

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) | PHYSICIAN | ORDERING PHYSICIAN | Yeh, Yi-Chen | SPECIMEN | SPECIMEN SITE | Brain |
| | NAME | Huang, Hung-Chin | | MEDICAL FACILITY | Taipei Veterans General Hospital | | SPECIMEN ID | S110-34515A (PF22037) |
| | DATE OF BIRTH | 02 March 1965 | | ADDITIONAL RECIPIENT | None | | SPECIMEN TYPE | Slide Deck |
| | SEX | Male | | MEDICAL FACILITY ID | 205872 | | DATE OF COLLECTION | 12 November 2021 |
| | MEDICAL RECORD # | 47863627 | | PATHOLOGIST | Not Provided | | SPECIMEN RECEIVED | 14 March 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 P596L, A289T, amplification
HGF amplification - equivocal[†]
MDM4 amplification
PIK3C2B amplification
RB1 E204*

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

[†] See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: **EGFR amplification** (p. 4)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cetuximab** (p. 7), **Erlotinib** (p. 7), **Gefitinib** (p. 8), **Panitumumab** (p. 8)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 3 Muts/Mb

GENOMIC FINDINGS

EGFR - P596L, A289T, amplification

7 Trials see p. 9

HGF - amplification - equivocal

2 Trials see p. 11

MDM4 - amplification

1 Trial see p. 12

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

| THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|----------------------------------------------------------------|------------------------------------------------------------|
| none | Cetuximab |
| | Erlotinib |
| | Gefitinib |
| | Panitumumab |
| none | none |
| none | none |

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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.

PIK3C2B - amplification **p. 6** **RB1 - E204*** **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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ORDERED TEST # ORD-1321261-01

BIOMARKER FINDINGS

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 inhibitors¹⁻³, including approved therapies nivolumab and pembrolizumab⁴. 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) samples⁶⁻⁸. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples⁶, although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs⁹. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM⁶, in GBMs with a previous lower grade astrocytoma⁷, and in giant cell GBM compared to classic GBM⁸.

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 tumor¹⁰. 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 PMS2¹⁰⁻¹². This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers¹³⁻¹⁵. 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-L1¹⁶⁻¹⁸, anti-PD-1 therapies¹⁶⁻¹⁹, and combination nivolumab and ipilimumab²⁰⁻²⁵. 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-1²⁸⁻²⁹ or anti-PD-L1³⁰ 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 (mut/Mb), and 4.2% of cases have high TMB (>20 mut/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 TMB³²⁻³³. Increased TMB has been reported to correlate with higher tumor grade in glioma³⁴ and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency

(bMMRD)²⁸, as well as with shorter OS of patients with diffuse glioma³⁵.

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 melanoma³⁶⁻³⁷ and cigarette smoke in lung cancer³⁸⁻³⁹, treatment with temozolomide-based chemotherapy in glioma⁴⁰⁻⁴¹, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁴²⁻⁴⁶, 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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ORDERED TEST # ORD-1321261-01

GENOMIC FINDINGS

GENE

EGFR

ALTERATION

P596L, A289T, amplification

TRANSCRIPT ID

NM_005228, NM_005228

CODING SEQUENCE EFFECT

1787C>T, 865G>A

VARIANT ALLELE FREQUENCY (% VAF)

16.2%, 35.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib⁴⁷, gefitinib⁴⁸, afatinib⁴⁹, dacomitinib⁵⁰, and osimertinib⁵¹; however, the data for patients with other tumor types are limited⁵²⁻⁵⁷. 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 osimertinib⁵⁸. 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 SD⁵⁵. 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 treatment⁵⁹. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy^{57,60-63}; however, a small subset of patients has experienced clinical benefit^{57,60-61}. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit

from erlotinib or gefitinib for patients with glioblastoma⁶⁴⁻⁶⁷. There are conflicting data on the efficacy of anti-EGFR antibodies for the treatment of EGFR-amplified tumors. A meta-analysis of colorectal cancer patients treated with second-line or higher cetuximab or panitumumab observed an association between EGFR copy number gain and increased OS and PFS⁶⁸. However, studies in head and neck squamous cell carcinoma and gastric cancer found either no association or a negative association between EGFR copy number gain and survival after treatment with first-line cetuximab or panitumumab in combination with chemotherapy⁶⁹⁻⁷⁰. The Phase 3 INTELLANCE trial of depatuxizumab mafodotin (ABT-414), an EGFR-targeted antibody-drug conjugate with a toxic payload, in patients with EGFR-amplified glioblastoma (GBM) was stopped for futility. Interim analysis demonstrated improved median PFS (mPFS) of ABT-414 monotherapy compared with placebo (HR=0.84); however, no OS benefit was observed (HR=1.01). Improved mPFS was also observed in patients harboring EGFRvIII (HR=0.73) but without an OS improvement (HR=0.95)⁷¹. The Phase 2 INTELLANCE trial demonstrated clinical benefit for EGFR-amplified GBM for the combination of ABT-414, temozolomide, and radiotherapy (HR=0.66, p=0.017), but there was no evidence of efficacy for ABT-414 monotherapy (HR=1.04, p=0.83)⁷².

FREQUENCY & PROGNOSIS

Across several genomic studies of CNS tumors, EGFR amplification has been reported in 16.9% of anaplastic astrocytomas, and 39.7% of glioblastoma multiformes (GBMs)⁷³⁻⁷⁶. Across several genomic studies of CNS tumors, EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas⁷³⁻⁷⁶. In the glioblastoma (GBM) TCGA dataset, putative high-level amplification of EGFR has been found in 48% of cases and mutation has been found in 21% of cases⁷⁴. Missense mutations in the EGFR extracellular domain have been found in 10-15% of

GBMs and approximately half have a low-level amplification of the mutated allele⁷⁷⁻⁷⁸. One study detected EGFR alterations 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 event⁷⁹. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM⁸⁰⁻⁸¹; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM⁸².

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 divide⁸³. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types⁸⁴⁻⁸⁶. EGFR mutations that have been characterized in biochemical assays to be activating, as observed here, are predicted to confer sensitivity to EGFR-targeted therapies^{77,87-103}. The EGFR A289V mutation, located in the extracellular domain, has been shown to be activating⁷⁷. Glioblastoma cell lines harboring an EGFR A289V or A289D mutation were shown to be dependent on EGFR kinase activity⁷⁸, and other mutations at this position are also likely activating. In addition, A289V is frequently associated with increased EGFR gene copy number⁷⁷.

POTENTIAL DIAGNOSTIC IMPLICATIONS

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)¹⁰⁴.

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GENOMIC FINDINGS
GENE
HGF
ALTERATION

amplification - equivocal

bevacizumab¹¹⁰, tumor HGF gene expression did not predict significant benefit from onartuzumab added to the EGFR-inhibitor erlotinib for patients with non-small cell lung cancer¹¹¹. Anti-HGF antibodies, such as ficlatuzumab, are also under clinical investigation¹¹²⁻¹¹³.

and increased microvessels, and tumor-derived HGF expression has been shown to correlate with reduced survival time¹²³. Elevated expression of HGF and MET mRNA have been reported in GBM¹²⁴⁻¹²⁵, and HGF expression in GBM models has been shown to be associated with responsiveness to MET inhibition¹⁰⁵.

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

On the basis of several preclinical studies in different cancer types, high HGF gene expression may associate with sensitivity to MET-targeted therapies, such as the approved multikinase inhibitors crizotinib and cabozantinib¹⁰⁵⁻¹⁰⁹. However, this hypothesis has not been extensively tested in clinical studies. Whereas patients with glioblastoma and high tumor HGF gene expression experienced longer survival and a higher objective response rate (5/14 vs. 0/16) on the MET-targeting antibody onartuzumab combined with the anti-VEGF antibody bevacizumab than with placebo plus

— Potential Resistance —

Preclinical studies have shown that increased HGF protein levels can induce resistance of EGFR-mutant lung tumors to EGFR inhibitors and of BRAF-mutant melanoma cells to RAF inhibitors; this resistance could be overcome by combination therapy with MET inhibitors¹¹⁴⁻¹¹⁹.

FREQUENCY & PROGNOSIS

HGF amplification has been reported in less than 1% of samples in lower-grade gliomas and in up to 1.6% of glioblastoma cases; mutation has been observed in <1% of gliomas (cBioPortal, COSMIC, Dec 2021)^{74,120-122}. HGF expression within tumor glioma cells is associated with high-grade glioma

FINDING SUMMARY

HGF encodes hepatocyte growth factor, also known as scatter factor, an activating ligand of the receptor tyrosine kinase MET. Certain splice isoforms of HGF may also act as MET antagonists¹²⁶⁻¹²⁷. HGF plays an important role in normal development, acting as a growth factor in a number of different tissues¹²⁶⁻¹²⁷. HGF and its receptor, MET, have been implicated in growth, invasion, and metastasis of many solid tumors¹²⁷. HGF has been reported to be amplified in cancer¹²², and may be biologically relevant in this context¹²⁸⁻¹²⁹.

GENE
MDM4
ALTERATION

amplification

been reported in Nutlin-3 non-responder chronic lymphocytic leukemia patients than in responder patients¹⁴¹. Additional therapeutic mechanisms that target MDM4 are also in preclinical development¹³⁵⁻¹³⁶.

MDM4 amplification in 4% (4/106) of GBMs and in 4% (1/27) of anaplastic oligodendrogliomas; MDM4 amplification was not detected in any of the 56 low-grade (Grade 1 or 2) gliomas investigated¹⁴⁷. The association of MDM4 amplification with tumor grade in astrocytomas is unclear¹⁴²⁻¹⁴³.

FREQUENCY & PROGNOSIS

In the TCGA dataset, amplification of MDM4 was observed in 8.5% of glioblastoma cases⁷⁴. MDM4 amplification or amplification of the 1q32.1 chromosomal locus, which encompasses MDM4 and PIK3C2B, has been frequently reported, particularly in Grade 3 and 4 astrocytoma or glioblastoma multiforme (GBM) cases; one study reported MDM4 amplification in 27% (23/86) of astrocytoma samples¹⁴²⁻¹⁴⁷. A study also reported

FINDING SUMMARY

MDM4 acts as a negative regulator of p53, but a fraction of MDM4 localized to the mitochondria acts in concert with p53 to promote apoptosis¹⁴⁸. MDM4 has been reported to be amplified in cancer and therapies targeting MDM4 or MDM2 have been shown to increase levels of the tumor suppressor p53 in cancer cells^{122,140,149-150}.

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

Numerous small molecules targeting MDM4 or the MDM2-MDM4 complex, including nutlins, are in preclinical and clinical development¹³⁰⁻¹³⁶ and have been shown to be effective against cancer cells in the presence of a wild-type p53 allele¹³⁷⁻¹⁴⁰. However, higher MDM4 protein expression has

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GENOMIC FINDINGS

GENE

PIK3C2B

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies known to effectively target mutations in PIK3C2B.

FREQUENCY & PROGNOSIS

Although PIK3C2B mutation has not been reported for many tumor types, microarray analysis of glioblastoma cell lines revealed that increased gene expression of PIK3C2B significantly correlated with insensitivity to erlotinib¹⁵¹. In addition, 8% of 465 glioblastoma multiforme (GBM) tumor samples analyzed in one study demonstrated copy number amplification of PIK3C2B¹⁴⁵. Although elevated expression of PIK3C2B has been observed in GBM, it is unclear if this plays any role in oncogenesis.

FINDING SUMMARY

PI3K signaling is implicated in the regulation of metabolic control, immunity, angiogenesis and cardiovascular homeostasis, and is one of the most frequently dysregulated pathways in cancer. In contrast to class I PI3Ks, including p110- α and p110- β , the functional roles of class II PI3Ks, encoded by PIK3C2A, PIK3C2B, and PIK3C2G, are not well understood¹⁵².

GENE

RB1

ALTERATION
E204*

TRANSCRIPT ID
NM_000321

CODING SEQUENCE EFFECT
610G>T

VARIANT ALLELE FREQUENCY (% VAF)
26.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data¹⁵³ and strong preclinical data¹⁵⁴⁻¹⁵⁶, RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer. It should be noted that a trial of the Aurora kinase A inhibitor alisertib in advanced prostate cancer did not find an association between RB1 deletion and clinical benefit¹⁵⁷. Other approaches to target RB1 inactivation under investigation in preclinical

studies include inhibitors of BCL-2 family members¹⁵⁸ and activation of the NOTCH pathway¹⁵⁹.

— Potential Resistance —

Rb inactivation may predict resistance to CDK4/6 inhibitors such as palbociclib, abemaciclib, and ribociclib, which act upstream of Rb¹⁶⁰⁻¹⁶⁹.

— Nontargeted Approaches —

Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer¹⁷⁰⁻¹⁷¹.

FREQUENCY & PROGNOSIS

In the TCGA datasets, RB1 mutation or homozygous deletion was observed in 9% of glioblastomas⁷⁴ and 2.5% of lower grade glioma cases¹⁷². In one study, loss of RB1 transcript expression was observed in 10.6% of glioblastomas and occurred more frequently in the proneural subtype¹⁷³. One study reports that mutation of RB1 is correlated with shorter

survival in glioblastoma patients¹⁷⁴. Several studies suggest that RB1, PTEN, and/or TP53 mutations are early events in the development of glioblastoma^{144,175-176}.

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle^{171,177}. Alterations such as seen here may disrupt RB1 function or expression¹⁷⁸⁻¹⁸⁴.

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year¹⁸⁵. Germline mutations in RB1 account for approximately 40% of RB tumors¹⁸⁶ and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma¹⁸⁷⁻¹⁸⁸. In the appropriate clinical context, germline testing of RB1 is recommended.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Cetuximab

Assay findings association

EGFR

P596L, A289T, amplification

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies⁶⁸.

SUPPORTING DATA

A clinical trial of cetuximab with bevacizumab (an anti-VEGF monoclonal antibody) in patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone¹⁸⁹. In preclinical trials, cetuximab, matuzumab, and panitumumab were reported to be ineffective at blocking EGFR dimerization and activation in GBM cells expressing EGFR extracellular

domain mutations¹⁹⁰. However, another study demonstrated that in patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly better progression-free survival (PFS) and numerical (although not statistically significant) improvement in overall survival (OS)¹⁹¹. A Phase 3 trial of combined cetuximab and platinum/5-FU in patients with HNSCC demonstrated improved response compared to platinum/5-FU alone, but EGFR amplification was not shown to predict response to this treatment⁶⁹. A Phase 3 study of patients with pancreatic adenocarcinoma did not report any improved outcome in patients treated with a combination of cetuximab plus gemcitabine vs gemcitabine alone¹⁹². In a Phase 1/2 trial of 36 patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cetuximab in combination with doxorubicin, stable disease was reported in approximately 63% of patients¹⁹³. A Phase 1 study of the combination therapy of cetuximab, erlotinib, and bevacizumab reported stable disease in 21% (7/34) of patients with non-small cell lung cancer (NSCLC)¹⁹⁴.

Erlotinib

Assay findings association

EGFR

P596L, A289T, amplification

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucicromab 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^{47,195-197}. For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival¹⁹⁸⁻²⁰².

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 adenocarcinoma²⁰³. A patient with EGFR-mutated metastatic lacrimal gland adenoid cystic carcinoma experienced clinical benefit from erlotinib treatment that was ongoing at 14 months²⁰⁴. 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 response⁶⁴. 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)²⁰⁵. 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 toxicity²⁰⁶. 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 clearance²⁰⁷.

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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

ORDERED TEST # ORD-1321261-01

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Gefitinib

Assay findings association

EGFR

P596L, A289T, amplification

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^{197,208-213}, and responses have been reported for patients with EGFR-rearranged NSCLC²¹⁴⁻²¹⁵. For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival¹⁹⁸⁻²⁰². Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)^{198,216}.

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 response⁶⁴. 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 expression⁶⁵. 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 radiotherapy⁶⁶. 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 changes⁶⁷.

Panitumumab

Assay findings association

EGFR

P596L, A289T, amplification

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies⁶⁸.

SUPPORTING DATA

A Phase 1 trial of EnGeneIC delivery vehicle (EDV) targeting EGFR with panitumumab in combination with

doxorubicin for 14 patients with glioblastoma (GBM) reported no responses and 28% (4/14) SDs²¹⁷.

Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer²¹⁸⁻²²⁰ and has been investigated in a variety of other tumor types. For patients with head and neck squamous cell carcinoma (HNSCC), data are conflicting; some trials of panitumumab in various lines and with different chemotherapy combinations have shown modest benefit²²¹⁻²²³ and others have reported no benefit²²⁴⁻²²⁶. A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility²²⁷. Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)²²⁸⁻²²⁹; biliary tract cancers, including cholangiocarcinoma²³⁰⁻²³¹; and renal cell carcinoma (RCC)²³².

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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CLINICAL TRIALS

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
EGFR
ALTERATION

P596L, A289T, amplification

RATIONALE

EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome

resistance to current agents include next-generation EGFR inhibitors and combination therapies.

NCT03239015
PHASE 2

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

TARGETS

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

LOCATIONS: Shanghai (China)

NCT03783403
PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRP α , 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

NCT03810872
PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS

EGFR, ERBB4, ERBB2

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

NCT03618667
PHASE 2

GC1118 in Recurrent Glioblastoma Patients With High EGFR Amplification

TARGETS

EGFR

LOCATIONS: Seoul (Korea, Republic of)

NCT04172597
PHASE 2

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

TARGETS

EGFR, ERBB2, ERBB4

LOCATIONS: California

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ORDERED TEST # ORD-1321261-01

CLINICAL TRIALS
NCT02800486
PHASE 2

Super Selective Intra-arterial Repeated Infusion of Cetuximab (Erbix) 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

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CLINICAL TRIALS
GENE
HGF
RATIONALE

HGF amplification or activating mutations may predict sensitivity to therapeutic agents targeting

its receptor, MET, or to agents directly targeting HGF.

ALTERATION

amplification - equivocal

NCT03175224
PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), Saransk (Russian Federation), North Adelaide (Australia), Bedford Park (Australia)

NCT04887194
PHASE 1

PK Study to Assess Drug-drug Interaction and QTc Between Sitravatinib and a Cocktail of Substrates

TARGETS
AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB, PD-1

LOCATIONS: Texas, Virginia

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CLINICAL TRIALS
GENE
MDM4
RATIONALE

Tumors with MDM4 amplification or overexpression and wild-type p53 may be

sensitive to inhibitors of MDM-p53 interactions.

ALTERATION

amplification

NCT03725436
PHASE 1

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

TARGETS
MDM2, MDM4

LOCATIONS: Texas

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APPENDIX
Variants of Unknown Significance

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.

ARAF
E578D

CARD11
R967C

EPHA3
V959F

GRM3
amplification

PDGFRB
T143I

RAD51
T88S

SMARCA4
A340T

SOCS1
T15I

TIPARP
E378A

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APPENDIX
Genes Assayed in FoundationOne®CDx

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

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

| | | | | | | | | |
|-------------|-----------------|-----------------|---------|---------------|---------|---------------|------------------|--------|
| ABL1 | ACVR1B | AKT1 | AKT2 | AKT3 | ALK | ALOX12B | AMER1 (FAM123B) | APC |
| AR | ARAF | ARFRP1 | ARID1A | ASXL1 | ATM | ATR | ATRX | AURKA |
| AURKB | AXIN1 | AXL | BAP1 | BARD1 | BCL2 | BCL2L1 | BCL2L2 | BCL6 |
| BCOR | BCORL1 | BRAF | BRCA1 | BRCA2 | BRD4 | BRIP1 | BTG1 | BTG2 |
| BTK | C11orf30 (EMSY) | C17orf39 (GID4) | CALR | CARD11 | CASP8 | CBFB | CBL | CCND1 |
| CCND2 | CCND3 | CCNE1 | CD22 | CD274 (PD-L1) | CD70 | CD79A | CD79B | CDC73 |
| CDH1 | CDK12 | CDK4 | CDK6 | CDK8 | CDKN1A | CDKN1B | CDKN2A | CDKN2B |
| CDKN2C | CEBPA | CHEK1 | CHEK2 | CIC | CREBBP | CRKL | CSF1R | CSF3R |
| CTCF | CTNNA1 | CTNNB1 | CUL3 | CUL4A | CXCR4 | CYP17A1 | DAXX | DDR1 |
| DDR2 | DIS3 | DNMT3A | DOT1L | EED | EGFR | EP300 | EPHA3 | EPHB1 |
| EPHB4 | ERBB2 | ERBB3 | ERBB4 | ERCC4 | ERG | ERRF1 | ESR1 | EZH2 |
| FAM46C | FANCA | FANCC | FANCG | FANCL | FAS | FBXW7 | FGF10 | FGF12 |
| FGF14 | FGF19 | FGF23 | FGF3 | FGF4 | FGF6 | FGFR1 | FGFR2 | FGFR3 |
| FGFR4 | FH | FLCN | FLT1 | FLT3 | FOXL2 | FUBP1 | GABRA6 | GATA3 |
| GATA4 | GATA6 | GNA11 | GNA13 | GNAQ | GNAS | GRM3 | GSK3B | H3F3A |
| HDAC1 | HGF | HNF1A | HRAS | HSD3B1 | ID3 | IDH1 | IDH2 | IGF1R |
| IKBKE | IKZF1 | INPP4B | IRF2 | IRF4 | IRS2 | JAK1 | JAK2 | JAK3 |
| JUN | KDMSA | 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 | MKKN1 | MLH1 | MPL | MRE11A | MSH2 | MSH3 |
| MSH6 | MST1R | MTAP | MTOR | MUTYH | MYC | MYCL (MYCL1) | MYCN | MYD88 |
| NBN | NF1 | NF2 | NFE2L2 | NFKB1A | NKX2-1 | NOTCH1 | NOTCH2 | NOTCH3 |
| NPM1 | NRAS | NSD3 (WHSC1L1) | NTSC2 | NTRK1 | NTRK2 | NTRK3 | P2RY8 | PALB2 |
| PARK2 | PARP1 | PARP2 | PARP3 | PAX5 | PBRM1 | PDCD1 (PD-1) | PDCD1LG2 (PD-L2) | PDGFRA |
| PDGFRB | PDK1 | PIK3C2B | PIK3C2G | PIK3CA | PIK3CB | PIK3R1 | PIM1 | PMS2 |
| POLD1 | POLE | PPARG | PPP2R1A | PPP2R2A | PRDM1 | PRKAR1A | PRKCI | PTCH1 |
| PTEN | PTPN11 | PTPRO | QKI | RAC1 | RAD21 | RAD51 | RAD51B | RAD51C |
| RAD51D | RAD52 | RAD54L | RAF1 | RARA | RB1 | RBM10 | REL | RET |
| RICTOR | RNF43 | ROS1 | RPTOR | SDHA | SDHB | SDHC | SDHD | SETD2 |
| SF3B1 | SGK1 | SMAD2 | SMAD4 | SMARCA4 | SMARCB1 | SMO | SNCAIP | SOC3 |
| SOX2 | SOX9 | SPEN | SPOP | SRC | STAG2 | STAT3 | STK11 | SUFU |
| SYK | TBX3 | TEK | TET2 | TGFBR2 | TIPARP | TNFAIP3 | TNFRSF14 | TP53 |
| TSC1 | TSC2 | TYRO3 | U2AF1 | VEGFA | VHL | WHSC1 | WT1 | XPO1 |
| XRCC2 | ZNF217 | ZNF703 | | | | | | |

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

| | | | | | | | | |
|-------------|------|------|-------|--------|-------|---------|-------|--------|
| ALK | BCL2 | BCR | BRAF | BRCA1 | BRCA2 | CD74 | EGFR | ETV1 |
| ETV4 | ETVS | ETV6 | EWRS1 | EZR | FGFR1 | FGFR2 | FGFR3 | KIT |
| KMT2A (MLL) | MSH2 | MYB | MYC | NOTCH2 | NTRK1 | NTRK2 | NUTM1 | PDGFRA |
| RAF1 | RARA | RET | ROS1 | RSPO2 | SDC4 | SLC34A2 | TERC* | TERT** |
| TPRSS2 | | | | | | | | |

*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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APPENDIX

About FoundationOne®CDx

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.



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-

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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

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About FoundationOne®CDx

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

- 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

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About FoundationOne®CDx

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 |
| mut/Mb | Mutations per megabase |
| NOS | Not otherwise specified |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| SD | Stable disease |
| TKI | Tyrosine kinase inhibitor |

MR Suite Version 6.1.0

The median exon coverage for this sample is 770x

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