FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Hsieh, Yu-Ying	Uterus endometrial adenocarcinoma papillary serous	16 Jan 2024
	COUNTRY CODE: TW	ORDERED TEST #: ORD-1794439-01

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 Uterus endometrial adenocarcinoma papillary serous
NAME Hsieh, Yu-Ying
DATE OF BIRTH 21 September 1963
SEX Female
MEDICAL RECORD # 33045679

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 Uterus
SPECIMEN ID S112-69102E (PF24003)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 29 December 2023
SPECIMEN RECEIVED 09 January 2024

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 7 Muts/Mb

Genomic Findings

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

KIT amplification - equivocal†
PDGFRA amplification
CCNE1 amplification
FBXW7 R479Q
MDM2 amplification
MYC amplification
BRAF D594N
FUBP1 deletion exons 2-11
KDR amplification - equivocal†
MED12 G44D
SPOP E46K
TP53 R248W

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Imatinib** (p. 13), **Nilotinib** (p. 13), **Sorafenib** (p. 14), **Sunitinib** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: **Microsatellite status MS-Stable** (p. 3), ***TP53*** **R248W** (p. 11)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 7 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)**
***KIT* -** amplification - equivocal	none	Imatinib
		Nilotinib
		Sorafenib
		Sunitinib
10 Trials see p. 19		
***PDGFRA* -** amplification	none	Imatinib
1 Trial see p. 24		

Electronically signed by Erik Williams, M.D. | 16 January 2024
Lauren L. Ritterhouse Casariego, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CCNE1 - amplification	none	none
7 Trials see p. 15		
FBXW7 - R479Q	none	none
6 Trials see p. 17		
MDM2 - amplification	none	none
2 Trials see p. 21		
MYC - amplification	none	none
10 Trials see p. 22		

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[4-5]. 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)[6].

FREQUENCY & PROGNOSIS

MSS has been reported in 73-89% of endometrial cancers[7-14]. TP53 mutations in microsatellite stable/mismatch repair-proficient (MMRp) POLE-wildtype endometrial carcinoma are indicative of a ProMisE/TCGA molecularly classified subtype, "p53abn" (NCCN Uterine Neoplasms Guidelines, v1.2023) ()[7,15-21], which is associated with high risk of recurrence[22], yet also with the highest degree of benefit from adjuvant chemoradiotherapy over radiotherapy relative to the other subtypes[23]. Additionally, classification as this molecular subtype refines FIGO disease stage to IIC (Stage "IICm-p53abn") for patients with histologically determined Stage I/II early endometrial cancer that is locally confined to the uterine corpus or with myometrial invasion[24]. Data regarding the role of microsatellite instability on prognosis and survival in endometrial cancer are mixed[8-10,12-13,25-29], although these studies often evaluated endometrial cancers of all International Federation of Gynecology and Obstetrics (FIGO) stages together.

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 MMR in the tumor[30]. 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[30-32]. 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[33-35]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[30,32,34-35].

BIOMARKER

Tumor Mutational Burden

RESULT
7 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[36-39], anti-PD-1 therapies[37-41], and combination nivolumab and ipilimumab[42-50]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[36-39,41,51-55]. 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[51]; similar findings were observed in the KEYNOTE 028 and 012 trials[41]. 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)[55]. 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[56]. 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[54]. 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[36] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[38].

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that endometrial adenocarcinomas harbored a median TMB of 4.5 Muts/Mb, and 15% of cases had an elevated TMB of greater than 20 Muts/Mb[57]. Another study evaluating TMB in endometrial adenocarcinoma reported that 24% of tumors had a mutational burden of greater than 10.4 Muts/Mb[58]. Increased tumor mutational burden (TMB) in endometrial carcinoma has been correlated with POLE mutation and advanced high-grade endometrioid subtypes[7,14,59-60]. Ultramutated endometrial tumors (elevated TMB with POLE mutations) have also been associated with improved PFS[7]. The same study associated lower mutational burden, independent of PD-L1 status, in endometrial carcinomas with poorer prognosis[7]. For patients with advanced microsatellite-stable endometrial carcinoma not treated with immunotherapy, OS did not significantly differ between patients with TMB-high (≥10 Muts/Mb) and TMB-low (11.4 vs. 13.5 months, adjusted HR=1.15) in 1 study[61].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions 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[62-63] and cigarette smoke in lung cancer[64-65], treatment with temozolomide-based chemotherapy in glioma[66-67], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[7,68-71], and microsatellite instability[7,70-71]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[38-39,51].

GENE
KIT

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, primarily in gastrointestinal stromal tumor (GIST), melanoma, AML, and systemic mastocytosis, KIT activating alterations are associated with sensitivity to TKIs including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, regorafenib, ponatinib, midostaurin, apatinib, avapritinib, and ripretinib[72-86]. The use of mTOR inhibitors as an alternative therapeutic strategy has demonstrated limited success in KIT-mutated, imatinib-resistant melanoma, with 1 PR and 3 SD observed for 4 patients treated with everolimus[87-88]. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation[89]. The role of KIT amplification as a biomarker for response to mTOR inhibitors has not been investigated (PubMed, Feb 2023). Clinical benefit has been observed for patients with KIT amplified or overexpressing tumors following treatment with imatinib[90-100], nilotinib[101], sorafenib[102-105], and sunitinib[106-107], suggesting that KIT amplification may be sensitive to these inhibitors. However, evidence demonstrating clinical benefit for regorafenib, dasatinib, pazopanib, or ponatinib in the context of KIT amplified or overexpressing tumors is limited.

FREQUENCY & PROGNOSIS

KIT amplifications are common in various solid tumors, most often seen in mucosal melanomas (8-10%), adenoid cystic carcinomas (4.0%), small cell lung cancer (2.7%), and seminomas (2.1%)[108]. KIT expression has been reported in 58% (42/72) of endometrial adenocarcinomas in one study[109]. KIT expression was correlated with worse overall survival for patients with endometrial cancer[109]. Published data investigating the prognostic implications of KIT alterations in endometrial cancer are limited (PubMed, Jun 2023).

FINDING SUMMARY

KIT (also called c-KIT) encodes a cell surface tyrosine kinase receptor that, upon ligand binding and dimerization, activates the PI3K-AKT and RAS-MAPK signaling pathways[110]. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein[111]. KIT has been reported to be amplified in cancer[112] and may be biologically relevant in this context[113-114].

GENE
PDGFRA

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited evidence of clinical benefit for patients with increased PDGFR expression, PDGFRA amplification may be associated with sensitivity to imatinib[115-116].

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrial Carcinoma Provisional TCGA dataset, putative high-level amplification of PDGFRA has been reported in fewer than 1% of cases[7]. High expression of PDGFR-alpha has been reported in both primary and recurrent endometrioid and uterine papillary serous endometrial carcinomas, and has been shown to be increased in recurrent as compared to primary cases[117]. Increased PDGFR-alpha expression has been correlated with lower grade (grades 1 and 2) endometrial carcinomas[117].

FINDING SUMMARY

PDGFRA encodes platelet-derived growth factor receptor alpha (PDGFR-alpha), a tyrosine kinase receptor that, upon binding of cognate ligands (PDGFA or PDGFB), activates several signaling pathways, including PI3K and MAPK[118]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[111]. Amplification of PDGFRA, frequently occurring with amplification of the genes KDR and KIT, has been associated with increased PDGFRA expression[119-122] and poor prognosis[119,123-125] in some subtypes of glioma.

GENE
CCNE1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target CCNE1 alterations. Because amplification or overexpression of CCNE1 leads to increased genomic instability though the ATR-CHK1-WEE1 pathway[126-127] and cyclin E1 promotes cell cycle progression in a complex with CDK2[128], clinical and preclinical studies have investigated inhibitors of ATR, CDK2, CHK1, HDAC, PKMYT1, and WEE1 as potential therapeutic approaches for tumors with CCNE1 activation. Clinical benefit has been reported for patients with recurrent high-grade serous ovarian carcinoma (HGSOC) with CCNE1 amplification or expression in response to treatment with the CHK1 inhibitor prexasertib[129]. Studies of the WEE1 inhibitor adavosertib observed PRs in patients with CCNE1-amplified HGSOC and ovarian cancer[130-132]. Similarly, in a Phase 2 study of patients with CCNE1-amplified solid tumors, adavosertib elicited an ORR of 27% with PRs reported for patients with ovarian cancer, urothelial carcinoma, or melanoma; median PFS was 4.1 months and median OS was 9.9 months[132-133]. One study has reported a reduction in tumor CCNE1 levels in 4/6 lung and esophageal cancer cases following treatment with the HDAC inhibitor vorinostat[134]. Preclinical studies have demonstrated that cell lines and murine models with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR[135-136], CDK2[137], PKMYT1[138-139], or WEE1[127,140]. However, other studies have shown that sensitivity of various cell lines to CDK2 inhibitors, including SNS-032, dinaciclib, and seliciclib, at clinically achievable doses, is largely independent of CCNE1 copy number or expression[141-144].

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrial Carcinoma TCGA dataset, putative amplification of CCNE1 has been found in 6% of cases[7]. CCNE1 amplification has been observed in 41% (11/27) of endometrial intraepithelial carcinomas[145] and in a study of ovarian cancer, CCNE1 amplification was observed in 12 of 12 serous carcinoma samples and in 2 of 6 endometrioid carcinomas[146]. Elevated cyclin E1 protein expression has been associated with poor prognosis in several cancer types, including endometrial and ovarian cancer[146-150].

FINDING SUMMARY

CCNE1 encodes the protein cyclin E1, which plays a role in the regulated transition from the G1 to S phase by binding to and activating cyclin-dependent protein kinase 2 (CDK2). It also has a direct role in initiation of replication and the maintenance of genomic stability[128]. Amplification of chromosomal region 19q12-q13 has been demonstrated in many types of cancer, and CCNE1 is a well-studied gene within this amplicon[151-152]. Increased copy number of CCNE1 is highly associated with overexpression of the cyclin E1 protein[146,150]. Cyclin E1 overexpression can lead to cell transformation as a result of an increase in cyclin E1 activity[128,153].

GENE
FBXW7

ALTERATION
R479Q

HGVS VARIANT
NM_033632.3:c.1436G>A (p.R479Q)

VARIANT CHROMOSOMAL POSITION
chr4:153247366

VARIANT ALLELE FREQUENCY (% VAF)
16.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[154-155]. Case series reported objective responses for 2 patients with FBXW7-mutated cervical squamous cell carcinoma treated with everolimus[156].

FREQUENCY & PROGNOSIS

FBXW7 mutations have been reported in up to 14% of endometrial cancers[7,157-158]. In primary endometrial carcinomas, FBXW7 mutations correlated with lymph node involvement[159]. Reduced FBXW7 expression has been associated with poor prognosis in some cancers such as colorectal cancer, gastric cancer, esophageal SCC, cervical SCC, melanoma, non-small cell lung carcinoma, and osteosarcoma[160-168].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[169]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[169-170]. Alterations such as seen here may disrupt FBXW7 function or expression[170-177].

GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[178]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[179-180]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[181-182] . A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[183]. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[184-185] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[186]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[187]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[188-189] .

FREQUENCY & PROGNOSIS

MDM2 amplification is common in various solid tumors and is often seen in soft tissue sarcomas (19%), bladder (7.8%), bone (7.5%), glioma (6.3%), non-small cell lung (5.4%), hepatobiliary (4.5%), esophagogastric (4.4%), breast (4.1%), and germ cell tumor (3.8%) cancer[157]. Expression of MDM2 protein has been identified in 42-70% (15/36-19/27) of endometrioid endometrial carcinomas and 36-67% (9/25-8/12) of papillary serous endometrial carcinomas[190-191]. One study observed that MDM2 protein expression was significantly associated with shorter overall survival (hazard ratio of 6) and an independent prognostic factor in high-risk endometrial cancer[190].

FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[192-194]. MDM2 has been reported to be amplified in cancer[114] and may be biologically relevant in this context[195-196].

GENE
MYC

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicates that MYC activation may predict sensitivity to the pan-MYC inhibitor OMO-103; a Phase 1 study for patients with solid tumors reported 7 SDs (n=18), including 8% tumor reduction in a patient with pancreas adenocarcinoma[197]. Preclinical data indicate MYC overexpression may predict sensitivity to investigational agents targeting CDK1[198-199], CDK2[200], Aurora kinase A[201-209], Aurora kinase B[210-213], glutaminase[214-217], or BET bromodomain-containing proteins[218-221], as well as agents targeting both HDAC and PI3K[222-224]. Exploratory biomarker analysis in a Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer, but not for patients without MYC overexpression[225]. A PR was reported for a patient with MYC-amplified invasive ductal breast carcinoma treated with an unspecified Aurora kinase inhibitor and taxol[226].

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[227-228]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[229-230].

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrioid Carcinoma TCGA dataset, putative high-level amplification of MYC has been found in 8% of cases[7]. In the scientific literature, MYC amplification has been detected in 15-27% of endometrial cancer cases[231-234]. In one study, MYC amplification has been associated with higher tumor grade in uterine corpus cancers[234].

FINDING SUMMARY

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[235]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[236]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[235,237-238].

GENE
BRAF

ALTERATION
D594N

HGVS VARIANT
NM_004333.4:c.1780G>A (p.D594N)

VARIANT CHROMOSOMAL POSITION
chr7:140453155

VARIANT ALLELE FREQUENCY (% VAF)
3.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical outcomes for patients with activating BRAF alterations treated with BRAF and MEK inhibitors are most extensive at the V600 codon; outcomes are more limited for BRAF class-3 kinase-impaired or inactivating mutations such as 1 or more of the alterations seen here. A retrospective study of immunotherapies in non-small cell lung cancer (NSCLC) reported a 78% (7/9) DCR for patients with BRAF class-3 mutations[239]. MEK inhibitors alone or in combination with BRAF inhibitors may be efficacious in these alterations; a basket trial of the single-agent MEK inhibitor trametinib reported 1 PR, 8 SDs, and 9 PDs for these patients[240], and combination therapies reported individual responses in other basket trials[241-242]. A retrospective analysis in melanoma with BRAF mutations reported PD as the best response in BRAF class-3 alterations for 2 patients treated with MEK inhibitors and 3 patients treated with RAF inhibitors[243]. The single-agent BRAF inhibitor vemurafenib was not effective in a Phase 2 trial in NSCLC, which reported no responses for 6 patients with class-3 BRAF alterations[244]; a basket trial of vemurafenib also observed no responses for these patients (n=3)[245]. Investigational BRAF inhibitors are also in development to target class-3 paradoxical activation[246-247] ; a Phase 1a/1b trial of the pan-RAF inhibitor exarafenib reported 1 PR for a patient with a BRAF class-3 mutation[246]. A basket trial of the ERK inhibitor ulixertinib reported no responses and 3 SDs for patients across tumors with class-3 mutations[248].

FREQUENCY & PROGNOSIS

BRAF mutations have been reported in 2.9% of endometrial carcinomas in the TCGA dataset[7]. In the literature, BRAF mutation has been generally been reported in 0-3% of endometrial carcinomas[249-252], with two reports of 11-21%[253-254]. Published data investigating the prognostic implications of BRAF alterations in endometrial carcinoma are limited (PubMed, Oct 2023).

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[255-256]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[257-258]. Alterations such as the class 3 mutation seen here have been shown to require concomitant upstream RAS activity in contrast with independently activating BRAF V600 or class 2 alterations[259-272], and may activate the MEK-ERK signaling pathway via CRAF[259-261,268,273].

GENE
FUBP1

ALTERATION
deletion exons 2-11

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapies targeting FUBP1 mutation directly or downstream effectors have not been tested preclinically or clinically in tumors that harbor FUBP1 mutations.

FREQUENCY & PROGNOSIS

FUBP1 alteration has been reported in 1.5% of samples analyzed in COSMIC, with the highest incidences reported in tumors of the endometrium (3.6%), central nervous system (3.2%), large intestine (3.0%), skin (2.8%), stomach (2.7%), and liver (2.6%) (COSMIC, Feb 2023)[274]. One study reported higher expression of FUBP1 in colorectal carcinoma tissues compared to adenoma and normal colon epithelial tissues[275]. A genetic signature defined by concomitant alterations in IDH1, CIC, and FUBP1 is associated with longer survival in patients with glioma[276]. FUBP1 has been shown to activate the expression of MYC[277-280], activate p27KIP1[281], and regulate the splicing of MDM2[282].

FINDING SUMMARY

FUBP1 encodes far upstream element binding protein 1 (also called FBP-1), a DNA-binding protein reported to have roles in transcriptional activation and splicing regulation of target genes. It is believed to act as an oncogene in some tumor types, such as hepatocellular carcinoma and non-small-cell lung cancer[283-284], and as a tumor suppressor in others, particularly oligodendroglioma, for which mutations and/or loss of FUBP1 often co-occur with alterations in CIC or IDH1[276,285-288].

GENE
KDR

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with recurrent fibrosarcoma harboring unspecified KDR mutations, a retrospective study reported an ORR of 25% (7/28) and DCR of 82% (23/28) following apatinib monotherapy treatment[289]. On the basis of clinical benefit for patients with clear cell renal cell carcinoma (ccRCC)[290-294] and a patient with breast angiosarcoma[295], high VEGFR-2 expression has been associated with sensitivity to sunitinib. However, because data supporting concordance between VEGFR-2 expression and KDR genomic biomarkers are limited, it is unclear whether these therapeutic strategies would be beneficial in this case. Limited preclinical data suggest that KDR activating mutations may increase sensitivity to VEGFR2-targeted agents such as linifanib[296]. On the basis of extensive clinical evidence across multiple tumor types, expression of plasma or tumor VEGFR-1 or VEGFR-2 has not been established as a reliable biomarker to predict response to the VEGFA-targeted agent bevacizumab[297-319].

FREQUENCY & PROGNOSIS

Amplification and mutation of KDR have been reported in fewer than 1% and 0.5-3.8% of endometrial cases, respectively[7,158]. VEGFR-2 expression in endometrial carcinomas has been reported in 15-68% of cases in the scientific literature[320-323]. In addition, increased levels of VEGF have been found in endometrial cancer tissue and correlated with increased expression and activity of VEGFR-2[320-321,324]. VEGFR-2 expression has been associated with tumor grade, tumor stage, and poor prognosis in endometrial carcinoma[320,322-323,325-327]. In one study, serum VEGF levels, but not tissue VEGFR-2 levels, correlated with tumor metastasis[328].

FINDING SUMMARY

KDR encodes vascular endothelial growth factor receptor 2 (VEGFR2), a member of the vascular endothelial growth factor receptor (VEGFR) family. It is a receptor tyrosine kinase that transmits signals from VEGFA and is involved in both tumor angiogenesis and vasculogenesis during development[329]. KDR amplification has been reported in many tumor types and may be oncogenic[329].

GENE
MED12

ALTERATION
G44D

HGVS VARIANT
NM_005120.2:c.131G>A (p.G44D)

VARIANT CHROMOSOMAL POSITION
chrX:70339254

VARIANT ALLELE FREQUENCY (% VAF)
31.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MED12. Uterine leiomyomas with tumorigenic MED12 alterations have been reported to overexpress IGF2[330]. Also, in a preclinical study, BRD4 inhibition has been shown to release the mediator complex from select genomic sites and to inhibit mediator-mediated transcription[331], but whether BET inhibitors and/or IGF2 pathway inhibitors would be beneficial for patients with oncogenic MED12 alterations is unknown.

FREQUENCY & PROGNOSIS

MED12 alterations, consisting predominantly of exon 2 mutations such as G44D, have been frequently reported in uterine leiomyomas (43-70%)[332-340], smooth muscle tumors of uncertain malignant potential (STUMP; 11%)[341-342], breast phyllodes tumors (PTs; 8-74%)[340,343-344], and breast fibroadenomas (46-59%)[340,345]. Similar alterations have also been reported in uterine leiomyosarcomas (2-30%)[342,346-347], and chronic lymphocytic leukemia (CLL; 5-8.8%)[348-349]. In prostate cancer, MED12 mutations, localized to the central part of the protein rather than exon 2, have been reported in 1-5% of cases[350-352]. MED12 alterations are rare in other cancer types[346]. In breast PTs, MED12 exon 2 mutation was diagnostic of breast PT compared to other spindle breast neoplasms[343], correlated with decreased pathological grade in some studies[353-354] but were independent of grade in others[344,355], and, according to one study, correlated with improved progression-free survival but increased risk of recurrence[334]. In one study, expression of an oncogenic MED12 exon 2 mutation in mice led to the development of leiomyomas and increased chromosome instability[356].

FINDING SUMMARY

MED12 encodes a subunit of the multi-protein mediator complex, an important transcriptional regulator[357-358]. MED12/mediator has been implicated in regulating WNT/beta-catenin[350,359], hedgehog/GLI[360], and TGF-beta[361-362] signaling, although the mechanisms by which MED12 mutations facilitate tumorigenesis are still poorly defined. Tumorigenic MED12 mutations have been shown to disrupt the composition and/or activity of the mediator complex[350,363-364].

GENE
SPOP

ALTERATION
E46K

HGVS VARIANT
NM_003563.3:c.136G>A (p.E46K)

VARIANT CHROMOSOMAL POSITION
chr17:47699372

VARIANT ALLELE FREQUENCY (% VAF)
19.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

SPOP inactivation leads to accumulation of its substrate proteins, including the androgen receptor (AR)[365], and SPOP inactivating alterations in prostate cancer have been associated with increased clinical benefit from AR signaling inhibitors such as abiraterone, apalutamide, and enzalutamide[366-370]. 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.

FREQUENCY & PROGNOSIS

In the large MSK MetTropism genomic study, SPOP mutation was most frequently observed in prostate cancer (12.5%), endometrial cancer (3.3%), ovarian cancer (1.1%), small bowel cancer (1.1%), gastrointestinal neuroendocrine cancer (0.7%), and bladder and breast cancer (<0.5%)[108]. Loss of SPOP protein expression is commonly observed and is reported most frequently in gastric (30%), colorectal (20%), and prostate (37%) tumors[371]. Published data investigating the prognostic implications of SPOP alterations in solid tumors other than prostate cancers are limited (PubMed, Mar 2023).

FINDING SUMMARY

SPOP encodes the substrate adapter of a ubiquitin ligase complex, which mediates the polyubiquitination and hence degradation of its substrate proteins such as the androgen, progesterone, and estrogen receptors, the bromodomain and extraterminal domain (BET) proteins BRD2, BRD3, and BRD4, and the DNA-damage response protein 53BP1[365,372-374]. SPOP is reported to function as a tumor suppressor in prostate cancer; however, it may play an oncogenic role in renal cell carcinoma (RCC)[375-376]. Most SPOP mutations in cancer cluster within the substrate-binding MATH domain (aa 31-161), and inactivating alterations in this domain inhibit the degradation of oncogenic protein substrates of SPOP[365,374,377-378]. Although alterations such as observed here have not been characterized and their functional effect is unknown, they have been reported as hotspot mutations in prostate and endometrial cancers[379-380]. Multiple mutations within the meprin and TRAF homology (MATH) MATH domain have been characterized and found to inactivate SPOP protein function[365,381].

GENE
TP53

ALTERATION
R248W

HGVS VARIANT
NM_000546.4:c.742C>T (p.R248W)

VARIANT CHROMOSOMAL POSITION
chr17:7577539

VARIANT ALLELE FREQUENCY (% VAF)
13.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data suggest that solid tumors with TP53 mutations, such as R175H, Y220C, G245S, and R248W, may benefit from adoptive cell therapy targeting these specific TP53 mutations[382-383]. Clinical benefit has been reported for patients with breast cancer (2 PRs)[383], ovarian cancer (1 PR)[383], and colorectal cancer (CRC; 1 SD)[382] treated with tumor infiltrating lymphocyte-based or modified T-cell receptor-based adoptive cell therapy. 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[384-387] or p53 gene therapy such as SGT53[388-393]. 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[394]. Phase 2 studies of adavosertib in combination with chemotherapy reported ORRs of 32% (30/94) and 41% (12/29) for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[395-396]. For patients with platinum-sensitive TP53-mutated ovarian cancer, the combination of adavosertib with paclitaxel and carboplatin significantly increased PFS compared with paclitaxel and carboplatin alone (9.9 vs. 8.0 months)[397]. 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[398]. 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[399]. 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[400]. 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[393]. 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[401]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[402].

— Nontargeted Approaches —

Adjuvant chemo(radio)therapy improved outcomes over radiotherapy alone for patients with endometrial carcinoma (EC) molecularly classified as TP53 abnormal (p53abn; as defined by TP53 mutation or either p53 IHC nuclear or cytoplasmic overexpression or null expression) in retrospective analyses[23,403], and this approach is recommended by the ESGO-ESTRO-ESP guidelines for this EC subtype[18]. For patients with p53abn high-risk EC treated in the PORTEC-3 trial, adjuvant platinum-based chemotherapy plus external beam radiotherapy (EBRT) significantly improved 5-year relapse-free survival (RFS; 59% vs. 36%, HR=0.52) and 5-year OS rates (65% vs. 42%, HR=0.55) versus EBRT alone[23]. In another retrospective study, patients with concurrent TP53 mutation and p53 overexpression experienced significantly improved RFS (median 12.8 vs. 7.4 months, HR=0.41) and OS (median 30.0 vs. 14.4 months, HR=0.28) from bevacizumab plus chemotherapy over temsirolimus plus chemotherapy[20].

FREQUENCY & PROGNOSIS

TP53 mutations are frequent in endometrial carcinomas, having been reported in 17-54% of cases across multiple studies[7,158,404]. Among endometrial carcinoma subtypes, TP53 alteration is most common in endometrial serous carcinomas (88-94% of cases)[7,158,404-405]. TP53 mutations in microsatellite stable/mismatch repair-proficient (MMRp) POLE-wildtype endometrial carcinoma are indicative of a ProMisE/TCGA molecularly classified subtype, "p53abn" (NCCN Uterine Neoplasms Guidelines, v1.2023) ()[7,15-21], which is associated with high risk of recurrence[22], yet also with the highest degree of benefit from adjuvant chemoradiotherapy over radiotherapy relative to the other subtypes[23]. Additionally, classification as this molecular subtype refines FIGO disease stage to IIC (Stage "IICm-p53abn") for patients with histologically determined Stage I/II early endometrial cancer that is locally confined to the uterine corpus or with myometrial invasion[24]. In the context of endometrial carcinomas that are microsatellite stable (MSS)/mismatch repair-proficient (MMRp) and lack pathogenic POLE mutations, TP53 inactivating mutation or p53 nuclear expression is associated with poor prognosis (NCCN Uterine Neoplasms Guidelines, v1.2023)()[7,15-22,406-407].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[195]. Alterations such as seen here may disrupt TP53 function or expression[408-412].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2023)[413]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[414-416], including sarcomas[417-418]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[419] to 1:20,000[418]. 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[420]. 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[421-426]. 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[421-422]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[427]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[425,428-429]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Imatinib

Assay findings association

KIT
amplification - equivocal

PDGFRA
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[91-92,430-431] , KIT-amplified[90-93] , or KIT-expressing tumors[95-100,432-433] , KIT activating alterations may confer sensitivity to imatinib. PDGFRA amplification may predict sensitivity to TKIs such as imatinib; a patient with Merkel cell carcinoma expressing PDGFRA achieved a CR to imatinib[115].

SUPPORTING DATA

A Phase 2 trial of imatinib for the treatment of uterine carcinosarcoma reported that the therapy was generally well tolerated but showed minimal activity in the 23 evaluable patients; positive PDGFR-beta or KIT expression was not correlated with patient characteristics or outcome[434]. A Phase 2 trial of imatinib plus docetaxel for patients with head and neck squamous cell carcinoma (HNSCC) or non-small cell lung cancer (NSCLC) was stopped due to toxicity and lack of efficacy[435]. A Phase 2 study of pulse dose imatinib in combination with paclitaxel for elderly patients with NSCLC reported a response rate of 32% (11/34); however, PFS and OS was similar to that commonly seen for elderly patients with NSCLC treated with single-agent chemotherapy, and the combination was not recommended for further evaluation[436]. Phase 2 clinical trials of imatinib for unselected patients with breast cancer did not demonstrate significant efficacy[437-438] . In addition, a Phase 2 study for 13 patients with metastatic breast cancer with no c-KIT expression and overexpression of PDGFR-beta reported that imatinib as a single agent displayed no clinical activity[439].

Nilotinib

Assay findings association

KIT
amplification - equivocal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[101,440-443] , KIT-amplified[101], or KIT-expressing tumors[444], KIT activating alterations may confer sensitivity to nilotinib.

SUPPORTING DATA

Clinical data on the efficacy of nilotinib for the treatment of endometrial cancer are limited (PubMed, Dec 2023). Nilotinib has been primarily investigated as a therapeutic option for the treatment of chronic myeloid leukemia (CML) or gastrointestinal stromal tumors (GIST). In the context of CML, a Phase 3 clinical trial for patients who are Philadelphia chromosome (Ph) positive treated with imatinib or nilotinib (300 or 400 mg) reported PFS rates of 93% and 97-98% and OS rates of 93% and 94-97%, respectively, at 4 years[445]. For Japanese patients with CML who are resistant to imatinib, a Phase 2 trial reported a 49% major medical response rate to treatment with nilotinib at 12 months[446]. A Phase 3 clinical trial of single-agent nilotinib in 240 patients with advanced GIST who failed prior treatment with imatinib or sunitinib reported no significant difference in PFS between nilotinib and the best supportive care but did report increased OS for patients treated with nilotinib[447]. A Phase 2 trial has shown that nilotinib was well tolerated and suggested it may be particularly useful for treating patients with GIST harboring mutations in KIT exon 17[448].

Sorafenib

Assay findings association

KIT
amplification - equivocal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[449-456] or KIT-expressing tumors[102-105] , KIT activating alterations may predict sensitivity to sorafenib.

SUPPORTING DATA

In a Phase 2 study of sorafenib for patients with advanced uterine carcinoma or carcinosarcoma, 5% (2/40) of patients with uterine carcinoma had a PR and 43% (17/40) had SD; no patients (0/16) with uterine carcinosarcoma had a PR and 25% (4/16) had SD[457]. Sorafenib was found to demonstrate modest clinical activity for patients with recurrent ovarian cancer or primary peritoneal carcinomatosis in a Phase 2 clinical trial; however, considerable toxicity was observed[458]. Another Phase 2 study of sorafenib as third-line treatment for patients with epithelial ovarian cancer or primary peritoneal cancer showed no benefit, with none of the 11 patients exhibiting a PR, CR, or sustained SD[459].

Sunitinib

Assay findings association

KIT
amplification - equivocal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[106,460-464] or KIT-expressing tumors[106-107] , KIT activating alterations may predict sensitivity to sunitinib.

SUPPORTING DATA

In a Phase 2 study, sunitinib elicited 18% (6/33) PR and 18% (6/33) SD rates in patients with endometrial carcinoma or carcinosarcoma, with median PFS and OS of 3 months and 19.4 months, respectively[465].

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
CCNE1

ALTERATION
amplification

RATIONALE
Strong preclinical and clinical data suggest that CCNE1 amplification may predict sensitivity to WEE1 inhibitors. Strong preclinical data suggest that CCNE1 amplification may predict sensitivity to PKMYT1 inhibitors.

NCT04768868

PHASE 1

The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients With Advanced Solid Tumors

TARGETS
WEE1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Shanghai (China), Wuhan (China), Beijing (China), Chengdu (China), Kansas, Texas

NCT05605509

PHASE 2

RP-6306 in Patients With Advanced Cancer

TARGETS
PKMYT1, ERBB2

LOCATIONS: Vancouver (Canada), Ottawa (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT04814108

PHASE 2

A Study of ZN-c3 in Women With Recurrent or Persistent Uterine Serous Carcinoma

TARGETS
WEE1

LOCATIONS: Oregon, Nevada, California, Arizona, Missouri, Ohio, Texas, New York

NCT03968653

PHASE 1

Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors

TARGETS
WEE1

LOCATIONS: Groningen (Netherlands), Nijmegen (Netherlands), Leiden (Netherlands), Barcelona (Spain)

NCT05109975

PHASE 1

A Study to Evaluate Safety and Preliminary Anti-tumor Activity of Debio 0123 as Monotherapy in Adult Participants With Advanced Solid Tumors

TARGETS
WEE1

LOCATIONS: Bellinzona (Switzerland), Zürich (Switzerland), Michigan, Texas

NCT04855656

PHASE 1

Study of RP-6306 Alone or in Combination With RP-3500 in Patients With Advanced Solid Tumors

TARGETS
PKMYT1, ATR

LOCATIONS: Copenhagen (Denmark), Utah, Toronto (Canada), Missouri, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, Texas

NCT05147272

PHASE 1

Study of RP-6306 With Gemcitabine in Advanced Solid Tumors

TARGETS
PKMYT1

LOCATIONS: London (United Kingdom), California, Arizona, Minnesota, Michigan, Toronto (Canada), New York, Pennsylvania, Florida

GENE
FBXW7

ALTERATION
R479Q

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors.

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (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)

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
ALK, ROS1, AXL, TRKA, MET, TRKC, EGFR, PARP, CDK4, CDK6, mTOR, MEK, BRAF, SMO

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

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

GENE
KIT

ALTERATION
amplification - equivocal

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

NCT05007106

PHASE 2

MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (MK-7684A-005)

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

LOCATIONS: Taoyuan (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Seoul (Korea, Republic of), Osaka (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Alaska, Adana (Turkey)

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: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kurume (Japan), Matsuyama (Japan), Seongnamsi Bundang (Korea, Republic of), Songpa-gu (Korea, Republic of), Seoul (Korea, Republic of), Seodaemun (Korea, Republic of)

NCT05112991

PHASE 2

Study of Envafolimab Alone or With Lenvatinib in Patients With Advanced Endometrial Cancer

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Fuzhou (China), Hangzhou (China), Ganzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Changsha (China), Wuhan (China), Yueyang (China), Linyi (China)

NCT05024214

PHASE 1/2

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

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

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

NCT05098847

PHASE 2

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

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

LOCATIONS: Shanghai (China)

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)

NCT04977453

PHASE 1/2

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

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

LOCATIONS: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of), New York, North Carolina

NCT05740215

PHASE 1/2

Efficacy and Safety Study of F520 Combined With Lenvatinib in the Treatment of Patients With Advanced Solid Tumors

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

LOCATIONS: Chongqing (China)

NCT05554341

PHASE 2

Testing the Use of Nilotinib and Paclitaxel as a Treatment for Patients With Prior Taxane Treatment, A ComboMATCH Treatment Trial

TARGETS
ABL, KIT

LOCATIONS: Washington, Oregon, Idaho, Montana

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: Washington, Oregon, California

GENE
MDM2

ALTERATION
amplification

RATIONALE
Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or amplification of MDM2 may increase sensitivity to these agents, but more data are required.

NCT04785196

PHASE 1/2

APG-115 in Combination With PD-1 Inhibitor in Patients With Advanced Liposarcoma or Advanced Solid Tumors

TARGETS
PD-1, MDM2

LOCATIONS: Shanghai (China), Guangzhou (China)

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Brisbane (Australia), South Brisbane (Australia), Bedford Park (Australia), Heidelberg (Australia), California, Arizona, Missouri, Arkansas, Ohio, Pennsylvania

GENE
MYC

ALTERATION
amplification

RATIONALE
MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

NCT05253053

PHASE 1/2

Study to Evaluate the Efficacy and Safety of TT-00420 as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors

TARGETS
FGFR2, FGFR1, FGFR3, PD-L1

LOCATIONS: Shanghai (China), Wuhu (China), Nanjing (China), Changsha (China), Zhengzhou (China), Jinan (China), Beijing (China), Changchun (China)

NCT05110807

PHASE 1

A Clinical Study to Evaluate the Tolerability and Pharmacokinetics of TQB3617 Capsule in Patients With Advanced Malignant Tumors

TARGETS
BRD3, BRD4 , BRD2, BRDT

LOCATIONS: Hangzhou (China), Guangzhou (China)

NCT04983810

PHASE 1/2

A Study to Investigate Fadraciclib (CYC065), in Subjects With Advanced Solid Tumors and Lymphoma

TARGETS
CDK2, CDK9

LOCATIONS: Seoul (Korea, Republic of), Barcelona (Spain), California, Texas

NCT04686682

PHASE 1/2

A First-in-Human, JAB-8263 in Adult Patients With Advanced Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Tianjin (China)

NCT05252390

PHASE 1/2

NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors

TARGETS
BRD4, PARP, AR

LOCATIONS: Nedlands (Australia), Waratah (Australia), North Ryde (Australia), Melbourne (Australia), Malvern (Australia), Montana, California, Colorado

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: California, Colorado, Illinois, Pennsylvania, Kentucky, Virginia, Texas

NCT05372640

PHASE 1

Testing the Safety and Efficacy of the Combination of Two Anti-cancer Drugs, ZEN003694 and Abemaciclib, for Adult and Pediatric Patients (12-17 Years) With Metastatic or Unresectable NUT Carcinoma and Other Solid Tumors

TARGETS
CDK4, CDK6, BRD3, BRD4, BRD2, BRDT

LOCATIONS: California, Pennsylvania, Massachusetts, Texas

NCT05053971

PHASE 1/2

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

TARGETS
BRD3, BRD4, BRD2, BRDT, HDAC

LOCATIONS: Oklahoma, Connecticut, Florida

NCT04840589

PHASE 1

Testing the Combination of ZEN003694 and Nivolumab With or Without Ipilimumab in Solid Tumors

TARGETS
PD-1, CTLA-4, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Ohio, Pennsylvania, New York, Maryland

NCT04587479

PHASE 1

A First-in-Human Study of JAB-8263 in Adult Patients With Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Colorado, Tennessee, Florida

GENE
PDGFRA

ALTERATION
amplification

RATIONALE
PDGFRA amplification may predict sensitivity to imatinib and to anti-PDGFRA antibodies.

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)

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.

ASXL1
NM_015338.5: c.1495C>T
(p.R499C)
chr20:31021496

ATM
NM_000051.3: c.691C>A
(p.H231N)
chr11:108115543

BCORL1
NM_021946.4: c.823C>G
(p.L275V)
chrX:129147571

CIC
NM_015125.4: c.4081G>C
(p.E1361Q)
chr19:42798127 and
NM_015125.4: c.3987G>C
(p.K1329N)
chr19:42797935

DAXX
NM_001350.4: c.1629A>G
(p.I543M)
chr6:33287468

DIS3
NM_001128226.1: c.1481C>T
(p.A494V)
chr13:73345967

KDR
rearrangement

KMT2D (MLL2)
NM_003482.4: c.10024C>T
(p.R3342C)
chr12:49431115

SPEN
NM_015001.2: c.2227C>G
(p.Q743E)
chr1:16254962 and
NM_015001.2: c.3455C>T
(p.S1152L)
chr1:16256190

TBX3
amplification

TNFAIP3
NM_006290.2: c.1398C>G
(p.S466R)
chr6:138199980

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® Sequencing platform (HiSeq 4000 or NovaSeq 6000), 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 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%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). 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.

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 7.15.0
MR Reporting Config Version Config 49
Analysis Pipeline Version v3.29.0
Computational Biology Suite Version 6.29.0

The median exon coverage for this sample is 905x

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