FOUNDATIONONE®CDx

PATIENT
Liao, Chin-Tsai

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
05 May 2022
ORDERED TEST #
ORD-1351899-01

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 Liao, Chin-Tsai
DATE OF BIRTH 10 February 1963
SEX Male
MEDICAL RECORD # 32487573

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 PF22058
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 13 April 2022
SPECIMEN RECEIVED 27 April 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

EGFR **exon 20 insertion (N771_P772insNN)**
CDK4 **amplification**
MDM2 **amplification**
PIK3R1 **deletion exons 14-16**
TERT **promoter -124C>T**

2 Disease relevant genes with no reportable alterations: *IDH1, PDGFRA*

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***TERT*** **promoter -124C>T** (p. 6)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Erlotinib** (p. 7), **Gefitinib** (p. 7)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 8)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***TERT*** **promoter -124C>T** (p. 6)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 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)**
EGFR **-** exon 20 insertion (N771_P772insNN)	none	*Erlotinib* ⊗ *Gefitinib* ⊗
5 Trials *see p. 10*		
CDK4 **-** amplification	none	none
10 Trials *see p. 8*		
MDM2 **-** amplification	none	none
6 Trials *see p. 11*		
PIK3R1 **-** deletion exons 14-16	none	none
2 Trials *see p. 12*		

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

TERT - promoter -124C>T ..... p. 6

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
3 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].

GENE
EGFR

ALTERATION
exon 20 insertion (N771_P772insNN)

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
2313_2314insAACAAC

VARIANT ALLELE FREQUENCY (% VAF)
30.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The EGFR/MET bispecific antibody amivantamab[47], the novel second-generation EGFR TKI poziotinib[48-50] , and dual EGFR/HER2 kinase inhibitors such as mobocertinib[51] and DZD9008[52] have demonstrated efficacy for NSCLC patients with EGFR exon 20 insertions. For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[53], gefitinib[54], afatinib[55], dacomitinib[56], and osimertinib[57]; however, the data for patients with other tumor types are limited[58-63]. A case study of a patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFR amplification and multiple missense mutations, reported a near-CR of the EGFR-amplified and -mutated tumor to osimertinib[64]. A case series of 11 patients with bithalamic gliomas with EGFR mutations suggested that treatment with EGFR inhibitors, including osimertinib, prolonged patient survival relative to other types of treatment; however, no patients attained PR or SD[61]. Another case series of 2 patients with osimertinib-treated bithalamic gliomas with EGFR exon 20 insertion mutations reported that one patient experienced no progression at 4 months of treatment and that another patient did not progress until after 6 months of treatment[65].

— Potential Resistance —

Both clinical and preclinical evidence suggest that insertions in the loop following the C-helix, such as alterations observed here, confer resistance to both irreversible and reversible EGFR inhibitors[66-77]. In particular, these insertions have been associated with lack of response to erlotinib and gefitinib in patients and preclinical studies[71,78-88], although 1 patient with the H773_V774dupHV mutation experienced a PR on combination treatment with gefitinib and chemotherapy[71]; SD has been observed in 2 patients with the H773dup mutation and 1 patient with the N771>SY mutation[86]. Structural data also predict that this alteration would not respond to the reversible pan-ERBB inhibitor lapatinib[89-90]. Clinical trials and case studies of afatinib in patients with NSCLC with EGFR exon 20 insertions have reported an ORR of only 11% (3/27) and a DCR of 15-22% (4/27 to 6/27), with median PFS of 2.7 months and median OS of 9.2 months[76-77,91]. However, a study of afatinib for patients with NSCLC after previous failure on erlotinib and/or gefitinib reported a median time to treatment failure (mTTF) of 18.9 months and an ORR of 43% for the subset of patients with tumors harboring EGFR exon 20 insertions; the mTTF and ORR were numerically higher than those for patients with tumors harboring other EGFR mutations[92]. Therefore, the efficacy of afatinib against these alterations is unclear. The activity of osimertinib for exon 20 insertions is unclear, although objective responses have been reported in retrospective and case studies for a subset of patients with NSCLC and these alterations[93-95].

FREQUENCY & PROGNOSIS

EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas in several genomic studies of CNS tumors[96-99]. In GBMs, Missense mutations in the EGFR extracellular domain have been found in 10-15% of cases and approximately half have a low-level amplification of the mutated allele[100-101]. In a study of IDH-wildtype GBM samples, EGFR alterations were detected in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event[102]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[103-104]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[105].

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[106]. EGFR alterations such as observed here are in-frame insertions into exon 20 of EGFR, in the loop following the C-helix of the kinase domain[73]; these alterations have been shown to be activating[107]. Insertions in exon 20 are predicted to force the kinase into an active conformation[66-77]. EGFR exon 20 insertions that occur closer to the C-terminus, such as those affecting D770 and N771, appear more likely to be resistant to reversible EGFR inhibitors, compared with insertions occurring earlier in exon 20[73].

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GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[108-111]. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib[112], palbociclib[108,113], and ribociclib[114].

FREQUENCY & PROGNOSIS

Across TCGA and MKSCC studies, CDK4 amplification has been reported in 4.0-9.4% of glioma cases and 14% of glioblastoma multiforme cases (cBioPortal, Sep 2021)[96-98,115-116]. A study has reported amplification of the 12q14-15 region, where CDK4 and MDM2 reside, in 5% (2/42) of glioblastomas[117]. Amplification of CDK4 and corresponding increased CDK4 protein expression has been reported to be associated with a poorer patient outcome in anaplastic astrocytoma and glioblastoma[118-121].

FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[122]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[123-124]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[108,125-131].

GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[132]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[133-134]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[135-136] . A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[137]. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[138-139] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[140]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[141]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[142-143] .

FREQUENCY & PROGNOSIS

In the Glioblastoma Multiforme (GBM) TCGA dataset, amplification of MDM2 has been found in 8% of cases[97]. A study has reported amplification of the 12q14-15 region, where MDM2 and CDK4 reside, in 5% (2/42) of GBMs[117]. Amplification of MDM2 has been associated with poor survival in patients with glioblastoma[117,144].

FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[145-147]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[148-149]. Overexpression or amplification of MDM2 is frequent in cancer[150]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[151] and 2/3 patients with MDM2 or MDM4 amplification[152] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[153]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[153].

GENE
PIK3R1

ALTERATION
deletion exons 14-16

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical[154-155] and preclinical[156-157] data, PIK3R1 alteration may predict sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. In patients with PIK3R1 mutation and no other alterations in the PI3K-AKT-mTOR pathway, 2 CRs have been achieved by patients with endometrial cancer treated with the pan-PI3K inhibitor pilaralisib[154], and 1 PR has been achieved by a patient with breast cancer treated with the PI3K-alpha inhibitor alpelisib in combination with ribociclib and letrozole[158]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[157,159-162] or AKT[163-164]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[165].

FREQUENCY & PROGNOSIS

One study detected PIK3R1 mutation in 10% (24/232) of IDH-wildtype glioblastoma (GBM) samples analyzed[102]. In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[42], glioblastoma (GBM; 11%)[97], uterine carcinosarcoma (11%)(cBioPortal, Jan 2022)[115-116], and lower grade glioma (5%)[166]. PIK3R1 is often inactivated by in-frame insertions or deletions (indels), and the majority of this class of mutation (80%) was observed in endometrial carcinoma[167-169], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[167]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[170] and metastasis-free survival in breast cancer[171]. PIK3R1 expression is not associated with overall survival in neuroendocrine tumors[172].

FINDING SUMMARY

PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[173]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[174-177], promote tumorigenesis[156,163,174], and promote hyperplasia in the context of PTEN-deficiency[178]. Alterations such as seen here may disrupt PIK3R1 function or expression[157,164-165,168-169,179-188].

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
46.0%

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[189]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[190]. 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[191].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[192-193], 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[192-196]. 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%)[192,194]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[102]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[197]. 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[192,194,197-198]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v2.2021).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[199]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[200-202]. 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)[203-205], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[203].

POTENTIAL DIAGNOSTIC IMPLICATIONS

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, v2.2021)[206]. 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, v2.2021)[207].

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Erlotinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
exon 20 insertion
(N771_P772insNN)

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[53,208-210] . Various EGFR exon 20 insertions have been associated with lack of response to erlotinib and gefitinib in patients and preclinical studies[79,81-83,211-212] , suggesting that this approach may not be beneficial in this case.

SUPPORTING DATA

In the MyPathway Phase 2a basket study for advanced solid tumors, 1 of 9 patients with EGFR activation mutations responded to erlotinib monotherapy; the responding patient had urethral adenocarcinoma[213]. A patient with EGFR-mutated metastatic lacrimal gland adenoid cystic carcinoma experienced clinical benefit from erlotinib treatment that was ongoing at 14 months[214]. A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[215]. In a Phase 2 study of 65 patients with GBM or gliosarcoma, treatment with erlotinib, temozolomide, and radiotherapy resulted in longer progression-free survival relative to a historical control study utilizing a regimen of temozolomide and radiotherapy alone (19.3 months vs. 14.1 months)[216]. However, in a Phase 1/2 trial of erlotinib monotherapy in 11 patients with relapsed or refractory GBM or anaplastic astrocytoma, all patients showed disease progression and the drug showed significant toxicity[217]. In addition, a Phase 2 trial of patients with recurrent or progressive GBM treated with erlotinib and sorafenib did not meet its objective of a 30% increase in overall survival time compared with historical controls; sorafenib was found to increase erlotinib clearance[218].

Gefitinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
exon 20 insertion
(N771_P772insNN)

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[210,219-224] , and responses have been reported for patients with EGFR-rearranged NSCLC[225-226] . Various EGFR exon 20 insertions have been associated with lack of response to erlotinib and gefitinib in patients and preclinical studies[79,81-83,211-212] , suggesting that this approach may not be beneficial in this case.

SUPPORTING DATA

A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[215]. A Phase 2 clinical study of gefitinib in patients with high-grade glioma (including GBM, anaplastic astrocytoma, and oligodendroglioma) reported 18% (5/28) disease stabilization; efficacy was not correlated with EGFR expression[227]. However, a Phase 1/2 clinical trial of gefitinib combined with radiotherapy in 178 patients with GBM reported no overall survival benefit of added gefitinib, and EGFR expression was found to be of no prognostic value for patients treated with gefitinib plus radiotherapy[228]. A Phase 2 trial of preoperative gefitinib treatment in patients with recurrent GBM reported that although EGFR phosphorylation was decreased in treated patients as compared to the control group, measurement of 12 downstream molecules revealed no significant changes[229].

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

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

GENE
CDK4

RATIONALE
CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

ALTERATION
amplification

NCT04282031

PHASE 1/2

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

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

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)

NCT04594005

PHASE 1/2

CDK4/6 Tumor, Abemaciclib, Paclitaxel

TARGETS
CDK4, CDK6

LOCATIONS: Seoul (Korea, Republic of)

NCT04391595

PHASE NULL

LY3214996 Plus Abemaciclib in Recurrent Glioblastoma Patients

TARGETS
CDK4, CDK6, ERK1, ERK2

LOCATIONS: Arizona

NCT02933736

PHASE NULL

Ribociclib (LEE011) in Preoperative Glioma and Meningioma Patients

TARGETS
CDK6, CDK4

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)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Nice (France), Lyon (France), Marseille (France), Toulouse (France), Bordeaux (France)

NCT03158389

PHASE 1/2

NCT Neuro Master Match - N^2M^2 (NOA-20)

TARGETS
ALK, RET, CDK4, CDK6, mTOR, MDM2, PD-L1, SMO

LOCATIONS: Berlin (Germany), Dresden (Germany), Regensburg (Germany), Bochum (Germany), Frankfurt am Main (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Cologne (Germany), Mannheim (Germany)

NCT02981940

PHASE 2

A Study of Abemaciclib in Recurrent Glioblastoma

TARGETS
CDK4, CDK6

LOCATIONS: Utah, California, Massachusetts

GENE
EGFR

ALTERATION
exon 20 insertion (N771_P772insNN)

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. Insertions in exon 20 of EGFR may reduce sensitivity to EGFR inhibitors. Although objective responses to osimertinib have been observed for patients with EGFR exon 20 insertions, a subset of patients have experienced PD; therefore, it is unclear whether this therapeutic approach would be relevant.

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRPα, in Subjects With Advanced Solid and Hematologic Cancers

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Heidelberg (Australia), Melbourne (Australia), Edmonton (Canada), Oregon, California, Arizona, Toronto (Canada), Oklahoma, Missouri, Pennsylvania

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

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

LOCATIONS: Utah

NCT04172597

PHASE 2

A Study of Poziotinib in Patients With EGFR or HER2 Activating Mutations in Advanced Malignancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: California

NCT02800486

PHASE 2

Super Selective Intra-arterial Repeated Infusion of Cetuximab (Erbitux) With Reirradiation for Treatment of Relapsed/Refractory GBM, AA, and AOA

TARGETS
EGFR

LOCATIONS: New York

NCT02861898

PHASE 1/2

Super-selective Intra-arterial Repeated Infusion of Cetuximab for the Treatment of Newly Diagnosed Glioblastoma

TARGETS
EGFR

LOCATIONS: New York

Electronically signed by Erik Williams, M.D. | 05 May 2022
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GENE
MDM2

ALTERATION
amplification

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

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

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing City (China), Beijing (China), Chengdu City (China)

NCT04785196

PHASE 1/2

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

TARGETS
PD-1, MDM2

LOCATIONS: Shanghai (China), Guangzhou (China)

NCT03449381

PHASE 1

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TARGETS
MDM2

LOCATIONS: Tokyo, Chuo-ku (Japan), Warsaw (Poland), Poznan (Poland), Berlin (Germany), Köln (Germany), Tübingen (Germany), Leuven (Belgium), Barcelona (Spain), Ottawa (Canada), Connecticut

NCT03611868

PHASE 1/2

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

TARGETS
MDM2, PD-1

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

NCT03158389

PHASE 1/2

NCT Neuro Master Match - N^2M^2 (NOA-20)

TARGETS
ALK, RET, CDK4, CDK6, mTOR, MDM2, PD-L1, SMO

LOCATIONS: Berlin (Germany), Dresden (Germany), Regensburg (Germany), Bochum (Germany), Frankfurt am Main (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Cologne (Germany), Mannheim (Germany)

NCT03725436

PHASE 1

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

TARGETS
MDM2, MDM4

LOCATIONS: Texas

GENE
PIK3R1

ALTERATION
deletion exons 14-16

RATIONALE
On the basis of clinical and strong preclinical data, PIK_3R_1 loss or inactivation may indicate sensitivity to pan-PI_3K or PI_3K-alpha-selective inhibitors.

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)

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

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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.

ALOX12B
A49V

AXL
I252V

BCORL1
V872G

MERTK
P481S

MLL2
N2965S

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*
KMT2A (MLL)	*MSH2*	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*
RAF1	*RARA*	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***
TMPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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 fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

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

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

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 6.2.0

The median exon coverage for this sample is 978x

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