷⁴. 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 CRC⁷⁵⁻⁷⁹. Both clinical⁸⁰⁻⁸¹ and preclinical⁸²⁻⁸³ 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 inhibitors⁸¹, RAF inhibitors⁸², pan-ERBB inhibitors⁸³, or chemotherapeutic agents⁸⁰. In a Phase 1 study evaluating the MEK-pan-RAF

dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NSCLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma⁸⁴. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study⁸⁵⁻⁸⁶. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors⁸⁷⁻⁸⁸. 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 mutations⁸⁹. 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 cancer⁹⁰. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors⁹¹⁻⁹². Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations⁹³⁻⁹⁴. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors⁹⁵. 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 surgery⁹⁶.

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab⁹⁷⁻¹⁰⁰ or panitumumab¹⁰¹⁻¹⁰³ for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v1.2022).

FREQUENCY & PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)¹⁰⁴⁻¹¹². Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC^{106-109,113-114}.

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^{70,115}. 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, E63K, R68S, and K117N have been characterized as activating and oncogenic^{70,116-138}.

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 cetuximab⁹⁷⁻¹⁰⁰ or panitumumab¹⁰¹⁻¹⁰³ for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v1.2022).

— Potential Resistance —

Based on clinical data, it is unclear whether the presence of PIK3CA mutations is associated with reduced sensitivity to cetuximab in patients with colorectal cancer (CRC). Detection of PIK3CA mutations at progression was observed for patients with CRC following treatment with cetuximab¹³⁹⁻¹⁴¹. A study comparing PIK3CA exon 9 and 20 mutations reported that for patients with chemotherapy-refractory CRC, PIK3CA exon 20 mutations were associated with less benefit from cetuximab compared with PIK3CA wildtype; this effect was not observed with PIK3CA exon 9 mutations¹⁴². In contrast, multiple studies and case reports of cetuximab treatment of CRC have reported similar responses in patients with PIK3CA exon 9 or 20 mutations compared with PIK3CA wildtype¹⁴³⁻¹⁴⁹.

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations^{21,112,142,150-154}. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis¹¹² and longer survival¹⁵⁴⁻¹⁵⁵ 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 pathways⁷⁰. No alterations in NRAS were identified in this case.

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GENOMIC FINDINGS

GENE
KIT

ALTERATION
W557C

TRANSCRIPT ID
NM_000222.2

CODING SEQUENCE EFFECT
1671G>T

VARIANT CHROMOSOMAL POSITION
chr4:55593605

VARIANT ALLELE FREQUENCY (% VAF)
37.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, primarily in gastrointestinal stromal tumor (GIST), melanoma, AML, and systemic mastocytosis, KIT activating alterations are associated with sensitivity to TKIs including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, regorafenib, ponatinib, midostaurin, apatinib, avapritinib, and ripretinib¹⁵⁶⁻¹⁶⁵. The use of mTOR inhibitors as an alternative therapeutic strategy has demonstrated

limited success in KIT-mutated, imatinib-resistant melanoma, with 1 PR and 3 SD observed for 4 patients treated with everolimus¹⁶⁶. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation¹⁶⁷. The role of KIT amplification as a biomarker for response to mTOR inhibitors has not been investigated (PubMed, Mar 2022).

— 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 pathway¹⁶⁸⁻¹⁷⁰.

FREQUENCY & PROGNOSIS

KIT mutation has been reported in 3-6% of colorectal carcinomas analyzed^{21,171}. KIT protein expression has been reported in 17-59% of colorectal carcinomas¹⁷²⁻¹⁷³. The prognostic significance of KIT expression in colorectal cancer is unclear, with some studies reporting an association with or a trend toward reduced disease-free survival, and another study finding a

trend toward better overall survival in patients with KIT-positive colorectal cancer¹⁷²⁻¹⁷⁴.

FINDING SUMMARY

KIT (also called c-KIT) encodes a cell surface tyrosine kinase receptor that, upon ligand binding and dimerization, activates the PI3K-AKT and RAS-MAPK signaling pathways¹⁷⁵. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein¹⁷⁶. This KIT alteration occurs within the autoinhibitory juxtamembrane domain (Y544-H579) of the c-KIT protein, a hotspot region for mutations (exon 11); such mutations are expected to disrupt an autoinhibitory mechanism of KIT, resulting in gain-of-function activation¹⁷⁷⁻¹⁸². Furthermore, mutation at the W557 position, specifically W557G¹⁸³, has been characterized as activating. KIT W557R was found in the germline of a family with autosomal dominant predisposition to GIST¹⁸⁴. Patients with GIST with the W557G or W557S mutations were reported to respond to imatinib¹⁸⁵⁻¹⁸⁶, and a patient with the W557G mutation responded to sunitinib¹⁸⁷. Therefore, any mutation at the W557 position is likely activating.

GENE
APC

ALTERATION
P1443fs*30

TRANSCRIPT ID
NM_000038.4

CODING SEQUENCE EFFECT
4328delC

VARIANT CHROMOSOMAL POSITION
chr5:112175617-112175618

VARIANT ALLELE FREQUENCY (% VAF)
77.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation

of WNT pathway transcription programs¹⁸⁸, and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP¹⁸⁹⁻¹⁹⁰. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days¹⁹¹; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386¹⁹²⁻¹⁹³.

FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset²¹. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples¹⁹⁴. The prognostic significance of APC mutations in sporadic CRC remains unclear¹⁹⁵. Solid tumors with WNT/beta-catenin pathway

alterations, as seen here, were observed to have significantly less T-cell inflammation in one study¹⁹⁶.

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 differentiation¹⁹⁷. Alterations such as seen here may disrupt APC function or expression¹⁹⁸⁻²⁰².

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)²⁰³⁻²⁰⁵. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth²⁰⁶, and in the appropriate clinical context germline testing of APC is recommended.

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GENOMIC FINDINGS

GENE

PIK3CA

ALTERATION

E545K

TRANSCRIPT ID

NM_006218.2

CODING SEQUENCE EFFECT

1633G>A

VARIANT CHROMOSOMAL POSITION

chr3:178936091

VARIANT ALLELE FREQUENCY (% VAF)

37.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K²⁰⁷⁻²¹⁴, AKT²¹⁵⁻²¹⁶, or mTOR²¹⁷⁻²²⁴. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate²¹⁴. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)²¹³. Two other

studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations²¹¹⁻²¹². 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 mutation²²⁵.

— 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 pathway¹⁶⁸⁻¹⁷⁰. Based on clinical data, it is unclear whether the presence of PIK3CA mutations is associated with reduced sensitivity to cetuximab in patients with colorectal cancer (CRC). Detection of PIK3CA mutations at progression was observed for patients with CRC following treatment with cetuximab¹³⁹⁻¹⁴¹. A study comparing PIK3CA exon 9 and 20 mutations reported that for patients with chemotherapy-refractory CRC, PIK3CA exon 20 mutations were associated with less benefit from

cetuximab compared with PIK3CA wildtype; this effect was not observed with PIK3CA exon 9 mutations¹⁴². In contrast, multiple studies and case reports of cetuximab treatment of CRC have reported similar responses in patients with PIK3CA exon 9 or 20 mutations compared with PIK3CA wildtype¹⁴³⁻¹⁴⁹.

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in up to 19% of colorectal cancers (CRCs)^{21,226}. 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 response²²⁷ and shorter progression-free and overall survival¹⁴². A study of 354 patients with metastatic colorectal cancer observed no difference in overall survival between patients with PIK3CA mutations versus those without (21.7 months vs. 22.4 months, respectively); however, the study did not include treatment information for the patients²²⁸.

FINDING SUMMARY

PIK3CA encodes p110-α, 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 survival²²⁹⁻²³⁰. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic²³¹⁻²⁵².

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ORDERED TEST # ORD-1523347-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

G245S

TRANSCRIPT ID

NM_000546.4

CODING SEQUENCE EFFECT

733G>A

VARIANT CHROMOSOMAL POSITION

chr17:7577548

VARIANT ALLELE FREQUENCY (% VAF)

66.2%

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 adavosertib²⁵³⁻²⁵⁶ or p53 gene therapy such as SGT53²⁵⁷⁻²⁶¹. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype²⁶². A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer²⁶³. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer²⁶⁴. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone²⁶⁵. In the Phase 2 VIKTORY trial, patients with TP53-mutated

metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel²⁶⁶. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations²⁶⁷. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring²⁶⁸. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage²⁶¹. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR²⁶⁹. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)²⁷⁰.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases^{21,271-276}. A study reported p53 expression in 49% of analyzed colorectal cancer cases²⁷⁷. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC²⁷⁸.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers²⁷⁹. Alterations such as seen here may disrupt TP53 function or

expression²⁸⁰⁻²⁸⁴.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)²⁸⁵. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers²⁸⁶⁻²⁸⁸, including sarcomas²⁸⁹⁻²⁹⁰. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000²⁹¹ to 1:20,000²⁹⁰. 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 30²⁹². 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 expansion²⁹³⁻²⁹⁸. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy²⁹³⁻²⁹⁴. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease²⁹⁹. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{297,300-301}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

Cetuximab

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

Assay findings association

KRAS

G12D

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^{97-100,302-303}; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v1.2022). Activating mutations in either KRAS⁹⁷⁻¹⁰⁰ or NRAS^{142,276}, 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 Guidelines v1.2022). A study comparing PIK3CA exon 9 and 20 mutations reported that for patients with chemotherapy-refractory CRC, PIK3CA exon 20 mutations were associated with less benefit from cetuximab compared with PIK3CA wildtype (ORR of 0.0% [0/9] vs. 37% [121/329], PFS of 11.5 vs. 24 weeks, and OS of 34 vs. 51 weeks); this effect was not observed with PIK3CA exon 9 mutations (ORR of 29% [6/21] vs. 36% [115/317], PFS of 23.5 vs. 24 weeks, and OS of 46 vs. 51 weeks)¹⁴². The presence of PIK3CA exon 9 and 20 mutations showed no correlation with objective tumor response to cetuximab but was associated with reduced PFS in response to cetuximab salvage therapy (HR=2.1)³⁰⁴. In contrast, multiple studies and case reports of cetuximab treatment of CRC have reported similar responses in patients with PIK3CA exon 9 or 20 mutations compared with PIK3CA wildtype^{143-149,305}.

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFIRI, FOLFOX4, or irinotecan^{97-98,302-303,306} and as monotherapy for chemotherapy-refractory patients^{100,147}. The Phase 3 study STRATEGIC-1 reported a similar duration of disease control (DDC) for patients with unresectable metastatic CRC (mCRC) and KRAS-, NRAS-, and BRAF-wildtype status treated with mFOLFOX-bevacizumab alternated with a cetuximab regimen in first or second line, respectively (overall DDC 22.5 vs. 23.5 months); in addition, the study reported similar OS (37.8 vs. 34.4 months) and higher numerical ORR for patients treated with cetuximab in the first line followed by mFOLFOX-bevacizumab compared with those receiving EGFR-directed antibodies in the second or third line³⁰⁷. A prospective study of cetuximab monotherapy for patients with KRAS-, NRAS-, and BRAF-wildtype mCRC reported 11% (2/19) PRs and 58% (11/19) SDs¹⁴⁸. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wildtype mCRC resulted in an ORR of 81% (4 CR and 27 PRs, n=37) and a DCR of 89%³⁰⁸. 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)³⁰⁹. 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)³¹⁰.

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

Panitumumab

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

Assay findings association

KRAS
G12D

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^{101,309,311}; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v1.2022). Activating mutations in either KRAS¹⁰¹⁻¹⁰³ or NRAS^{102,274}, 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 v1.2022, NCCN Rectal Cancer Guidelines v1.2022).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFOX4, FOLFIRI, irinotecan, or best supportive care^{101,312-315}, and as

monotherapy for chemotherapy-refractory patients^{274,309,311}. The Phase 3 PARADIGM trial comparing panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 as first-line treatment for patients with RAS-wildtype left-sided metastatic CRC demonstrated that treatment with panitumumab significantly improved median OS (mOS; 36.2 months vs. 31.3 months) compared with bevacizumab³¹⁶. A Phase 2 trial reported that, for patients with unresectable RAS-wildtype colorectal adenocarcinoma treated with panitumumab plus FOLFOX4, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS OF 59% vs. 49%)³¹⁷. 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)³⁰⁹. 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)³¹⁰.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Dasatinib

Assay findings association
KIT
W557C

AREAS OF THERAPEUTIC USE

Dasatinib is a kinase inhibitor that targets the BCR-ABL fusion protein, SRC family kinase receptors, KIT, EPHA2, and PDGFR-beta. It is FDA approved for the treatment of certain subtypes of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in melanoma³¹⁸⁻³¹⁹ and preclinical evidence in other cancer types³²⁰⁻³²¹, activating KIT alterations may confer sensitivity to dasatinib.

Preclinical and limited clinical data indicate that secondary imatinib-resistant mutations, including V654A and A-loop alterations at residues D816, D820, N822, and A829, remain sensitive to dasatinib³²¹⁻³²⁶.

SUPPORTING DATA

Dasatinib has been primarily evaluated for the treatment of CML and ALL. A Phase 2 study of single-agent dasatinib in metastatic colorectal cancer did not report activity for the drug³²⁷. Dasatinib in combination with other targeted therapies has shown efficacy in preclinical investigations of colorectal cancer cells and models³²⁸⁻³³⁰.

Imatinib

Assay findings association
KIT
W557C

AREAS OF THERAPEUTIC USE

Imatinib targets the BCR-ABL fusion protein, PDGFR, and KIT. It is FDA approved for the treatment of KIT-positive gastrointestinal stromal tumors (GIST), Ph+ chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL), myelodysplastic syndrome/myeloproliferative syndrome (MDS/MPS), aggressive systemic mastocytosis without a D816V KIT mutation, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-

mutated³³¹⁻³³⁴, KIT-amplified^{331,334-336}, or KIT-expressing tumors³³⁷⁻³⁴⁴, KIT activating alterations may confer sensitivity to imatinib.

SUPPORTING DATA

A Phase 1 study reported stable disease in 20% (7/35) patients with refractory Stage 4 CRC for more than 6 months upon treatment with bevacizumab, cyclophosphamide, and imatinib³⁴⁵. Of 49 patients with metastatic CRC who were treated with XELOX (capecitabine plus oxaliplatin), bevacizumab, and imatinib as a first-line therapy, a 6 month progression-free survival (PFS) of 76%, median PFS of 10.6 months, and median overall survival of 23.2 months was observed³⁴⁶.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Nilotinib

Assay findings association
KIT
W557C

AREAS OF THERAPEUTIC USE

Nilotinib targets tyrosine kinases such as ABL (including BCR-ABL), PDGFRs, KIT, CSF1R, DDR1, and DDR2. It is FDA approved to treat newly diagnosed pediatric or adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, adults with Ph+ CML in chronic or accelerated phase with resistance or intolerance to prior therapy including imatinib, and pediatric patients with Ph+ CML in chronic phase with resistance or intolerance to prior tyrosine-kinase inhibitor therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated³⁴⁷⁻³⁵¹, KIT-amplified³⁴⁷, or KIT-expressing tumors³⁵², KIT activating alterations may confer sensitivity to nilotinib.

SUPPORTING DATA

Clinical data on the efficacy of nilotinib for the treatment of colorectal cancer are limited (PubMed, Jul 2022). Nilotinib has been primarily investigated as a therapeutic

option for the treatment of CML or gastrointestinal stromal tumors (GIST). In the context of CML, a Phase 3 clinical trial of Ph+ patients treated with imatinib or nilotinib (300 mg or 400 mg) reported progression-free survival (PFS) rates of 93% and 97-98% and overall survival (OS) rates of 93% and 94-97%, respectively, at 4 years³⁵³. For imatinib-resistant Japanese patients with CML, a Phase 2 trial reported a 47.8% major medical response rate to treatment with nilotinib at 12 months³⁵⁴. A Phase 3 clinical trial of single-agent nilotinib in 240 patients with advanced GIST who failed prior treatment with imatinib or sunitinib reported no significant difference in progression-free survival between nilotinib and the best supportive care, but did report increased overall survival for nilotinib-treated patients³⁵⁵. A Phase 2 trial has shown that nilotinib was well tolerated and suggested it may be particularly useful for treating patients with GIST harboring mutations in KIT exon 17³⁵⁶. Preclinical, cell-based assays have reported efficacy for nilotinib alone and in combination with additional therapies in the context of leiomyosarcoma and synovial sarcoma³⁵⁷.

Ponatinib

Assay findings association
KIT
W557C

AREAS OF THERAPEUTIC USE

Ponatinib is a multikinase inhibitor targeting BCR-ABL, RET, KIT, FLT-3, PDGFRs, VEGFRs, FGFRs, and other tyrosine kinases. It is FDA approved for the treatment of advanced, T315I-mutated chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), as well as for CML and Ph+ ALL patients for whom no other tyrosine kinase inhibitor is indicated. Please see the drug label for full prescribing information.

GENE ASSOCIATION

KIT exon 9 and 11 activating mutations have demonstrated sensitivity to ponatinib in several

preclinical cell models³⁵⁸⁻³⁶³, with clinical efficacy demonstrated in patients with GIST exhibiting exon 11 mutations³⁶⁴⁻³⁶⁵ and imatinib resistance³⁶⁶.

SUPPORTING DATA

Clinical data on the efficacy of ponatinib for the treatment of colorectal cancer are limited (PubMed, Sep 2022). Clinically, ponatinib has been most extensively studied in patients with BCR-ABL-positive hematological malignancies. Ponatinib has shown efficacy in preclinical models of endometrial, bladder, gastric, breast, lung, colon, and medullary thyroid carcinomas and is being clinically tested in some solid tumor types³⁶⁷⁻³⁶⁹.

Sorafenib

Assay findings association
KIT
W557C

AREAS OF THERAPEUTIC USE

Sorafenib is a kinase inhibitor that targets the RAF kinases, KIT, FLT3, RET, VEGFRs, and PDGFRs. It is FDA approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and recurrent or metastatic differentiated thyroid carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated^{326,370-376} or KIT-expressing tumors³⁷⁷⁻³⁸⁰, KIT

activating alterations may predict sensitivity to sorafenib.

SUPPORTING DATA

A Phase 2b study of sorafenib in combination with mFOLFOX6 in the treatment of metastatic colorectal cancer (CRC) reports no benefit of this combination³⁸¹. A Phase 1b study reports a modest response rate for the combination of sorafenib and cetuximab or irinotecan in CRC³⁸². A patient with CRC with a FLT3 amplification and a KRAS mutation has been reported to achieve significant benefit from sorafenib treatment³⁸³.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Sunitinib

Assay findings association
KIT
W557C

AREAS OF THERAPEUTIC USE

Sunitinib is a small-molecule tyrosine kinase inhibitor that targets PDGFRs, VEGFRs, KIT, FLT3, CSF-1R, and RET. It is FDA approved for the treatment of advanced or metastatic pancreatic neuroendocrine tumors, gastrointestinal stromal tumors (GISTs) in patients who have progressed on or are intolerant to imatinib, and advanced renal cell carcinoma (RCC) as well as for the adjuvant treatment of patients at high risk of recurrent RCC after nephrectomy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated^{187,384-388} or KIT-expressing tumors^{187,389}, KIT activating alterations may predict sensitivity to sunitinib.

SUPPORTING DATA

Sunitinib is in clinical trials in metastatic colorectal carcinoma (CRC)³⁹⁰⁻³⁹². A PR was reported in 1 patient with CRC in a clinical study of sunitinib in solid tumors³⁹³. No objective responses were reported in a clinical study of sunitinib in metastatic CRC³⁹², although 20% of evaluable patients with CRC in a Phase 1 clinical trial of alternative dosing of sunitinib reached a PFS of more than 5 months³⁹⁴. A clinical study of sunitinib combination therapy in metastatic CRC reported no objective responses but did observe subjective response in 13/29 patients³⁹⁵. A Phase 3 clinical trial of 768 patients with metastatic CRC treated with fluorouracil, leucovorin, and irinotecan (FOLFIRI) in combination with sunitinib did not show significant clinical benefit; sunitinib in combination with FOLFIRI also showed a poor safety profile³⁹⁶.

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.

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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.clinicaltrials.gov). Or, visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

GENE
APC
ALTERATION

P1443fs*30

RATIONALE

Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT05091346
PHASE 1/2

A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors

TARGETS
CBP, Beta-catenin, PD-1

LOCATIONS: Fukuoka (Japan), Osaka (Japan), Shizouka (Japan), Tokyo (Japan), Chiba-shi (Japan), Kashiwa (Japan), Sapporo shi (Japan), Manchester (United Kingdom), Barcelona (Spain), Valencia (Spain)

NCT04008797
PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Osakasayama (Japan), Nagoya (Japan), Chuo-Ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT03264664
PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)

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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

ORDERED TEST # ORD-1523347-01

CLINICAL TRIALS
GENE
KIT
ALTERATION
W557C
RATIONALE

KIT amplification or activating mutations may predict sensitivity to small molecule tyrosine kinase inhibitors. Also, because KIT activation leads to activation of the PI3K-AKT-mTOR pathway, PI3K and mTOR pathway inhibitors may be relevant in a tumor with KIT activation. 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.

NCT05098847
PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

TARGETS

FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China)

NCT05024214
PHASE 1/2

Phase Ib/II Trial of Envafolelimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS

PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT05014828
PHASE 2

To Evaluate the Efficacy and Safety of Tislelizumab in Combination With Lenvatinib in Patients With Selected Solid Tumors

TARGETS

PD-1, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Hangzhou (China), Nanchang (China), Nanjing (China), Hefei (China), Changsha (China), Wuhan (China), Nanning (China), Chongqing (China), Beijing (China), Harbin (China)

NCT04976634
PHASE 2

Pembrolizumab Plus Lenvatinib in Combination With Belzutifan in Solid Tumors (MK-6482-016)

TARGETS

HIF2a, PD-1, KIT, VEGFRs, FGFRs, PDGFRA, RET

LOCATIONS: Seoul (Korea, Republic of), Gosford (Australia), Westmead (Australia), Epping (Australia), Malvern (Australia), Haifa (Israel), Jerusalem (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Utrecht (Netherlands)

NCT04803318
PHASE 2

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

TARGETS

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

LOCATIONS: Guangzhou (China)

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CLINICAL TRIALS
NCT04008797
PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET,
PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Osakasayama (Japan), Nagoya (Japan), Chuo-Ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT04977453
PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT,
PD-1, CTLA-4

LOCATIONS: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT03564691
PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs,
KIT, PD-1

LOCATIONS: Seoul (Korea, Republic of), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland), Thessaloniki (Greece), Heraklion (Greece)

NCT04729348
PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

TARGETS
PD-1, KIT, VEGFRs, FGFRs, PDGFRA,
RET

LOCATIONS: Massachusetts

NCT02379416
PHASE 1

Combination Nilotinib and Paclitaxel in Adults With Relapsed Solid Tumors

TARGETS
ABL, KIT

LOCATIONS: Maryland

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ORDERED TEST # ORD-1523347-01

CLINICAL TRIALS
GENE
KRAS
ALTERATION
G12D
RATIONALE

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. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity

to MEK-pan-RAF dual 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.

NCT04985604
PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT04803318
PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03284502
PHASE 1

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

TARGETS
MEK, RAFs, NRAS

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

NCT04303403
PHASE 1

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

TARGETS
JAK2, JAK1, MEK

LOCATIONS: Singapore (Singapore)

NCT04870034
PHASE NULL

Binimetinib and Palbociclib Before Surgery for the Treatment of Operable KRAS-Positive Lung, Colorectal, or Pancreatic Cancer

TARGETS
MEK, CDK4, CDK6

LOCATIONS: New York

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)

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CLINICAL TRIALS
NCT04720976
PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

NCT04965818
PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS
MEK, FGFRs

LOCATIONS: California, Indiana, Texas

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), California, Texas

NCT04551521
PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

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ORDERED TEST # ORD-1523347-01

CLINICAL TRIALS
GENE
PIK3CA
ALTERATION
E545K
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

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

NCT04803318
PHASE 2

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

TARGETS

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

LOCATIONS: Guangzhou (China)

NCT04526470
PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS

PI3K-alpha

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

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)

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)

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CLINICAL TRIALS
NCT04317105
PHASE 1/2

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Texas, Virginia

NCT04551521
PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

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, CDK6, CDK4

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

NCT03673787
PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03842228
PHASE 1

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TARGETS
PI3K, PD-L1, PARP

LOCATIONS: Massachusetts, Texas

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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.

ATRX
 I901V

AXL
 P87L and R791Q

GNAS
 P221S

PDGFRB
 R370C

PIK3C2G
 S125F

RET
 R417H

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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 or WTX)	
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	BTK	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	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNFI1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	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	MRE11 (MRE11A)	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	NTRK3
P2RY8	PALB2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCC1 (PD-1)	PDCC1LG2 (PD-L2)
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1
PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI
PRKN (PARK2)	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	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)	TET2	TET2	TGFB2
TIPARP	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA
VHL	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**	TPRSS2

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Homologous Recombination status
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, Ciplstraat 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 PRINCIPLE

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. 2022. 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. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

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- analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- 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 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.
 - Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score $\geq 16\%$ will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
 - 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%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal

hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

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

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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 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/Mb	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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.4.0

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APPENDIX
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