FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Yang, Shih Chang	Colon adenocarcinoma (CRC)	17 Apr 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1606878-01

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 Yang, Shih Chang
DATE OF BIRTH 24 October 1969
SEX Male
MEDICAL RECORD # 46204846

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 Colon
SPECIMEN ID S110-34021 D (PF23035)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 09 November 2021
SPECIMEN RECEIVED 10 April 2023

Biomarker Findings

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

Genomic Findings

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

KRAS wildtype
NRAS wildtype
NF1 loss exons 37-58
APC R232*
CCND2 amplification
ERBB2 T798I
FGF23 amplification
FGF6 amplification
KDM5A amplification
NOTCH3 splice site 119-156_197+54>GGGGG
SMAD4 loss
TP53 P151R

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

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Cetuximab** (p. 11), **Panitumumab** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 1 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* -** wildtype	Cetuximab	2A	none
0 Trials	Panitumumab	2A	
***NRAS* -** wildtype	Cetuximab	2A	none
0 Trials	Panitumumab	2A	

NCCN category

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
NF1 **-** loss exons 37-58	none	Cobimetinib
		Selumetinib
10 Trials see p. 19		Trametinib
APC **-** R232*	none	none
3 Trials see p. 14		
CCND2 **-** amplification	none	none
10 Trials see p. 15		
ERBB2 **-** T798I	none	none
9 Trials see p. 17		

☐ *NCCN category*

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
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-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
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[69-72] or panitumumab[73-75] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v3.2022, Rectal Cancer Guidelines, v4.2022).

FREQUENCY & PROGNOSIS

Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations[76-84].

Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC[78-81,85-86].

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[87-88]. No alterations in KRAS were identified in this case.

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[69-72] or panitumumab[73-75] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v3.2022, Rectal Cancer Guidelines, v4.2022).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[21,84,89-94]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[84] and longer survival[94-95] 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[87]. No alterations in NRAS were identified in this case.

GENE
NF1

ALTERATION
loss exons 37-58

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[96-99], glioma or glioblastoma[99-103], and non-small cell lung cancer[104], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. On the basis of limited clinical data[105-107] and preclinical data[108-109], loss or inactivation of NF1 may predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient malignant peripheral nerve sheath tumors (MPNST)[110].

— Potential Resistance —

Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat CRC, even for tumors that harbor alterations in PIK3CA or PTEN; data are more limited for alterations in other genes in this pathway[111-113].

FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, NF1 mutations have been found in 1.4% of sequenced tumors[21]. For patients with colorectal cancer (CRC), NF1 mutations have been reported to be associated with significantly worse OS following treatment with cetuximab or bevacizumab (p=0.04 and 0.007, HR=2.62 and 2.05); low NF1 expression was associated with significantly worse OS (p=0.003, HR=1.49) and PFS (p=0.02, HR=1.36) when compared with high NF1 expression[114].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[115]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[116]. Alterations such as seen here may disrupt NF1 function or expression[116-125].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[126-128]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[129-130], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
APC

ALTERATION
R232*

HGVS VARIANT
NM_000038.4: c.694C>T (p.R232*)

VARIANT CHROMOSOMAL POSITION
chr5:112128191

VARIANT ALLELE FREQUENCY (% VAF)
56.7%

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 programs[131], 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 CBP[132-133]. 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 days[134]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[135-136].

FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset[21]. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples[137]. The prognostic significance of APC mutations in sporadic CRC remains unclear[138]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[139].

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 differentiation[140]. Alterations such as seen here may disrupt APC function or expression[141-145].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Sep 2022)[146]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[147-149]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[150], and in the appropriate clinical context germline testing of APC is recommended.

GENE
CCND2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although preclinical studies suggest that cyclin D2 activates CDK4/6[151-152], it is unknown whether CCND2 amplification or activating mutation predicts response to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib. Clinical studies of CDK4/6 inhibitors have shown the most promise for estrogen receptor-positive breast cancer[153-154].

FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, putative high-level amplification of CCND2 has been found in 1.4% of cases[21]. Cyclin D2 has also reportedly been overexpressed in 53% of colorectal adenocarcinomas[155]. Overexpression of CCND2 mRNA in CRC has been correlated with poor patient prognosis[156]. In addition, the expression of cyclin D2 at the invasive margin has been associated with liver metastasis in colorectal cancer, and in patients with Stage 1 and 2 tumors, cyclin D2 expression has also been associated with reduced patient survival[157].

FINDING SUMMARY

CCND2 encodes the protein cyclin D2, which binds and regulates the cyclin-dependent kinases that control cell cycle progression, and is a downstream target of cancer signaling pathways including hedgehog and PI3K[158-159]. CCND2 has been reported to be amplified in cancer[160], and may be biologically relevant in this context[161-162].

GENE
ERBB2

ALTERATION
T798I

HGVS VARIANT
NM_004448.2: c.2393C>T (p.T798I)

VARIANT CHROMOSOMAL POSITION
chr17:37881064

VARIANT ALLELE FREQUENCY (% VAF)
39.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[163-168], pertuzumab in combination with trastuzumab[165,169-171], and zanidatamab (ZW25)[172], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[173] and fam-trastuzumab deruxtecan (T-DXd)[174-176], HER2 kinase inhibitors such as tucatinib[177-180], and dual EGFR/HER2 kinase inhibitors such as lapatinib[181-189], afatinib[168,190-199], neratinib[200-203], dacomitinib[204], and pyrotinib[205-206]. The Phase 1 trial of HER2-selective TKI BI-1810631 for patients with HER2-aberration-positive metastatic solid tumors reported a 3.7% ORR (7/19) and an 84% DCR; for patients with NSCLC, a 45% ORR (5/11) and a 91% DCR were reported[207]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

— Potential Resistance —

Tyrosine kinase inhibitors such as afatinib and lapatinib have yielded limited clinical efficacy as monotherapies in CRC, suggesting antibody therapeutics or combination therapies may be more beneficial in this tumor type[208-211]. Limited clinical and preclinical data indicate that ERBB2 T798I may confer resistance to lapatinib[212-213] and neratinib[214] and remain sensitive to afatinib[215] and PD168393[213].

FREQUENCY & PROGNOSIS

ERBB2 mutation or amplification was observed in 4% and 2-6% of colorectal adenocarcinoma cases, respectively[21,216-218]. For patients with colorectal cancer, multiple studies have shown that ERBB2 overexpression does not correlate with survival[218-220] and is not considered prognostic (NCCN Colon Cancer Guidelines, v3.2022, NCCN Rectal Guidelines, v4.2022); however, studies have shown an association of ERBB2 amplification with reduced response and/or shorter survival for patients treated with anti-EGFR antibodies[221-222].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. The ERBB2 gatekeeper mutation T798I has been found to lack transforming ability[212,215], but was reported to be an emergent mutation associated with acquired resistance to neratinib[215]. Preclinical studies have reported that this mutation also confers reduced sensitivity to lapatinib[212-213]. ERBB2 T798I retains sensitivity to other irreversible pan-HER inhibitors such as afatinib[215] and PD168393[213].

GENE
FGF23

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF23. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[223].

FREQUENCY & PROGNOSIS

FGF23 alterations have been reported with highest incidence in uterine carcinosarcoma (7.0%), ovarian carcinoma (6.5%), testicular germ cell cancer (5.4%), cutaneous melanoma (5.0%), low-grade glioma (4.9%), lung squamous cell carcinoma (4.5%), sarcoma (4.3%), colorectal adenocarcinoma (4.2%), lung adenocarcinoma (3.7%), and head and neck squamous cell carcinoma (3.4%) (cBioPortal, 2023)[160,224].

FINDING SUMMARY

FGF23 encodes a member of the fibroblast growth factor protein family that plays a central role in phosphate homeostasis[225]. Overexpression of FGF23 by tumor cells can cause hypophosphatemia through excessive renal phosphate clearance[226], while germline gain-of-function (protein stabilizing) mutations in FGF23 cause autosomal dominant hypophosphatemic rickets[227].

GENE
FGF6

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF6. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[223].

FREQUENCY & PROGNOSIS

Somatic alterations affecting FGF6 are infrequently documented, with the highest rates reported in penile cancer (4%), cutaneous melanoma (1-3%), stomach carcinoma (1-3%) and colorectal cancer (1%) (cBioPortal, COSMIC, 2023)[160,224,228]. Amplification of FGF6 has been frequently observed in testicular germ cell cancer (5%) and ovarian serous cystadenocarcinoma (5%), and in 2-6% of lower-grade gliomas, glioblastomas, sarcomas, breast invasive carcinomas, uterine carcinosarcomas, lung squamous cell carcinomas (SCC), head and neck SCC, pancreatic adenocarcinomas, and esophageal carcinomas (cBioPortal, 2023)[160,224]. FGF6 is co-localized with FGF23 and CCND2 at chromosomal locus 12p13 and has been reported to be co-amplified with these genes in 1.3% of patients with breast cancer[229]. FGF6 expression has been reported in 54% (14/26) of prostate cancer samples, which also frequently express FGFR4[230]. FGF6 expression has also been observed in 71% (12/17) of patients with childhood acute lymphoblastic leukemia[231].

FINDING SUMMARY

FGF6 (also known as HST-2) encodes a member of the fibroblast growth factor protein family and is hypothesized to play a role in muscle tissue regeneration[232] by signaling through FGFR4, and to a lesser extent FGFR1 and FGFR2[233]. FGF6 expression has been observed in several cancers[230-231,234] and was shown to be oncogenic in preclinical models[234-235]. FGF6 has been reported as amplified in cancer[160] and may be biologically relevant in this context[161-162].

GENE
KDM5A

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to directly address genomic alterations in KDM5A. However, multiple preclinical studies have identified potential targets in KDM5A amplified or activated cells that may respond to therapy. KDM5A-mediated chromatin remodeling induces CCND1 expression and represses CDKI expression[236-240]; therefore, KDM5A activation or amplification may sensitize cells to CDK4/CDK6 inhibitors. Drug-resistant cell populations, characterized by elevated KDM5A expression, responded to histone deacetylase (HDAC) inhibition[241], suggesting that HDAC inhibitors may be a potential therapeutic option. KDM5A also induces expression of VEGF and promotes angiogenesis, oncogenic transformation, and tumorigenesis, which can be inhibited by KDM5A knockdown[242-243], suggesting that tumors harboring KDM5A amplification may be sensitive to angiogenesis inhibitors, including kinase inhibitors that target the VEGF receptors, such as sunitinib, sorafenib, vandetanib, ponatinib, cabozantinib, regorafenib, pazopanib, and axitinib. However, these inhibitors have yet to be extensively tested in the context of KDM5A amplification or activation; therefore, it is not known if these therapeutic strategies are relevant.

FREQUENCY & PROGNOSIS

KDM5A amplification has been reported with the highest incidence in TCGA datasets in ovarian serous cystadenocarcinoma (7.2%), testicular germ cell cancer (5.8%), pancreatic adenocarcinoma (4.3%), and lung squamous cell carcinoma (3.9%) (cBioPortal, Jan 2023)[160,224]. Elevated levels of KDM5A expression have also been reported in a range of solid tumor types[237-238,240,242,244-245], and fusion of KDM5A to NUP98 has been documented in acute myeloid leukemia[246-247]. KDM5A expression is significantly correlated with HIF-1alpha and VEGF expression, as well as tumor size, angiogenesis, and poor patient prognosis in lung cancer[243].

FINDING SUMMARY

KDM5A encodes a lysine-specific histone demethylase that potentiates the expression of genes involved in cellular proliferation, senescence, angiogenesis, and migration[236-237,242,248-249]. KDM5A overexpression alters the transcriptional regulation of cell cycle genes, including CCND1, and a variety of cyclin-dependent kinase inhibitors (CDKIs), including CDKN1A, CDKN1B, and CDKN2A, and results in cell cycle progression[236-240,242]. Additionally, elevated KDM5A expression and associated chromatin remodeling has been implicated in resistance to various tyrosine kinase inhibitors in vitro, including erlotinib and gefitinib[241,244,250].

GENE
NOTCH3

ALTERATION
splice site 119-156_197+54>GGGGG

HGVS VARIANT
NM_000435.2: c.119-156_197+54delinsGGGGG (p.?)

VARIANT CHROMOSOMAL POSITION
chr19:15308257-15308545

VARIANT ALLELE FREQUENCY (% VAF)
11.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[251], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI)[252-254]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[255]. Phase 2 studies have evaluated the efficacy of tarextumab in combination with chemotherapy in metastatic pancreatic cancer or extensive-stage small cell lung cancer, though NOTCH3 expression was not found to be a predictor of OS or PFS in either study[256]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

NOTCH3 mutations have been reported in 6% of colorectal adenocarcinomas (CRC), whereas NOTCH3 amplification was reported in 1% of cases[21]. NOTCH3 rearrangements were reported in <0.1% of colorectal cancers[257]. NOTCH3 activation has been reported to be frequent in CRC, with mRNA and/or protein overexpression reported in 19.7-38% of samples[258-260]. NOTCH3 expression is more frequent in aggressive colorectal micropapillary carcinoma (35/51, 69%) than in microsatellite-stable CRC (42/97, 43%) cases (P=0.005)[261]. Nuclear (activated) NOTCH3 expression has been associated with advanced disease and tumor recurrence in patients with Stage 2 and 3 colorectal cancer[259].

FINDING SUMMARY

NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[262-263]. Alterations that disrupt or remove the transmembrane domain (amino acids 1644-1664), RAM domain (amino acids 1665-1837), and/or ANK repeats region (amino acids 1838-2000), which are necessary for the transcriptional activity of NOTCH family proteins, as well as internal deletions that remove EGF repeats (7-10 and 21-22), have been shown in vitro to negatively affect ligand binding and reduce NOTCH3 transcriptional activity and are predicted to be inactivating[263-267].

GENE
SMAD4

ALTERATION
loss

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[268] and the Wnt/beta-catenin pathway[269].

— 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[270-272] and non-small cell lung cancer (NSCLC)[273]. Other clinical studies in pancreatic cancer have reported an association of high SMAD4 expression with better responses to neoadjuvant chemotherapy[274] and adjuvant chemoradiotherapy[275].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[276], pancreatic acinar cell carcinoma (26%)[277], cholangiocarcinoma (25%)[278], small intestine cancer (20%)[279], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[280-281], colorectal adenocarcinoma (CRC; 14%)[21], esophageal adenocarcinoma (14%)[282], and stomach adenocarcinoma (13%)[283]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[284] and intraductal papillary mucinous neoplasms (IPMN)[285]; 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[286]. SMAD4 gene alterations have been associated with reduced OS for patients with pancreatic adenocarcinoma[287]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[288-290], appendiceal mucinous neoplasm[291], gastric adenocarcinoma[292-293], esophageal adenocarcinoma[294], esophageal squamous cell carcinoma[295], breast cancer[296], and prostate cancer[297].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[298-299]. 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[300-313].

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[314-316], which is associated with an increased risk of gastrointestinal cancers[317]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[318]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

GENE
TP53

ALTERATION
P151R

HGVS VARIANT
NM_000546.4: c.452C>G (p.P151R)

VARIANT CHROMOSOMAL POSITION
chr17:7578478

VARIANT ALLELE FREQUENCY (% VAF)
67.3%

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[319-322] or p53 gene therapy such as SGT53[323-327]. 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[328]. 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[329]. 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[330]. 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[331]. 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[332]. 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[333]. 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[334]. 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[327]. 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[335]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[336].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases[21,337-342]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[343]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[344].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[345]. Alterations such as seen here may disrupt TP53 function or expression[346-350].

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[351-353], including sarcomas[354-355]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[356] to 1:20,000[355]. 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[357]. 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[358-363]. 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[358-359]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[364]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[362,365-366]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Cetuximab

Assay findings association

KRAS
wildtype

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[69-72,367-368] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines, v3.2022, NCCN Rectal Cancer Guidelines, v4.2022).

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[69-70,367-369] and as monotherapy for chemotherapy-refractory patients[72,370] . 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[371]. 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[372]. 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%[373]. 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)[374]. 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)[375].

Panitumumab

Assay findings association

KRAS
wildtype

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[73,374,376] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2022)(NCCN Rectal Cancers Guidelines, v4.2022).

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[73,377-380] , and as monotherapy for chemotherapy-refractory patients[340,374,376] . 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[381]. 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%)[382]. 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)[374]. 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)[375].

Cobimetinib

Assay findings association

NF1
loss exons 37-58

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor that is FDA approved to treat patients with histiocytic neoplasms. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[96-99,383-387] , glioma[99-103,388] , and non-small cell lung cancer[104], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

The Phase 3 IMblaze370 study of cobimetinib plus atezolizumab for patients with chemotherapy-refractory metastatic colorectal cancer (CRC) reported similar median OS (8.9 vs. 7.1 vs. 8.5 months, HR=1.0–1.2), median PFS (1.9 vs. 1.9 vs. 2.0 months), and ORR (2.7% vs. 2.2% vs. 2.2%) to atezolizumab monotherapy or regorafenib, respectively[389].

Selumetinib

Assay findings association

NF1
loss exons 37-58

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients with neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[96-99,383-387] , glioma[99-103,388] , and non-small cell lung cancer[104], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

In Phase 2 studies for chemotherapy-refractory metastatic colorectal cancer (CRC), single-agent selumetinib demonstrated similar outcomes compared with capecitabine in genomically unselected patients (ORR, 0% [0/34] vs. 2.8% [1/35]; median PFS [mPFS], 81 vs. 88 days)[390], and combination of selumetinib with irinotecan elicited an ORR of 9.7% (3/31 PRs), mPFS of 105 days, and median OS of 267 days in patients with KRAS mutation[391]. Phase 1 and 2 studies have evaluated selumetinib in combination with the AKT inhibitor MK-2206[392-393] , the EGFR-targeting monoclonal antibody cetuximab[394], the EGFR-targeting TKI afatinib[395], or Cyclosporin A[396], but have reported limited activity and no confirmed objective responses for patients with CRC.

Trametinib

Assay findings association

NF1
loss exons 37-58

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[96-99,383-387] , glioma[99-103,388] , and non-small cell lung cancer[104], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Trametinib has shown limited activity as a single agent in advanced or metastatic colorectal cancer (CRC), with no objective responses in 28 patients (including 13 with KRAS and 3 with BRAF mutation) included in a Phase 1 study[397] nor in 7 patients with non-V600 BRAF mutation included in the Phase 2 NCI-MATCH trial[398]. In Phase 1/2 studies for metastatic CRC (mCRC), combination of trametinib with the EGFR-targeting antibody panitumumab demonstrated modest activity for BRAF/KRAS/NRAS-wildtype patients, with 38% (5/13) confirmed ORR, 92% (12/13) DCR, and 4.4 months median PFS[399], but limited activity for patients with BRAF V600 mutation, with 0% (0/31) ORR, 55% (17/31) DCR, 2.6 months mPFS, and 8.2 months median OS[400]. Combination of trametinib with the PD-1-targeting antibody pembrolizumab did not elicit any objective responses in 15 patients with genomically unselected CRC in the Phase 1/2 KEYNOTE-022 study[401], and trametinib plus the PD-L1-targeting antibody durvalumab showed limited activity in microsatellite stable mCRC with 3.4% (1/29) ORR and 41% (12/29) DCR[402]. Early phase studies examining combination of trametinib with agents targeting the PI3K-AKT-mTOR pathway[403-406] , CDK4/6 inhibitors palbociclib or ribociclib[407-408] , the multi-TKI pazopanib[409], or the BCL-2 inhibitor navitoclax[410] have shown minimal anti-tumor activity for included patients with CRC. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[403], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[411].

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.

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
APC

ALTERATION
R232*

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), Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom)

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), Seodaemun (Korea, Republic of), Osakasayama (Japan), Nagoya (Japan), Kawasaki (Japan), Chuo-Ku (Japan), Koto-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), London (United Kingdom), Sutton (United Kingdom)

GENE
CCND2

ALTERATION
amplification

RATIONALE
CCND2 amplification or activation may predict sensitivity to CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT05480280

PHASE 2

mFOLFOX6 Combined With Dalpiciclib in Patients With Metastatic Colorectal Cancer

TARGETS
CDK6, CDK4

LOCATIONS: Guangzhou (China)

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)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Illinois, Massachusetts, Arkansas, New York, Virginia, Texas, Florida

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT04616183

PHASE 1/2

LY3214996 and Cetuximab Alone or in Combination With Abemaciclib for the Treatment of Unresectable or Metastatic Colorectal Cancer

TARGETS
ERK1, ERK2, EGFR, CDK4, CDK6

LOCATIONS: Texas

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT03310879

PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT03454035

PHASE 1

Ulixertinib/Palbociclib in Patients With Advanced Pancreatic and Other Solid Tumors

TARGETS
MAPK3, MAPK1, CDK4, CDK6

LOCATIONS: North Carolina

GENE
ERBB2

ALTERATION
T798I

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors. Based on limited clinical and preclinical evidence, ERBB2 T798I may confer reduced sensitivity to lapatinib and neratinib. Tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, and lapatinib have yielded limited clinical efficacy as monotherapies in CRC, suggesting that antibody therapeutics or combination therapies may be more beneficial in this tumor type. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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: 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), Tianjin (China)

NCT04579380

PHASE 2

Basket Study of Tucatinib and Trastuzumab in Solid Tumors With HER2 Alterations

TARGETS
ERBB2, ER

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Osakasayama (Japan), Nagoya-shi (Japan), Kawasaki-shi (Japan), Chuo-Ku (Japan), Tokyo (Japan), Kashiwa-shi (Japan), Poznan (Poland), Berlin (Germany)

NCT04999761

PHASE 1

AB122 Platform Study

TARGETS
PD-1, HSP90, FGFRs

LOCATIONS: Ehime (Japan), Wakayama (Japan), Osaka (Japan), Aichi (Japan), Shizuoka (Japan), Kanagawa (Japan), Tokyo (Japan), Chiba (Japan), Hokkaido (Japan)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, PD-L1, TRKB, ALK, TRKC, ROS1, TRKA, FGFRs

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT04294628

PHASE 1

Testing the Biological Effects of DS-8201a on Patients With Advanced Cancer

TARGETS
ERBB2

LOCATIONS: Ohio, Pennsylvania, Massachusetts, New York, Maryland

NCT05395052

PHASE 1

FT536 Monotherapy and in Combination With Monoclonal Antibodies in Advanced Solid Tumors

TARGETS
MET, EGFR, PD-1, PD-L1, ERBB2

LOCATIONS: California, Arizona, New Jersey, Texas, North Carolina

GENE
NF1

ALTERATION
loss exons 37-58

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors. 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.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (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)

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

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

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

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

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, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

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.

ALK
NM_004304.4: c.1528C>T
(p.R510W)
chr2:29543635

BRD4
NM_014299.2: c.682G>A
(p.V228I)
chr19:15376332

ERBB4
NM_005235.2: c.2936G>A
(p.R979Q)
chr2:212286760

FANCC
NM_000136.2: c.973G>A
(p.A325T)
chr9:97887391

MTOR
NM_004958.3: c.836G>A
(p.G279E)
chr1:11313900

POLE
NM_006231.2: c.4603G>A
(p.G1535S)
chr12:133219531 and
NM_006231.2: c.5035C>T
(p.R1679C)
chr12:133218901

RAD52
amplification

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)

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

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. 2023. 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

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

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) 7.7.0

The median exon coverage for this sample is 946x

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