FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Tseng, Yen Ju	Lung small cell undifferentiated carcinoma	05 Jun 2023
	COUNTRY CODE: TW	ORDERED TEST #: ORD-1637925-01

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 Lung small cell undifferentiated carcinoma
NAME Tseng, Yen Ju
DATE OF BIRTH 10 April 1985
SEX Male
MEDICAL RECORD # 43071132

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 Pleura
SPECIMEN ID S112-22777A
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 18 May 2023
SPECIMEN RECEIVED 26 May 2023

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.

CCNE1 amplification
EGFR exon 19 deletion (L747_P753>S)
PIK3CA E545K
RB1 loss exons 25-27, rearrangement intron 20
FGF10 amplification - equivocal†
RICTOR amplification - equivocal†
TP53 F134C

† See About the Test in appendix for details.

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***CCNE1* -** amplification	none	none
5 Trials see p. 8		
***EGFR* -** exon 19 deletion (L747_P753>S)	none	none
6 Trials see p. 9		
***PIK3CA* -** E545K	none	none
10 Trials see p. 11		
***RB1* -** loss exons 25-27, rearrangement intron 20	none	none
3 Trials see p. 13		

Electronically signed by Erik Williams, M.D. | 05 June 2023
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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.

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

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. Published data investigating the prognostic implications of MSI in SCLC are limited (PubMed, Jun 2023).

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[16]. 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[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

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[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. In SCLC specifically, the Phase 1/2 CheckMate 032 trial as well as 2 large-scale retrospective analyses reported that patients with tumors harboring TMB ≥13 Muts/Mb experienced higher rates of clinical benefit and longer PFS and OS on treatment with the PD-1 inhibitors pembrolizumab or nivolumab (alone or in combination with ipilimumab) or the PD-L1 inhibitor atezolizumab, compared with patients with tumors with TMB <13 Muts/Mb (based on this assay or others)[29,32-33]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[22-25,34-38]. 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[34]; similar findings were observed in the KEYNOTE 028 and 012 trials[25]. 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)[38]. 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[39]. 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[37]. 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[40] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[23].

FREQUENCY & PROGNOSIS

Studies of small cell lung cancer (SCLC) reported a median tumor mutational burden (mTMB) of 8-10 Muts/Mb, with 40% of cases harboring a TMB ≥10 Muts/Mb[41-43]. In one study, large cell neuroendocrine carcinomas (LCNEC) were reported to have an average nonsynonymous TMB of 10.5 Muts/Mb, which was higher than the TMB of non-small cell lung cancer or SCLC[41]. High tumor mutational burden (TMB) (≥10 Muts/Mb) in small cell lung cancer (SCLC) not treated with immunotherapy was not significantly associated with OS compared with lower TMB (<10 Muts/Mb) (6.4 vs. 7.4 months, adjusted HR 1.03) in one study[43]. In another study, higher nonsynonymous mutation burden correlated with immune cell infiltration of tumors and higher PD-L1 expression on immune cells in patients with SCLC and large cell neuroendocrine carcinoma[44].

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[45-46] and cigarette smoke in lung cancer[47-48], treatment with temozolomide-based chemotherapy in glioma[49-50], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[51-55], and microsatellite instability (MSI)[51,54-55]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[29,32-34].

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[56-57] and cyclin E1 promotes cell cycle progression in a complex with CDK2[58], 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[59]. Studies of the WEE1 inhibitor adavosertib observed PRs in patients with CCNE1-amplified HGSOC and ovarian cancer[60-62]. 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[62]. 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[63]. Preclinical studies have demonstrated that cell lines and murine models with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR[64-65], CDK2[66], PKMYT1[67-68], or WEE1[57,69]. 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[70-73].

FREQUENCY & PROGNOSIS

CCNE1 amplification was detected in 2.3% (1/43) of small cell lung carcinoma (SCLC) cases analyzed in one study[74]. In one study of lung neuroendocrine tumors, including small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma, cyclin E was overexpressed in 21% (4/19) large cell neuroendocrine carcinoma samples and 71% (25/35) of SCLC samples[75]. A meta-analysis reports that cyclin E overexpression is correlated with poor prognosis in lung cancers[76].

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[58]. Amplification of chromosomal region 19q12-q13 has been demonstrated in many types of cancer, and CCNE1 is a well-studied gene within this amplicon[77-78]. Increased copy number of CCNE1 is highly associated with overexpression of the cyclin E1 protein[79-80]. Cyclin E1 overexpression can lead to cell transformation as a result of an increase in cyclin E1 activity[58,81].

GENE
EGFR

ALTERATION
exon 19 deletion (L747_P753>S)

HGVS VARIANT
NM_005228.3:c.2240_2257del (p.L747_P753delinsS)

VARIANT CHROMOSOMAL POSITION
chr7:55242469-55242487

VARIANT ALLELE FREQUENCY (% VAF)
22.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer (NSCLC), EGFR activating mutations may predict sensitivity to EGFR-TKIs, including erlotinib[82], gefitinib[83-86], afatinib[87-90], dacomitinib[91], and osimertinib[88,92]; however, the data for patients with other tumor types are limited[93-98]. Transformation of EGFR-mutated non-small cell lung cancer to small cell lung cancer (SCLC) or large cell neuroendocrine carcinoma (LCNEC) has been reported to be a mechanism of acquired resistance to EGFR inhibitors[99-101]. Case studies have reported 2 patients with SCLC[102] and 1 patient with LCNEC[103] with EGFR mutations who benefited from treatment with osimertinib; however, lack of benefit from osimertinib has been reported for 8 patients with EGFR-mutated SCLC[104-106] and 3 patients with EGFR-mutated LCNEC[107-109].

— Nontargeted Approaches —

In retrospective analyses, patients with EGFR-mutated non-small cell lung cancer that transformed to small cell lung cancer demonstrated response rates of 50% to taxane and 54% (with a median PFS of 3.4 months) to platinum-etoposide[99,110]. In a retrospective multi-center study, patients with EGFR-mutated non-small cell lung cancer transformed to small cell lung cancer under EGFR inhibitor therapy experienced high response rates on platinum-etoposide (54% [25/46] ORR, 3.4 median PFS) or taxane (50% [10/20] ORR, 2.7 months median PFS) chemotherapy and a median OS of 10.9 months post-transformation; however, none of the included patients benefitted from treatment with immune checkpoint inhibitors (0/17 ORR)[99].

FREQUENCY & PROGNOSIS

Activating mutations in EGFR have been reported in 3-5% of small cell lung cancers in the scientific literature[111-113]. Transformation to SCLC or large-cell neuroendocrine carcinoma has been observed as mechanism of acquired resistance to EGFR inhibitors in 3-14% of patients with advanced EGFR-mutated non-small cell lung cancer[99,101,114-115].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[116]. EGFR exon 19 deletion mutations, such as seen here, have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib[117-119], afatinib[120], osimertinib[121], and dacomitinib[91,122], although limited preclinical data suggest reduced sensitivity to lapatinib[123-124].

GENE
PIK3CA

ALTERATION
E545K

HGVS VARIANT
NM_006218.2:c.1633G>A (p.E545K)

VARIANT CHROMOSOMAL POSITION
chr3:178936091

VARIANT ALLELE FREQUENCY (% VAF)
61.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[125-132], AKT[133-134], or mTOR[135-142]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[132]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[131]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[129-130]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[143]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[144]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[145]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[146], but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)[126].

FREQUENCY & PROGNOSIS

PIK3CA mutation and amplification have each been reported in 3% of small cell lung carcinomas (SCLC)[147]. p110-alpha has been reported to be overexpressed in 25% of small cell lung carcinomas as compared to normal lung tissue[148]. The prognostic significance of PIK3CA alteration in SCLC has not been extensively studied (PubMed, Aug 2022).

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[149-150]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[151-172].

GENE
RB1

ALTERATION
loss exons 25-27, rearrangement intron 20

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data[173] and strong preclinical data[174-177], RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer (SCLC). A clinical study evaluating the Aurora kinase A inhibitor alisertib for patients with prostate cancer did not find an association between RB1 deletion and clinical benefit[178]. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members[179] and activation of the NOTCH pathway[180].

FREQUENCY & PROGNOSIS

RB1 mutation has been observed in 33-74% of small cell lung cancer (SCLC) cases[181-183]. Inactivation of RB1 and subsequent loss of Rb protein expression is a hallmark molecular event in SCLC, cited in more than 90% of cases in some studies[183-185]. In SCLC, RB wild-type status has been reported to be associated with worse OS and PFS and an increased chemo-refractory tumor response[186-187]. In a retrospective multi-center study, patients with EGFR-mutated non-small cell lung cancer transformed to small cell lung cancer under EGFR inhibitor therapy experienced high response rates on platinum-etoposide (54% [25/46] ORR, 3.4 median PFS) or taxane (50% [10/20] ORR, 2.7 months median PFS) chemotherapy and a median OS of 10.9 months post-transformation; however, none of the included patients benefitted from treatment with immune checkpoint inhibitors (0/17 ORR)[99]. Inactivation of both Rb and p53 in a mouse model led to the development of SCLC tumors, supporting the suggestion that Rb loss is critically involved in SCLC development[188].

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[184,189]. Alterations such as seen here may disrupt RB1 function or expression[190-196].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Mutations in TP53 or RB1 are characteristic of poorly differentiated neuroendocrine carcinomas (NECs) and may help distinguish NECs from well differentiated or unclearly differentiated tumors (NCCN Neuroendocrine and Adrenal Tumors, v2.2022)[197-201].

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[202]. Germline mutations in RB1 account for approximately 40% of RB tumors[203] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[204-205]. In the appropriate clinical context, germline testing of RB1 is recommended.

GENE
FGF10

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A preclinical study reported that FGF10-driven migration and invasion of pancreatic cancer cell lines could be blocked by inhibitory antibodies targeting FGFR2[206], and a second study found that expression of dominant-negative FGFR1 or FGFR2 led to a decrease in tumor size in a prostate cancer xenograft model driven by FGF10, although the decrease was not statistically significant[207]. Clinical trials are ongoing for multiple inhibitors that target FGFR2 and other kinases, including the approved agents pazopanib, ponatinib, and lenvatinib, as well as pan-FGFR inhibitors such as AZD4547, infigratinib, CH5183284, and TAS-120; however, these agents have not been comprehensively tested in the context of FGF10 amplification or overexpression.

FREQUENCY & PROGNOSIS

Infrequent but recurrent amplification of FGF10 has been reported in multiple solid tumor types, including gallbladder cancer[208], gastric cancer[209], and esophageal squamous cell carcinoma (SCC)[210]; one small-scale study reported FGF10 amplification in 7/7 oral SCC cases[211]. Preclinical studies have shown that increased FGF10 expression and FGF10-FGFR1/2 signaling promotes cancer cell proliferation, invasion, migration, and tumorigenesis in a variety of tumor models[206-207,212-213].

FINDING SUMMARY

FGF10 encodes fibroblast growth factor 10, a ligand that primarily binds to FGFR2, but also FGFR1[214], with a broad range of functions in development and wound healing. FGF10 has been implicated in regulating the epithelial-mesenchymal transition in cancer cells[215] and during normal development[216]. Germline mutations in FGF10 have been implicated in aplasia of the lacrimal and salivary glands, an autosomal dominant developmental disorder[217]. Amplification of FGF10 has been reported in cancer[218] and may be biologically relevant in this context[219-220].

GENE
RICTOR

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

RICTOR amplification may indicate sensitivity to mTORC1/2 inhibitors[221] or dual PI3K/mTOR inhibitors[222]. A patient with RICTOR-amplified lung adenocarcinoma experienced SD for >18 months upon treatment with the dual mTORC1/2 inhibitor CC-223[221], and a patient with RICTOR-amplified metastatic thymic carcinoma achieved a PR upon treatment with a pan-PI3K/mTORC1/2 inhibitor PQR309[222]. In contrast, no clinical benefit was reported for 4 patients with RICTOR-amplified small cell lung cancer treated with the mTORC1/2 inhibitor vistusertib[223] and additional trials of this compound were terminated due to lack of efficacy[224].

FREQUENCY & PROGNOSIS

In a genomic study of 1,070 lung cancer cases, focal amplification of RICTOR was detected in 14.6% of small cell lung cancers (7/48), 8.7% of large cell neuroendocrine carcinomas (2/23), 8.4% of adenocarcinomas (61/724), and 7.4% of squamous cell carcinomas (8/108)[221]. Published data investigating the prognostic implications of RICTOR alterations in lung cancer are limited (PubMed, Jul 2022). One study reported an association between RICTOR amplification and brain metastases in lung cancer[225]. RICTOR amplification in lung cancer often co-occurs with mutations in KRAS, EGFR, or the PI3K–AKT–mTOR pathway, but has also been characterized as a driver alteration in lung cancer[221,226].

FINDING SUMMARY

RICTOR encodes an mTOR-binding protein that forms part of the rapamycin-insensitive mTORC2 complex, a regulator of cell metabolism and the cytoskeleton[227-229]. RICTOR amplification has been reported in cancer[147] and has been associated with clinical response to mTORC1/2 inhibition[230-231] .

GENE
TP53

ALTERATION
F134C

HGVS VARIANT
NM_000546.4:c.401T>G (p.F134C)

VARIANT CHROMOSOMAL POSITION
chr17:7578529

VARIANT ALLELE FREQUENCY (% VAF)
90.1%

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[232-235] or p53 gene therapy such as SGT53[236-240]. 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[241]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[242]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[243]. 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[244]. 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[224]. 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[245]. 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[246]. 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[240]. 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[247]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[248].

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in small cell lung cancer (SCLC), with mutations present in 79-92% of tumors[181-183]. Deletion of TP53 has been reported in 8-52% of SCLC tumors analyzed, which may be higher than in tumors in general (35%)[249]. TP53 alteration has been reported to be important for SCLC carcinogenesis[185]. One study reported significant association between presence of TP53 mutation and worse OS in patients with SCLC with limited disease[250]. In a retrospective multi-center study, patients with EGFR-mutated non-small cell lung cancer transformed to small cell lung cancer under EGFR inhibitor therapy experienced high response rates on platinum-etoposide (54% [25/46] ORR, 3.4 median PFS) or taxane (50% [10/20] ORR, 2.7 months median PFS) chemotherapy and a median OS of 10.9 months post-transformation; however, none of the included patients benefitted from treatment with immune checkpoint inhibitors (0/17 ORR)[99].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[251]. Alterations such as seen here may disrupt TP53 function or expression[252-256].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Mutations in TP53 or RB1 are characteristic of poorly differentiated neuroendocrine carcinomas (NECs) and may help distinguish NECs from well differentiated or unclearly differentiated tumors (NCCN Neuroendocrine and Adrenal Tumors, v2.2022)[197-201].

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[257-259], including sarcomas[260-261]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[262] to 1:20,000[261]. 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[263]. 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[264-269]. 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[264-265]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[270]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[268,271-272]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Erik Williams, M.D. | 05 June 2023
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

NCT05128825

PHASE 2

A Study of ZN-c3 in Subjects With Malignant Tumors

TARGETS
WEE1

LOCATIONS: Nevada, South Dakota, Wisconsin, Missouri, Ohio, Texas, Pennsylvania

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

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
EGFR

ALTERATION
exon 19 deletion (L747_P753>S)

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

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)

NCT04946968

PHASE 2

Phase-2 Dacomitinib Study on Patients With EGFR-Driven Advanced Solid Tumours With Low EGFR-AS1 lncRNA Expr or Other Novel Emerging Biomarkers

TARGETS
ERBB4, EGFR, ERBB2

LOCATIONS: Singapore (Singapore)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

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

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

NCT04670679

PHASE 1

A Dose Escalation/Expansion Study of ERAS-601 in Patients With Advanced or Metastatic Solid Tumors

TARGETS
SHP2, EGFR

LOCATIONS: Perth (Australia), Melbourne (Australia), Nevada, California, Missouri, Texas, Massachusetts, New York, Pennsylvania, Tennessee

NCT04085315

PHASE 1

Alisertib in Combination With Osimertinib in Metastatic EGFR-mutant Lung Cancer

TARGETS
EGFR, Aurora kinase A

LOCATIONS: California

GENE
PIK3CA

ALTERATION
E545K

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

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

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Xi'an (China)

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)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

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

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

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

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

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04317105

PHASE 1/2

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

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Texas, Virginia

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

GENE
RB1

ALTERATION
loss exons 25-27, rearrangement intron 20

RATIONALE
On the basis of preclinical evidence, RB1 loss or inactivation may predict sensitivity to Aurora kinase A inhibitors.

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
Aurora kinase A, Aurora kinase B, PD-L1

LOCATIONS: Jinan (China), Beijing (China)

NCT04742959

PHASE 1/2

Crossover Relative Bioavailability and Dose Escalation Study of TT-00420 Tablet in Patients With Advanced Solid Tumors

TARGETS
Aurora kinase A, Aurora kinase B

LOCATIONS: California, Illinois, Ohio, Texas, New Jersey

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

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.

KMT2D (MLL2)
NM_003482.4: c.7046C>T (p.P2349L)
chr12:49434507

MSH2
NM_000251.1: c.2425G>A (p.E809K)
chr2:47705625

NSD2 (WHSC1 OR MMSET)
NM_133335.3: c.2849G>A (p.G950E)
chr4:1957883

RAD51
NM_133487.3: c.701C>T (p.S234L)
chr15:41021756

SDHA
amplification

TSC1
NM_000368.4: c.2485A>C (p.S829R)
chr9:135776993

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLE

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.9.0

The median exon coverage for this sample is 445x

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