FOUNDATIONONE®CDx

PATIENT
Li Chen, Su-Lien

TUMOR TYPE
Uterus endometrial adenocarcinoma mixed histology

COUNTRY CODE
TW

REPORT DATE
11 Jan 2022

ORDERED TEST #
ORD-1267528-01

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 mixed histology
NAME Li Chen, Su-Lien
DATE OF BIRTH 23 June 1952
SEX Female
MEDICAL RECORD # 25229598

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 S110-68484 F (PF21073)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 10 December 2021
SPECIMEN RECEIVED 24 December 2021

Biomarker Findings

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

Genomic Findings

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

NF1 F944fs*10
MYC amplification - equivocal†
APC duplication exon 16
CBFB loss exons 1-5
IGF1R amplification - equivocal†
RAD21 amplification - equivocal†
SMAD4 loss
TBX3 S409fs*1
TP53 T102fs*21

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type: Selumetinib** (p. 9), **Trametinib** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***NF1* -** F944fs*10	none	Selumetinib
10 Trials *see p. 11*		Trametinib
***MYC* -** amplification - equivocal	none	none
4 Trials *see p. 10*		

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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].

FREQUENCY & PROGNOSIS

MSS has been reported in 73-89% of endometrial cancers[6-13]. Data regarding the role of MSI status on prognosis and survival in endometrial cancer are conflicting, with most studies finding no relationship between MSI-H endometrial cancers and survival[8-9,11,14-16], and one study predicting improved disease-free and disease-specific survival[7]. However, these studies often evaluated endometrial cancers of all FIGO stages together. Studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[8,12,17-18], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

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[19]. 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[19-21]. 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[22-24]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19,21,23-24].

BIOMARKER

Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-34]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[25-28,35]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[25]. 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[26]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[28,35]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

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[37]. Another study evaluating TMB in endometrial adenocarcinoma reported that 24% of tumors had a mutational burden of greater than 10.4 Muts/Mb[38]. Increased tumor mutational burden (TMB) in endometrial carcinoma has been correlated with POLE mutation and advanced high-grade endometrioid subtypes[6,13,39-40]. Ultramutated endometrial tumors (elevated TMB with POLE mutations) have also been associated with improved PFS[6]. The same study associated lower mutational burden, independent of PD-L1 status, in endometrial carcinomas with poorer prognosis[6]. 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[41].

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[42-43] and cigarette smoke in lung cancer[44-45], treatment with temozolomide-based chemotherapy in glioma[46-47], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[6,48-51], and microsatellite instability (MSI)[6,50-51]. 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[26-27,35].

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GENE
NF1

ALTERATION
F944fs*10

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
2830_2831TT>G

VARIANT ALLELE FREQUENCY (% VAF)
69.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[52-55], glioma or glioblastoma[55-59], and non-small cell lung cancer[60], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus, based on limited clinical data[61-63] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[64-65]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[66]. 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[67], 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[68].

FREQUENCY & PROGNOSIS

NF1 alterations have been reported in 5-9% of endometrial carcinomas[6,69-70]. Loss of NF1 has been reported in 13% (4/31) of endometrial carcinomas[71]. Published data investigating the prognostic implications of NF1 mutation in endometrial carcinomas are limited (PubMed, Feb 2021).

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[72]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[73]. Alterations such as seen here may disrupt NF1 function or expression[73-82].

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[83-85]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[86-87], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
MYC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1[88-89], CDK2[90], Aurora kinase A[91-98], Aurora kinase B[99-102], glutaminase[103-106], or BET bromodomain-containing proteins[107-110], as well as agents targeting both HDAC and PI3K[111-113]. 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[114]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor[115]. The glutaminase inhibitor CB-839, in combination with either everolimus or cabozantinib, has demonstrated encouraging efficacy in Phase 1 and 2 studies enrolling patients with pretreated advanced renal cell carcinoma[116-117] .

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[118-119]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[120-121].

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrioid Carcinoma TCGA dataset, putative high-level amplification of MYC has been found in 8% of cases[6]. In the scientific literature, MYC amplification has been detected in 15-27% of endometrial cancer cases[122-125]. In one study, MYC amplification has been associated with higher tumor grade in uterine corpus cancers[125].

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[126]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[127]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[126,128-129].

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GENE
APC

ALTERATION
duplication exon 16

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[130]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[131-132]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[133].

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrial Carcinoma TCGA dataset, APC mutations are reported in 12% of cases[6]. Studies have reported APC mutations at varying frequencies in endometrial carcinoma, from no mutations being detected in 128 samples to 43% (12/28) of analyzed endometrial carcinomas having APC mutations[134-135]. APC methylation has been detected at a higher frequency in endometrial adenocarcinomas with microsatellite instability (MSI) (43%, 17/40), than in cases without MSI (16%, 12/74)[135-136]. Two studies of endometrial carcinomas have reported the absence of APC protein expression in 8% (2/24) and 71% (30/42) of cases[134,137]. A preclinical study using a mouse model demonstrated that loss of APC could induce endometrial cancer[138]. The prognostic significance of APC mutations in endometrial cancer remains unclear (PubMed, Jul 2021). 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

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[146-148]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[149], and in the appropriate clinical context germline testing of APC is recommended.

GENE
CBFB

ALTERATION
loss exons 1-5

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CBFB.

FREQUENCY & PROGNOSIS

A significant frequency of CBFB mutation has been documented in breast cancer[150-151], while elevated CBFB expression has been characterized as enabling RUNX2-mediated invasive phenotypes in in vitro models of breast cancer cell growth and proliferation[152].

FINDING SUMMARY

CBFB encodes the regulatory beta subunit of core binding factor. It complexes with any one of the RUNX proteins (1, 2, or 3) to produce a family of transcription factors required for normal hematopoiesis and osteogenesis[153]. Many cases of acute myeloid leukemia (AML) are characterized by a pericentric inversion of chromosome 16, which creates a fusion gene combining N-terminal CBFB with the C-terminus of MYH11[154]. The resulting fusion protein is hypothesized to contribute to leukemogenesis via dominant-negative inhibition of RUNX1-mediated transcriptional activity[155], although additional, RUNX1-independent mechanisms have also been proposed[156].

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GENE
IGF1R

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IGF1R-based therapies including monoclonal antibodies (mAbs; dalotuzumab, figitumumab, cixutumumab, ganitumab, R1508, and AVE1642), tyrosine kinase inhibitors targeting IGF1R (linsitinib), and mAbs against IGF1R ligands (MEDI-573 and BI836845) are in preclinical and clinical development[157-159]. Phase 2 studies evaluating single-agent IGF1R mAbs in patients with sarcoma reported stable disease (SD) in 16-40% of cases, partial responses (PRs) in 2-12% of cases, and complete responses in 2/2 patients with Ewing sarcoma[157,160-162]. Clinical benefit was also reported for patients with thymic malignancies treated with cixutumumab monotherapy in a Phase 2 study, with a disease control rate of 89% (33/37), including 5 PRs, for patients with thymomas and SD in 42% (5/12) of patients with thymic carcinoma[163]. Limited clinical efficacy has been reported for single-agent ganitumab in genomically unstratified patients with neuroendocrine tumors[164], ganitumab plus hormonal therapy in previously treated breast cancer[165], and single-agent linsitinib in adrenocortical carcinoma[166]. Because IGF1R signaling is upstream of critical signaling pathways, combination therapies with IGF1R inhibitors and mTOR inhibitors may be beneficial[167-169]. It is unclear if the combination of IGFR1 mAb with mTOR inhibitors is superior to IGF1R mAb alone for the treatment of sarcomas[157]. Phase 1 studies evaluating the combination of IGF1R mAbs with mTOR inhibitors in breast cancer have been mixed[170-171]. Although the combination of linsitinib with everolimus to treat colorectal cancer did not lead to clinical benefit[172], clinical activity was reported in a Phase 1 study evaluating the combination of linsitinib and erlotinib in patients with various solid tumors[173]. Preclinical studies indicate that IGF1R kinase inhibitors synergize with CDK4 inhibitors to suppress the growth of cancers that depend on CDK4[174-175].

— Potential Resistance —

Preclinical evidence has implicated IGF1R signaling in resistance to second- and third-generation EGFR inhibitors in lung cancer models[176-178] and to alpha-specific PI3K inhibitors in breast cancer cells[179].

FREQUENCY & PROGNOSIS

In the Uterine Corpus Endometrioid Carcinoma dataset, IGF1R mutation and amplification have been reported in 4.6% and 2% of cases, respectively[6]. IGF1R has been reported to be highly overexpressed in both primary and metastatic uterine serous carcinoma samples[180]. Elevated IGF1R expression has been associated with better OS and favorable pathological parameters in patients with endometrial carcinoma[181-182].

FINDING SUMMARY

IGF1R encodes insulin-like growth factor-1 receptor, a receptor tyrosine kinase that is activated by IGF-1 and IGF-2 and mediates anti-apoptotic signals[183]. Overexpression or activation of IGF-1R may lead to tumor formation[184]. IGF1R has been reported to be amplified in cancer[185] and may be biologically relevant in this context[186-187].

GENE
RAD21

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS

RAD21 amplifications, point mutations, and truncating mutations have been reported in various cancers[188]. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes[189-190], including sporadic Grade 3 but not Grade 1 cancers[189], as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers[189]. Furthermore, SNPs in or near RAD21 have been linked with risk of breast cancer development[191-192]. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer[193] and in colorectal cancer (CRC), especially in KRAS-mutant CRC[194]. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer[195]. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression[196]. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic[197]. Downregulation of RAD21 expression resulted in sensitization of cultured breast[190,198] and CRC[194] cells to chemotherapy, thereby suggesting that RAD21 overexpression confers resistance to chemotherapy.

FINDING SUMMARY

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[199-202]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[203], but also leads to an increase in deletions, insertions, and other rearrangements[204]. High RAD21 expression has also been associated with increased genomic instability[189]. Cohesin complex also organizes chromatin domains and regulates gene expression[205-206]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[207]. RAD21 amplification has been correlated with increased expression in breast[189-190,208] and endometrial[193] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

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GENE
SMAD4

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to address SMAD4 alterations in cancer. Preclinical studies[209-210] and a clinical study of pancreatic cancer suggest that low SMAD4 expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[211].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[212], pancreatic acinar cell carcinoma[213], cholangiocarcinoma (25%)[214], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[215-216], colorectal adenocarcinoma (CRC; 14%)[50], esophageal adenocarcinoma (14%)[217], and stomach adenocarcinoma (13%)[218]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[219] and intraductal papillary mucinous neoplasms (IPMN)[220]; 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[221]. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma[222]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[223-225], appendiceal mucinous neoplasm[226], gastric adenocarcinoma[227-228], esophageal adenocarcinoma[229], esophageal squamous cell carcinoma[230], breast cancer[231], and prostate cancer[232].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[233-234]. 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[235-248].

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[249-251], which is associated with an increased risk of gastrointestinal cancers[252]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[253]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

GENE
TBX3

ALTERATION
S409fs*1

TRANSCRIPT ID
NM_016569

CODING SEQUENCE EFFECT
1225_1256del32

VARIANT ALLELE FREQUENCY (% VAF)
68.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The role of TBX3 in tumorigenesis is complex, and there are no approved therapies to address genomic alterations in TBX3.

FREQUENCY & PROGNOSIS

TBX3 overexpression has been identified in several tumor types, including melanoma[254-255], breast cancer[256], liver cancer[257], and head and neck squamous cell carcinoma[258]. Expression of TBX3 can be induced downstream of either WNT/beta-catenin or BRAF V600E signaling and has been shown to promote tumor invasiveness by directly repressing E-cadherin expression[255,257,259]. Knockdown of TBX3 in melanoma cells increased proliferation but reduced cell migration[260].

FINDING SUMMARY

TBX3 encodes a transcriptional repressor, mutations of which underlie the developmental disorder ulnar-mammary syndrome that is characterized by mammary gland hypoplasia, limb defects, and other congenital abnormalities[261]. TBX3 is a negative regulator of apoptosis, at least in part by repressing p14ARF expression[262-265]. The TBX3 C-terminus contains a repressor domain required for transcriptional repression and cell immortalization[266]; however, somatic truncating mutations have recurrently been identified in breast cancer[267]. Overexpression of TBX3 has been associated with cell transformation, anchorage-independent growth, and increased tumor invasion, but reduced proliferation[255,257,260,265,268-269]. Conversely, TBX3 inactivation may contribute to increased proliferation[260].

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GENE
TP53

ALTERATION
T102fs*21

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
304delA

VARIANT ALLELE FREQUENCY (% VAF)
67.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[270-273], or p53 gene therapy and immunotherapeutics such as SGT-53[274-278] and ALT-801[279]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[280]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[281]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[282]. 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[283]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[284]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[285]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[278]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[286]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[287-288]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[289-290]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 29% of endometrial carcinomas analyzed in COSMIC, including 60% of serous carcinomas, 36% of clear cell carcinomas, and 23% of endometrioid carcinomas (Feb 2021)[291]. In one large study, high (pathologic) expression of p53 was found in 24% of endometrial carcinoma samples and was associated with non-endometrioid histology, high grade (Grade 3 vs. Grade 1-2), and advanced FIGO stage, as well as with lymph node metastasis and poor disease-specific survival, but was not an independent factor for poor prognosis in multivariate analysis[292]. In other studies, p53 alterations (defined as TP53 mutation or p53 nuclear expression) have been found to be associated with poor prognosis in patients with endometrial cancer[293-294].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[295]. Alterations such as seen here may disrupt TP53 function or expression[296-300].

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[301-303], including sarcomas[304-305]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[306] to 1:20,000[305]. 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[307]. 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[308-313]. 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[308-309]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[314]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[312,315-316]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Selumetinib

Assay findings association

NF1
F944fs*10

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable 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[52-55,317-321], glioma[55-59,322], and non-small cell lung cancer[60], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

A Phase 2 study evaluating selumetinib in patients with recurrent endometrial cancer who had received prior treatment with 1-2 therapies did not reach its primary endpoints of efficacy and 6-month event-free survival, reporting mPFS of 2.3 months and mOS of 8.5 months with 1 CR and 2 PR observed in 52 patients[323]. Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[53,317-318] and a Phase 1 study[52]. Phase 2 studies reported clinical responses in low-grade glioma[56,324], melanoma[325-329], and in lung[60,330-331] and endometrial cancer[323]. A Phase 2 study of selumetinib for patients with activating alterations in the MAPK pathway reported a DCR of 15% (3/20), with no objective responses observed[332]. Phase 1 studies of selumetinib to treat patients with solid tumors reported 1/15 PR for a patient with colorectal cancer (CRC) and 5/15 SDs for patients with tonsil squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and CRC[333]; 2/39 PRs (for patients with CRC) and 18/39 SDs were achieved when selumetinib was administered in combination with cyclosporin A[334]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[335], docetaxel or dacarbazine[336], AKT inhibitors[337], or cixutumumab (an anti-IGF-1R antibody)[338] reported clinical responses for patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

Trametinib

Assay findings association

NF1
F944fs*10

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[52-55,317-321], glioma[55-59,322], and non-small cell lung cancer[60], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Although very little clinical data has been reported on the use of MEK inhibitors in endometrial or uterine cancer, a Phase 1 trial of trametinib in combination with an AKT inhibitor (GSK2141795), reported 3/3 objective responses in uterine/endometrial tumors, with 2 patients achieving stable disease (SD) and 1 partial response (PR) occurring in a patient with mutant KRAS and PTEN loss[339]. In other solid tumor types, a Phase 1 trial of trametinib in 206 patients with solid tumors reported 21 (10%) objective responses[340]. Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown significant response rates in patients with melanoma, including those with BRAF and NRAS mutations, but very low response rates in patients with other solid tumors, including those with KRAS mutations[341-342]. A Phase 1b trial of trametinib in combination with gemcitabine in patients with solid tumors showed a complete response in a patient with breast cancer, as well as partial responses in patients with pancreatic or salivary gland cancer[343]. A Phase 1b trial of combination treatment with the MEK inhibitor MEK162 and the PI3K-alpha inhibitor BYL719 reported disease control (partial responses or stable disease) in 47% (21/45) of patients, including partial responses in 2 of 3 patients with KRAS-mutant ovarian cancer and 1 of 3 patients with NRAS-mutant melanoma; a 43% rate of stable disease was observed in patients with KRAS-mutant colorectal cancer, with responses independent of PIK3CA mutation status[344]. 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[67], 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[68].

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

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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
MYC

ALTERATION
amplification - equivocal

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.

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Kashiwa (Japan), Meldola (Italy), Napoli, Campania (Italy), Rozzano (MI) (Italy), Villejuif (France), Bordeaux (France), Barcelona (Spain), Madrid (Spain)

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Arizona, New York, Texas, Virginia, Florida

NCT04555837

PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS
Aurora kinase A, PD-1

LOCATIONS: Texas

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK9, CDK5, CDK2

LOCATIONS: Massachusetts

GENE
NF1

ALTERATION
F944fs*10

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.

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)

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)

NCT03989115

PHASE 1/2

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

TARGETS
SHP2, MEK

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

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

NCT04185831

PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS
PD-L1, MEK, mTOR

LOCATIONS: Uppsala (Sweden), Gothenburg (Sweden)

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, ERBB3, MEK, BRAF, SMO

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

NCT03008408

PHASE 2

Phase II Ribociclib, Everolimus and Letrozole in Endometrial Cancer

TARGETS
Aromatase, mTOR, CDK4, CDK6

LOCATIONS: Texas

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

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.

BCL6
amplification

BRAF
S675fs*2

CIC
T973K

FAM123B
S280R

FANCG
P590A

LTK
G213_A214insGGG

MAP3K1
T948_T949del

NSD3 (WHSC1L1)
rearrangement

SMO
V129I

SOCS1
T15I

TP53
N268K

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APPENDIX Genes Assayed in FoundationOne®CDx

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*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*	*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*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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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 PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by 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. 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.
4. 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.
5. 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.
6. 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

MR Suite Version 5.2.0

The median exon coverage for this sample is 1,034x

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