FOUNDATIONONE®CDx

PATIENT
Chang, Chih Chao

TUMOR TYPE
Brain glioblastoma (GBM)

COUNTRY CODE
TW

REPORT DATE
30 Dec 2022

ORDERED TEST #
ORD-1528067-01

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 Brain glioblastoma (GBM)
NAME Chang, Chih Chao
DATE OF BIRTH 22 January 1954
SEX Male
MEDICAL RECORD # 27693396

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 Brain
SPECIMEN ID S111-50616A (PF22145)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 03 December 2022
SPECIMEN RECEIVED 19 December 2022

Biomarker Findings

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

Genomic Findings

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

IDH1 R132H
NF1 splice site 1062G>A
PIK3CA H1047R
ERBB4 R838Q
FUBP1 S124fs*15
MERTK S428G
SETD2 D372fs*111
TERT promoter -146C>T
TP53 R306* - subclonal†

2 Disease relevant genes with no reportable alterations: *EGFR, PDGFRA*

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***IDH1*** **R132H** (p. 4), ***TERT*** **promoter -146C>T** (p. 9)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cobimetinib** (p. 11), **Ivosidenib** (p. 11), **Olutasidenib** (p. 11), **Selumetinib** (p. 12), **Trametinib** (p. 12)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***IDH1*** **R132H** (p. 4)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***IDH1*** **R132H** (p. 4), ***TERT*** **promoter -146C>T** (p. 9)

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)**
IDH1 **-** R132H	none	Ivosidenib
10 Trials see p. 13		Olutasidenib
NF1 **-** splice site 1062G>A	none	Cobimetinib
		Selumetinib
		Trametinib
10 Trials see p. 15		
PIK3CA **-** H1047R	none	none
10 Trials see p. 17		

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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.

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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

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[6-8]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[6], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[9]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[6], in GBMs with a previous lower grade astrocytoma[7], and in giant cell GBM compared to classic GBM[8].

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[10]. 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[10-12]. 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[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

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[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[16,26-27]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[28-29] or anti-PD-L1[30] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)[31]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[35].

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[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. 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[16,26-30].

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GENE
IDH1

ALTERATION
R132H

TRANSCRIPT ID
NM_005896.2

CODING SEQUENCE EFFECT
395G>A

VARIANT CHROMOSOMAL POSITION
chr2:209113112

VARIANT ALLELE FREQUENCY (% VAF)
29.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib[47] and olutasidenib[48]. A Phase 1B/2 basket study of the IDH1 inhibitor olutasidenib reported a DCR of 48% (12/25, 2 PR) in patients with glioma; patients with other solid tumors including intrahepatic cholangiocarcinoma and chondrosarcoma achieved SD[48]. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)[49]. Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors[50-53]. In a Phase 1 trial of the PD-L1 inhibitor atezolizumab for patients with glioblastoma (GBM), 2/3 patients with IDH1-mutated tumors experienced clinical benefit (1 PR, 1 long-term SD, 1 short-term SD), whereas none of the 8 patients with IDH1-wildtype GBM experienced benefit (8/8 PD); significantly longer PFS and a trend toward longer OS were observed for patients with IDH1-mutated tumors compared with the patients with IDH1-wildtype tumors[30]. A Phase 1 trial of the oral brain-penetrant mutated IDH1 selective inhibitor DS-1001 for patients with recurrent or progressive IDH1-mutated glioma reported 2 CRs and 4 PRs for 35 patients with enhancing tumors and 1 PR and 3 minor responses (MRs) for 12 patients with non-enhancing tumors[54]. Preclinical data indicate that IDH1-mutated glioma may be sensitive to the glutaminase inhibitor telaglenastat in combination with radiotherapy[55].

— Nontargeted Approaches —

IDH1/2 mutations are associated with improved survival outcomes for patients with glioma treated with radiation or alkylating chemotherapy (NCCN CNS Cancers Guidelines, v1.2022). Addition of procarbazine, lomustine, and vincristine (PCV) to radiotherapy significantly improved OS for patients with IDH-mutated (9.4 vs. 5.7 years, HR=0.59) but not IDH-non-mutated (1.3 versus 1.8 years, HR=1.14) anaplastic oligodendroglioma/oligoastrocytoma[56]. As adjuvant therapy after radiation for patients with IDH1/2-mutated anaplastic astrocytoma, temozolomide[57] or PCV[58] improved median PFS and median OS relative to radiotherapy or temozolomide alone, respectively.

FREQUENCY & PROGNOSIS

IDH1 mutation is characteristic of low-grade gliomas and secondary glioblastoma, and is relatively rare in primary glioblastoma[59-63]. In the TCGA datasets, IDH1 mutation has been found in 77% of lower grade glioma cases and in 5% of glioblastoma cases[64-65]. In the context of IDH-mutated gliomas, TERT mutations are associated with improved OS (NCCN CNS Cancers Guidelines, v1.2022)[66]. IDH1/2 mutations are a strong favorable prognostic marker for OS in Grade 2-3 glioma, particularly in combination with 1p/19q codeletion (NCCN CNS Cancers Guidelines, v1.2022). Several studies have found IDH1 mutations to be associated with improved prognosis and longer PFS and OS in patients with various types of glioma including anaplastic astrocytoma and GBM[63,67-73].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis[74]. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer[74-78]. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)[76-80], which promotes tumorigenesis[76,81-84].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Co-occurring TERT mutation, IDH mutation, and 1p/19q co-deletion is indicative of oligodendroglioma (NCCN CNS Cancers Guidelines, v1.2022)[85]. IDH1/2 mutation is associated with Grade 2 and 3 astrocytomas and oligodendrogliomas, with the latter also harboring 1p19q deletion, and distinguishes secondary glioblastoma (GBM) from primary GBM (NCCN CNS Cancers Guidelines, v1.2022).

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GENE
NF1

ALTERATION
splice site 1062G>A

TRANSCRIPT ID
NM_001042492.2

CODING SEQUENCE EFFECT
1062G>A

VARIANT CHROMOSOMAL POSITION
chr17:29527613

VARIANT ALLELE FREQUENCY (% VAF)
83.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[86-89], glioma or glioblastoma[89-93], and non-small cell lung cancer[94], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. On the basis of limited clinical data[95-97] and preclinical data[98-99], loss or inactivation of NF1 may predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient malignant peripheral nerve sheath tumors (MPNST)[100]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

NF1 mutation has been observed in 5-6% of lower grade gliomas and 9-14% of glioblastoma multiforme (GBM) cases; homozygous deletion of NF1 was observed in 1% of lower grade gliomas and 2-3% of GBMs[40,64-65,101]. Among GBM subtypes, NF1 mutation and loss were reported most frequently in the mesenchymal subtype, 37% (14/28) and 38% (21/55) of cases, respectively[102]. NF1 loss was significantly associated with decreased overall and disease-specific survival in patients with lower grade gliomas (II-III), but not in those with GBM[103].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[104]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[105]. The consequences of alterations that may leave the GAP-related domain intact, such as seen here, are unclear; however, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the NF1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with neurofibromatosis type 1 (ClinVar, Sep 2022)[106]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. 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[107-109]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[110-111], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE
PIK3CA

ALTERATION
H1047R

TRANSCRIPT ID
NM_006218.2

CODING SEQUENCE EFFECT
3140A>G

VARIANT CHROMOSOMAL POSITION
chr3:178952085

VARIANT ALLELE FREQUENCY (% VAF)
51.3%

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[112-119], AKT[120-121], or mTOR[122-129]. 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[119]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[118]. 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[116-117]. 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[130]. 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)[131]. 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)[132]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[133], 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)[113].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 9% of glioblastoma (GBM) samples analyzed in the TCGA dataset[65], and other studies report the incidence of PIK3CA mutations in primary GBMs as 5-18%[134-136]. One study detected PIK3CA mutation in 16% (36/232) of IDH-wildtype GBM samples analyzed[137]. PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)[101,134-136,138]. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity[136]. One study found that PIK3CA mutation in glioblastoma (GBM) was associated with shorter median PFS in both a discovery cohort (6.9 vs. 12.4 months, HR=2.89, p=0.01) and in the TCGA cohort (6.1 vs. 9 months, p=0.008), but was not consistently associated with median OS[139]. In a study of IDH-wildtype GBM, patients with alterations in PI3K class I genes (PIK3CA, PIK3R1, PIK3CG, and PIK3R2) had significantly longer OS (20.0 months altered vs. 16.9 months wildtype, HR=0.62, p=0.002) and PFS (11.0 months altered vs. 7.4 months wildtype, p=0.0043); patients with PIK3CA alterations experienced an improved OS but this association was not highly significant (20.0 months altered vs. 18.1 months wildtype, p=0.0407)[137].

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[140-141]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[142-163].

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GENE
ERBB4

ALTERATION
R838Q

TRANSCRIPT ID
NM_005235.2

CODING SEQUENCE EFFECT
2513G>A

VARIANT CHROMOSOMAL POSITION
chr2:212295800

VARIANT ALLELE FREQUENCY (% VAF)
58.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The ERBB family kinase inhibitors afatinib and lapatinib, the EGFR inhibitors erlotinib and gefitinib, and the Bruton tyrosine kinase inhibitor ibrutinib have been shown to inhibit ERBB4 at clinically achievable concentrations[164-169]. However, whether these inhibitors would be clinically effective for patients with ERBB4 mutation is unclear. Retrospective analyses of the Phase 3 LUX-Lung 8 trial reported that patients with squamous non-small cell lung cancer (NSCLC) harboring mutations in ERBB family members exhibited long-term benefit following afatinib treatment compared with patients with ERBB-wildtype tumors; there was no difference for patients treated with erlotinib[170-171]. A meta-analysis showed that patients with ERBB4-mutated NSCLC treated with immune checkpoint inhibitors exhibited longer PFS and OS compared with patients who had ERBB4-wildtype tumors (p=0.036 and p=0.0378)[172].

FREQUENCY & PROGNOSIS

ERBB4 mutations have been identified in various solid tumors, including stomach (13%), salivary gland (11%, 2/18), esophageal (9%), lung (8-9%), endometrioid (6%), colorectal (5%), head and neck (5%), and gallbladder carcinomas (3.9%, 2/51), and melanoma (1.8%)[172-177]. In hematological malignancies, ERBB4 mutations are rare, and have been reported at low frequency in diffuse large B-cell lymphoma (DLBCL)(2.2%-5.7%), chronic lymphocytic leukemia (CLL)(0.6-1.1%), and multiple myeloma (0.5%)[178-184]. ERBB4 amplification has been predominantly detected in gastric tumors (67%)[185]. ERBB4 fusions have been identified infrequently in solid tumors and peripheral T-cell lymphoma, although evidence for ERBB4 fusions as driver alterations is generally limited[186-189]. Expression of N-terminally truncated oncogenic ERBB4 variants has been reported in ALK fusion-negative anaplastic large cell lymphomas[190]. ERBB4 mutation correlates with poorer survival for patients with colorectal cancer (CRC)[191]. Increased ERBB4 expression has been associated with worse clinical outcomes for patients with CRC[192-193], bone sarcoma[194], esophageal squamous cell carcinoma (SCC)[195], oral SCC[196], metastatic Ewing sarcoma[197], gastric cancer[198], osteosarcoma[199], or triple-negative breast cancer[200]. In contrast, high ERBB4 expression has been described as a positive prognostic factor in breast cancer[201-203], ovarian cancer[204], cervical carcinomas[205], hormone-sensitive and castrate-resistant prostate cancer[206], and EGFR-negative intrahepatic cholangiocarcinoma[207].

FINDING SUMMARY

ERBB4 (also known as HER4) encodes a member of the ErbB receptor tyrosine kinase family that plays a role in cell proliferation and apoptosis[208]. Activating alterations are predicted to be oncogenic, and gain-of-function mutations have been identified throughout the gene[173,208-210]. The variants N181S, V348L, P854Q, and T926M have demonstrated similar activity as wildtype ERBB4 in limited preclinical studies[209,211]. A single-nucleotide polymorphism in ERBB4 has been associated with increased risk of non-small cell lung cancer (NSCLC) in the Chinese Han population[212].

GENE
FUBP1

ALTERATION
S124fs*15

TRANSCRIPT ID
NM_003902.3

CODING SEQUENCE EFFECT
370_371delTC

VARIANT CHROMOSOMAL POSITION
chr1:78432611-78432613

VARIANT ALLELE FREQUENCY (% VAF)
79.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

FUBP1 alteration has been reported in 1.5% of samples analyzed in COSMIC, with the highest incidences reported in tumors of the endometrium (3%), central nervous system (3%), large intestine (3%), stomach (3%), liver (3%), and skin (2%) (COSMIC, 2022)[213]. One study reported higher expression of FUBP1 in colorectal carcinoma tissues compared to adenoma and normal colon epithelial tissues[214]. A genetic signature defined by concomitant alterations in IDH1, CIC, and FUBP1 is associated with longer survival in patients with glioma[215]. FUBP1 has been shown to activate the expression of MYC[216-219], activate p27KIP1[220], and regulate the splicing of MDM2[221].

FINDING SUMMARY

FUBP1 encodes far upstream element binding protein 1 (also called FBP-1), a DNA-binding protein reported to have roles in transcriptional activation and splicing regulation of target genes. It is believed to act as an oncogene in some tumor types, such as hepatocellular carcinoma and non-small-cell lung cancer[222-223], and as a tumor suppressor in others, particularly oligodendroglioma, for which mutations and/or loss of FUBP1 often co-occur with alterations in CIC or IDH1[215,224-227].

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GENE
MERTK

ALTERATION
S428G

TRANSCRIPT ID
NM_006343.2

CODING SEQUENCE EFFECT
1282A>G

VARIANT CHROMOSOMAL POSITION
chr2:112740556

VARIANT ALLELE FREQUENCY (% VAF)
57.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MERTK activation may predict sensitivity to MERTK inhibitors. Multiple preclinical studies have demonstrated that inhibition of MERTK with the dual MERTK/FLT3 inhibitor, UNC2025, reduces proliferation, anchorage-independent growth and xenograft growth of GBM, NSCLC, and acute myeloid leukemia (AML) cell lines[228-230].The multikinase inhibitor foretinib has also been observed to inhibit MERTK phoshorylation in GBM cell lines[231]. MERTK inhibition has been shown preclinically to enhance chemosensitivity of acute lymphoblastic leukemia, neuroblastoma, and NSCLC cells[230,232-233]. Moreover, MERTK overexpression in EGFR-mutated NSCLC cells conferred resistance to erlotinib by maintaining AKT signaling[234].

FREQUENCY & PROGNOSIS

Mutation of MERTK has been primarily reported in desmoplastic melanoma (10%)[235], skin cutaneous melanoma (8%), uterine carcinosarcoma (5%)[236], and bladder urothelial carcinomas (4%), whereas putative high-level amplification of MERTK has been observed in neuroendocrine prostate cancer (8%)[237], esophageal carcinoma (4%), sarcoma (2%)[238], and at lower frequencies in other tissue types (cBioPortal, 2022)[239-240]. In the scientific literature, MERTK overexpression has been reported in astrocytomas[241], gliomas[242], neuroblastomas[233], and non-small cell lung cancer (NSCLC)[232,234]. Although MERTK is overexpressed in NSCLC, no association has been found between MERTK expression and survival, stage, histology, or differentiation of NSCLC tumors[232,234]. In glioblastoma (GBM), MERTK expression has not been extensively studied in the clinical setting as a poor prognostic factor (PubMed, 2022); however, expression of the MERTK ligand, GAS6, is associated with reduced median survival of patients with GBM[228]. In a mouse xenograft model of prostate cancer, knockdown of MERTK significantly increased metastasis-free survival[243].

FINDING SUMMARY

MERTK encodes the Mer receptor tyrosine kinase (RTK), a member of the TAM (TYRO3, AXL, MER) family of atypical RTKs. Mer has been shown to activate the AKT and ERK signaling pathways and promote cell proliferation, cell invasion, anchorage-independent growth, and tumor growth in xenograft mouse models[231,233-234,241-244]. MERTK mutations in the context of cancer have not been an area of significant study in the scientific literature (PubMed, 2022). However, one preclinical study identified a role for MERTK P802S in enhancing cell motility[244].

GENE
SETD2

ALTERATION
D372fs*111

TRANSCRIPT ID
NM_014159.6

CODING SEQUENCE EFFECT
1116_1119delCAGA

VARIANT CHROMOSOMAL POSITION
chr3:47165006-47165010

VARIANT ALLELE FREQUENCY (% VAF)
26.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS

Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[245]. SETD2 has been associated with favorable prognosis in gastric cancer[246]. SETD2 has also been associated with poor prognosis in RCC and MDS[247-248], while data in other tumor types is limited (PubMed, Jun 2022).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[249] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[250]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[251]. SETD2 alterations such as observed here have been shown to be inactivating[252-257].

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GENE
TERT

ALTERATION
promoter -146C>T

TRANSCRIPT ID
NM_198253.2

CODING SEQUENCE EFFECT
-146C>T

VARIANT CHROMOSOMAL POSITION
chr5:1295250

VARIANT ALLELE FREQUENCY (% VAF)
47.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[258]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[259]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[260].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[261-262], most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas[261-265]. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)[261,263]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[137]. In the context of IDH-mutated gliomas, TERT mutations are associated with improved OS (NCCN CNS Cancers Guidelines, v1.2022)[66]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[266]. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM[261,263,266-267]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v1.2022).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[268]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[269-271]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[272-274], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[272].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Co-occurring TERT mutation, IDH mutation, and 1p/19q co-deletion is indicative of oligodendroglioma (NCCN CNS Cancers Guidelines, v1.2022)[85]. TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v1.2022)[85]. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v1.2022)[275].

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GENE
TP53

ALTERATION
R306* - subclonal

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
916C>T

VARIANT CHROMOSOMAL POSITION
chr17:7577022

VARIANT ALLELE FREQUENCY (% VAF)
5.1%

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[276-279] or p53 gene therapy such as SGT53[280-284]. 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[285]. 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[286]. 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[287]. 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[288]. 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[289]. 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[290]. 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[291]. 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[284]. 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[292]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[293].

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs[101,294]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[137]. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively[295-300]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[301]. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM[137]. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN[302].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[303]. Alterations such as seen here may disrupt TP53 function or expression[304-308].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[106]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[309-311], including sarcomas[312-313]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[314] to 1:20,000[313]. 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[315]. 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[316-321]. 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[316-317]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[322]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[320,323-324]. 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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Cobimetinib

Assay findings association

NF1
splice site 1062G>A

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[86-89,325-329] , glioma[89-93,330] , and non-small cell lung cancer[94], NF1 inactivation may predict sensitivity to MEK inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 1/2 study evaluating the use of cobimetinib for pediatric and young adult patients with relapsed or refractory solid tumors reported an ORR of 9.4% (3/32) among patients with low-grade glioma[331]. A patient with anaplastic pleomorphic xanthoastrocytoma with leptomeningeal dissemination harboring an ATG7-RAF1 fusion exhibited a complete cytologic response and clinical benefit following treatment with cobimetinib[332]. Single-agent cobimetinib has shown clinical activity in the context of histiocytic neoplasms, including Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease, nodular histiocytosis, and mixed histiocytosis[333-340] . A Phase 1 study of cobimetinib monotherapy in solid tumors reported CRs for 1.0% (1/97) of patients and PRs for 6.2% (6/97) of patients, all of whom had melanoma[341]. Clinical benefit following treatment with cobimetinib has been seen for patients with non-small cell lung cancer (NSCLC)[341-342] , adenoid cystic carcinoma[341], and anaplastic pleomorphic xanthoastrocytoma[332].

Ivosidenib

Assay findings association

IDH1
R132H

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML) or previously treated locally advanced or metastatic cholangiocarcinoma. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML[343] and cholangiocarcinoma[344-345] and limited clinical data in myelodysplastic syndrome (MDS)[343] and glioma[47,346] , IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

In a Phase 1 study of ivosidenib for patients with IDH1-mutated advanced solid tumors, 1 patient achieved PR in the non-enhancing glioma population (ORR=2.9% [1/35]); for patients with non-enhancing glioma and enhancing glioma, SD rates were 85.7% (30/35) and 45.2% (14/31), respectively, and median PFS was 13.6 months and 1.4 months, respectively[47,346] .

Olutasidenib

Assay findings association

IDH1
R132H

AREAS OF THERAPEUTIC USE

Olutasidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical data in acute myeloid leukemia (AML)[347] and limited clinical data in both myelodysplastic syndrome (MDS)[348] and glioma[48], IDH1 R132 mutation may confer sensitivity to olutasidenib.

SUPPORTING DATA

The Phase 1b/2 trial investigating olutasidenib for patients with IDH1-mutated glioma reported a DCR of 48% (12/25, 2 PRs) and a median duration of disease control of 8.6 months; both PRs were observed for patients with enhancing high-grade glioma[48].

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Selumetinib

Assay findings association

NF1
splice site 1062G>A

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[86-89,325-329] , glioma[89-93,330] , and non-small cell lung cancer[94], NF1 inactivation may predict sensitivity to MEK inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Selumetinib has demonstrated clinical activity in low-grade glioma. A Phase 2 study of selumetinib for patients with low-grade glioma (LGG) reported 8/25 PRs for patients with BRAF alterations and 10/25 PRs for those with NF1-associated LGG[90]; a Phase 1 study of selumetinib reported 5/25 PRs for patients with LGG[349]. A Phase 2 study of selumetinib for patients with tumors with activating alterations in the MAPK pathway evaluated 8 patients with high-grade glioma (HGG); 2 SDs and no objective responses were observed in this subset[350].

Trametinib

Assay findings association

NF1
splice site 1062G>A

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[86-89,325-329] , glioma[89-93,330] , and non-small cell lung cancer[94], NF1 inactivation may predict sensitivity to MEK inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Case studies of trametinib in NF1-associated low-grade glioma have reported 7 PRs, including 2 patients with pilocytic astrocytoma, 2 patients with diffuse astrocytoma, 3 patients with low-grade glioma experiencing PRs of over 6 months[89,91-92,330] . A study of 2 pediatric patients with optic astrocytomas harboring BRAF duplications reported clinical benefit in response to trametinib with reductions in tumor volume (56-66%) and treatment ongoing at 484 and 468 days[351]. A study of 5 patients with KIAA1549-BRAF-fusion-positive pilocytic astrocytoma reported 1 PR and 3 minor responses[92] and, similarly, a patient with low-grade glioma harboring this fusion benefited from trametinib[352]. A patient with pilocytic astrocytoma harboring an NFIA-RAF1 fusion who had progressed on multiple lines of prior treatment exhibited ongoing SD following treatment with trametinib[353]. 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[354], 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[355].

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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Electronically signed by Erik Williams, M.D. | 30 December 2022
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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
IDH1

ALTERATION
R132H

RATIONALE
IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP inhibitors in solid tumors. Preclinical data indicate that IDH1 mutations may predict sensitivity to glutaminase inhibitors.

NCT04521686

PHASE 1

Study of LY3410738 Administered to Patients With Advanced Solid Tumors With IDH1 Mutations

TARGETS
PD-L1, IDH2, IDH1

LOCATIONS: Taichung City (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Suita-shi (Japan), Nagaizumi (Japan), Yokohama (Japan), Chuo-ku (Japan), Kashiwa (Japan), Singapore (Singapore)

NCT05417594

PHASE 1/2

Study of AZD9574 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Advanced Solid Malignancies

TARGETS
PARP

LOCATIONS: Seoul (Korea, Republic of), Melbourne (Australia), Sant Cugat del Valles (Spain), Pozuelo de Alarcon (Spain), A Coruña (Spain), Sevilla (Spain), Texas

NCT04740190

PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT04715620

PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
PARP

LOCATIONS: Tianjin (China)

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NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

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)

NCT05076513

PHASE NULL

Trial of Niraparib in Participants With Newly-diagnosed Glioblastoma and Recurrent Glioma

TARGETS
PARP

LOCATIONS: Arizona

NCT04614909

PHASE NULL

Phase 0/2 Study of Pamiparib in Newly Diagnosed and rGBM

TARGETS
PARP

LOCATIONS: Arizona

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

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GENE
NF1

ALTERATION
splice site 1062G>A

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. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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)

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

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NCT04965818

PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS
MEK, FGFRs

LOCATIONS: California, Indiana, Texas

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

NCT05159245

PHASE 2

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

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

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

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

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GENE
PIK3CA

ALTERATION
H1047R

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: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

NCT04341259

PHASE 1

A Study Of The Pharmacokinetics And Safety Of Ipatasertib In Chinese Participants With Locally Advanced Or Metastatic Solid Tumors.

TARGETS
AKTs

LOCATIONS: Shanghai City (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)

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)

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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)

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)

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

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NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BCOR
S473R

BRAF
D22N

NOTCH3
R1175W

PBRM1
E1189K

SOX9
M469V

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ORDERED TEST # ORD-1528067-01

APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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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. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the 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

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

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

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.4.0

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The median exon coverage for this sample is 846x

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