FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Liao, She Chuan	Colon adenocarcinoma (CRC)	11 Oct 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1469834-01

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 Liao, She Chuan
DATE OF BIRTH 28 March 1966
SEX Male
MEDICAL RECORD # 23549066

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Omentum
SPECIMEN ID S111-09223A (PF22112)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 07 March 2022
SPECIMEN RECEIVED 03 October 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

KRAS G12D
NRAS wildtype
RNF43 splice site 582+2T>G, G400fs*10
KEAP1 loss exons 3-6
SMAD4 W524L
TET2 E1151* - subclonal†
TP53 L252_I254del

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

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **potential resistance** based on this patient's genomic findings: ⊗ **Cetuximab** (p. 10), **Panitumumab** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***TET2*** **E1151*** (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section	
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. 12	***Panitumumab*** ⊗	
***NRAS* -** wildtype	***Cetuximab*** ⊗	none
0 Trials	***Panitumumab*** ⊗	
***RNF43* -** splice site 582+2T>G, G400fs*10	none	none
4 Trials see p. 14		

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

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VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

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.

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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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 inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. 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 months[8] and 5.7 months[9], and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR[10].

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX[11-12] and FOLFIRI[13-14]. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy[15-16] but less likely to benefit from irinotecan chemotherapy[17].

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 instability[22]. 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 tumor[20]. 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

Tumor Mutational Burden

RESULT
4 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-L1[34-36], anti-PD-1 therapies[34-37], and combination nivolumab and ipilimumab[38-43]. 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 types[44]; similar findings were observed in the KEYNOTE 028 and 012 trials[37]. 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 samples[49]. 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/Mb[47]. Similarly, 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 chemotherapy[50] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[35]. 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 inhibitors[51].

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 MMR[52]. 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 APC[21]. 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 ones[54]. 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 OS[55]. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival[56]. 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 therapies[57]. 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 population[58].

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 melanoma[59-60] and cigarette smoke in lung cancer[61-62], treatment with temozolomide-based chemotherapy in glioma[63-64], 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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GENE
KRAS

ALTERATION
G12D

TRANSCRIPT ID
NM_004985.3

CODING SEQUENCE EFFECT
35G>A

VARIANT CHROMOSOMAL POSITION
chr12:25398284

VARIANT ALLELE FREQUENCY (% VAF)
89.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[69-74]. 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 CRC[75-79]. Both clinical[80-81] and preclinical[82-83] 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 inhibitors[81], RAF inhibitors[82], pan-ERBB inhibitors[83], or chemotherapeutic agents[80]. 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 (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[84]. 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 study[85-86] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[87-88]. 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 mutations[89]. 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 cancer[90]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[91-92]. 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 mutations[93-94] . Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors[95]. 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 surgery[96].

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab[97-100] or panitumumab[101-103] 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 cetuximab[97-100] or panitumumab[101-103] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v1.2022).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[21,112,139-144]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[112] and longer survival[144-145] 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 pathways[70]. No alterations in NRAS were identified in this case.

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GENE
RNF43

ALTERATION
splice site 582+2T>G, G400fs*10

TRANSCRIPT ID
NM_017763.4, NM_017763.4

CODING SEQUENCE EFFECT
582+2T>G, 1197_1224del28

VARIANT CHROMOSOMAL POSITION
chr17:56440634 , chr17:56435912-56435940

VARIANT ALLELE FREQUENCY (% VAF)
87.6%, 79.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies have reported that RNF43 is a negative regulator of WNT signaling, and RNF43 loss or inactivation leads to WNT activation and confers sensitivity to WNT pathway inhibitors, particularly Porcupine inhibitors, in multiple tumor types[146-150]. In a Phase 1 basket study for the Porcupine inhibitor RXC004, 1 of 2 patients with tumors harboring an RNF43 mutation achieved SD[151]. Of the patients with WNT-ligand-dependent tumors, including those with RNF43 mutations, RSPO fusions, or those with biliary tract or thymus cancer, 71% (5/7) experienced SD[151]. Therefore, patients whose tumors harbor inactivating alterations in RNF43 may benefit from WNT pathway inhibitors, which are under investigation in clinical trials.

FREQUENCY & PROGNOSIS

Mutations in RNF43 have been reported in 18-27% of endometrial cancers[152-153], 3-5% of pancreatic cancers[154], 21% of ovarian mucinous carcinomas[155], 9% of liver fluke-associated cholangiocarcinomas[156], and up to 18% of colorectal cancers[21,153]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[153], endometrial[153], and gastric cancers[157-158]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[157].

FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[159] that was discovered because it is overexpressed in colon cancer[160]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[146-150]. An additional tumor-suppressor-like role for RNF43 in colon cancer is hypothesized to occur via its interaction with the ubiquitin-protein ligase NEDL1, which is predicted to enhance the pro-apoptotic effects of p53[161].

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GENE
KEAP1

ALTERATION
loss exons 3-6

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A study of patients with localized non-small cell lung cancer (NSCLC) identified pathogenic KEAP1 and NFE2L2 mutations as predictors of local recurrence following radiotherapy but not surgery; limited preclinical data also showed that treatment with a glutaminase inhibitor sensitized KEAP1-mutated NSCLC cells to radiation[162]. In other preclinical studies, treatment with AKT inhibitors sensitized lung cancer cells harboring KEAP1 or NFE2L2 mutations to both chemotherapy and radiation therapy[163-164]. Mixed clinical data have been reported for the association between KEAP1 mutations and the response to immunotherapy. A pan-cancer study of immunotherapy showed that patients with KEAP1 mutations had shorter OS (10 vs. 20 months) than those without[165]. However, another study across solid tumors showed that KEAP1 mutations were associated with higher tumor mutational burden (TMB) and PD-L1 expression, as well as improved survival outcomes with immunotherapy compared with other treatments (20.0 vs. 11.5 months)[166]. For patients with non-small cell lung cancer (NSCLC), a study of PD-L1 inhibitors showed that patients with concurrent mutations of STK11 and KEAP1 (n=39) experienced significantly shorter PFS (1.6 vs. 2.5 months, HR=1.5) and OS (4 vs. 11 months, HR=1.9) compared with patients with STK11- and KEAP1-wildtype tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[167]. Retrospective analyses of patients with NSCLC who received immunotherapy reported reduced OS (p=0.040) for patients harboring KEAP1- or NFE2L2-mutated tumors[168] or STK11- or KEAP1-mutated tumors (p <0.001)[169] compared with those without. Studies of immune checkpoint inhibitors for patients with lung adenocarcinoma showed that coexisting mutations between KEAP1, PBRM1, SMARCA4, STK11, and KRAS were associated with worse OS[170]. An exploratory analysis of a subset of patients with PD-L1-positive NSCLC treated in the first-line setting with pembrolizumab showed similar ORR, PFS, and OS when comparing patients with STK11 or KEAP1 mutations and those without[171]. In addition, preclinical data suggest that KEAP1 inactivation increases tumor demand for glutamine and increases tumor sensitivity to glutaminase inhibitors like telaglenastat[172-174]. Limited clinical data suggest that KEAP1 mutations may predict improved clinical benefit from combinations of glutaminase inhibitors and anti-PD-1 inhibitors[175]; a Phase 1/2 study of the glutaminase inhibitor telaglenastat (CB-839) plus nivolumab to treat advanced NSCLC reported better clinical benefit rates and median PFS for patients with KEAP1 mutations (75% [3/4] vs. 15% [2/13], 6.4 vs. 3.7 months), KRAS mutations (38% [3/8] vs. 20% [2/10], 4.5 vs. 3.7 months), or KEAP1 and KRAS concurrent mutations (100% [2/2] vs. 13% [1/8], 7.2 vs. 3.7 months) compared with patients without these mutations[175]. The KEAP1 mutation has also been identified as a potential biomarker for sensitivity to combined AKT and TXNRD1 inhibition in lung cancer[176].

FREQUENCY & PROGNOSIS

Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[177]. KEAP1 mutations are rare in hematological malignancies, occurring in fewer than 1% of samples analyzed (COSMIC, 2022)[178]. In a retrospective analysis of the pan-solid MSKCC dataset, KEAP1 mutation correlated with reduced OS (13.28 vs. 26.53 months)[166].

FINDING SUMMARY

KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate specificity for a CUL3-dependent ubiquitin ligase[179]. KEAP1 exerts anti-tumor effects through negative regulation of NRF2, a transcription factor encoded by NFE2L2[180-182]; KEAP1 inactivation promotes cancer progression through NRF2-mediated chemoresistance and cell growth[181-182].

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GENE
SMAD4

ALTERATION
W524L

TRANSCRIPT ID
NM_005359.5

CODING SEQUENCE EFFECT
1571G>T

VARIANT CHROMOSOMAL POSITION
chr18:48604749

VARIANT ALLELE FREQUENCY (% VAF)
74.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SMAD4. Preclinical studies in colorectal cancer have reported associations of SMAD4 inactivation or loss with sensitivity to inhibitors of Aurora kinase A[183] and the Wnt/beta-catenin pathway[184].

— Nontargeted Approaches —

Clinical studies have reported associations of SMAD4 loss or low SMAD4 expression with improved responses to chemotherapeutic agents in patients with pancreatic cancer[185-187] and non-small cell lung cancer (NSCLC)[188]. Other clinical studies in pancreatic cancer have reported an association of high SMAD4 expression with better responses to neoadjuvant chemotherapy[189] and adjuvant chemoradiotherapy[190].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[191], pancreatic acinar cell carcinoma (26%)[192], cholangiocarcinoma (25%)[193], small intestine cancer (20%)[194], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[195-196], colorectal adenocarcinoma (CRC; 14%)[21], esophageal adenocarcinoma (14%)[197], and stomach adenocarcinoma (13%)[158]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[198] and intraductal papillary mucinous neoplasms (IPMN)[199]; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs[200]. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma[201]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[202-204], appendiceal mucinous neoplasm[205], gastric adenocarcinoma[206-207], esophageal adenocarcinoma[208], esophageal squamous cell carcinoma[209], breast cancer[210], and prostate cancer[211].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[212-213]. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating[214-227].

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[228-230], which is associated with an increased risk of gastrointestinal cancers[231]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[232]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

GENE
TET2

ALTERATION
E1151* - subclonal

TRANSCRIPT ID
NM_017628.4

CODING SEQUENCE EFFECT
3451G>T

VARIANT CHROMOSOMAL POSITION
chr4:106158550

VARIANT ALLELE FREQUENCY (% VAF)
8.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2022)[233-234]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2022).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[235-236]. Alterations such as seen here may disrupt TET2 function or expression[237-241].

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 expansion[242-247]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[242-243]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[248]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[246,249-250]. 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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GENE
TP53

ALTERATION
L252_I254del

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
754_762delCTCACCATC

VARIANT CHROMOSOMAL POSITION
chr17:7577518-7577527

VARIANT ALLELE FREQUENCY (% VAF)
80.4%

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 adavosertib[251-254] or p53 gene therapy such as SGT53[255-259]. 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 wildtype[260]. 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 cancer[261]. 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 cancer[262]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[263]. 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 paclitaxel[264]. 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 alterations[265]. 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 monitoring[266]. 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 shrinkage[259]. 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% DCR[267]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[268].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases[21,269-274]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[275]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[276].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[277]. Alterations such as seen here may disrupt TP53 function or expression[278-282].

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 cancers[283-285], including sarcomas[286-287]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[288] to 1:20,000[287]. 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 30[289]. 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 expansion[242-247]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[242-243]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[248]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[246,249-250]. 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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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[97-100,290-291] ; 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 KRAS[97-100] or NRAS[142,274] , 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).

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[97-98,290-292] and as monotherapy for chemotherapy-refractory patients[100,293] . 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 line[294]. A prospective study of cetuximab monotherapy for patients with KRAS-, NRAS-, and BRAF-wildtype mCRC reported 11% (2/19) PRs and 58% (11/19) SDs[295]. 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%[296]. 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)[297]. 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)[298].

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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[101,297,299] ; 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 KRAS[101-103] or NRAS[102,272] , 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[101,300-303] , and as monotherapy for chemotherapy-refractory patients[272,297,299] . 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 bevacizumab[304]. 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%)[305]. 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)[297]. 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)[298].

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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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. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

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.

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

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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NCT03829410

PHASE 1/2

Onvansertib in Combination With FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer Patients With a Kras Mutation

TARGETS PLK1, VEGFA

LOCATIONS: California, Arizona, Minnesota, Kansas, Arkansas, Virginia, Florida

NCT02079740

PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS BCL2, BCL-XL, BCL-W, MEK

LOCATIONS: Massachusetts

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)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

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

LOCATIONS: Utah

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GENE
RNF43

ALTERATION
splice site 582+2T>G, G400fs*10

RATIONALE
Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway.

NCT04907539

PHASE 2

A Study to Assess Efficacy of RXC004 +/- Nivolumab in Ring Finger Protein 43 (RNF43) or R-spondin (RSPO) Aberrated, Metastatic, Microsatellite Stable, Colorectal Cancer After Progression on Standard of Care (SOC)

TARGETS
PD-1, RANKL, PORCN

LOCATIONS: Seoul (Korea, Republic of), Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Oxford (United Kingdom), Barcelona (Spain), Madrid (Spain), Sevilla (Spain), Texas

NCT02521844

PHASE 1

A Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours

TARGETS
PORCN

LOCATIONS: Singapore (Singapore), Colorado, Texas, North Carolina

NCT01351103

PHASE 1

A Study of LGK974 in Patients With Malignancies Dependent on Wnt Ligands

TARGETS
PORCN, PD-1

LOCATIONS: Essen (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Napoli (Italy), Milano (Italy), Villejuif Cedex (France), Barcelona (Spain), Hospitalet de LLobregat (Spain), Valencia (Spain), Madrid (Spain)

NCT03447470

PHASE 1

Study to Evaluate the Safety and Tolerability of RXC004 in Advanced Malignancies

TARGETS
PORCN

LOCATIONS: Newcastle (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

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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.

BARD1
R335T

FGFR3
G44S

GNAS
G306V and L42F

MSH2
I169V

MSH3
L971F

MTOR
T1834_T1837del

PRDM1
M823I

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Electronically signed by Douglas A. Mata, MD, MPH | 11 October 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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-1469834-01

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*	*ERRFI1*	*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*	*HNF1A*	*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*
P2RY8	*PALB2*	*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*
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	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
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*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*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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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 fractional-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.

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 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.
3. 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 ≥ 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.
4. 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.
5. 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.
6. 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.
7. 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
muts/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) 7.2.0

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The median exon coverage for this sample is 801x

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