

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 Chiang, Mei-Hsia		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S111-07318A (PF22035)
	DATE OF BIRTH 17 November 1951		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Female		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 23 February 2022
	MEDICAL RECORD # 27866553		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 14 March 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 5 Muts/Mb

Genomic Findings

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

PIK3CA E542V - subclonal[†]
CCND2 amplification - equivocal[†]
ATRX D1940fs*14
CDKN2A/B p16INK4a loss exons 1-2 and p14ARF loss exon 2
FGF23 amplification - equivocal[†]
FGF6 amplification - equivocal[†]
KDMSA amplification - equivocal[†]
TP53 R273C

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

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

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: Everolimus (p. 9), Temsirolimus (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 5 Muts/Mb

GENOMIC FINDINGS

PIK3CA - E542V - subclonal

10 Trials *see p. 13*

CCND2 - amplification - equivocal

10 Trials *see p. 11*

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	Everolimus
	Temsirolimus
none	none

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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531
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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.

ATRX - D1940fs*14	p. 5	FGF6 - amplification - equivocal	p. 7
CDKN2A/B - p16INK4a loss exons 1-2 and		KDM5A - amplification - equivocal	p. 7
p14ARF loss exon 2	p. 6	TP53 - R273C	p. 8
FGF23 - amplification - equivocal	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-1321248-01

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

5 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-1321248-01

GENOMIC FINDINGS

GENE

PIK3CA

ALTERATION

E542V - subclonal

TRANSCRIPT ID

NM_006218

CODING SEQUENCE EFFECT

1625A>T

VARIANT ALLELE FREQUENCY (% VAF)

2.1%

solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)⁶¹. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)⁶². The PI3K inhibitor alpelisib demonstrated an ORR of 6.0% (8/134) and a DCR of 58% (78/134) in a study for patients with PIK3CA-mutated solid tumors⁶³. However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-mutated tumors⁶⁴⁻⁶⁵.

in glioblastoma (GBM) was associated with shorter median PFS in both a discovery cohort (6.9 vs. 12.4 months, HR=2.89, p=0.01) and in the TCGA cohort (6.1 vs. 9 months, p=0.008), but was not consistently associated with median OS⁷³. In a study of IDH-wildtype GBM, patients with alterations in PI3K class I genes (PIK3CA, PIK3R1, PIK3CG, and PIK3R2) had significantly longer OS (20.0 months altered vs. 16.9 months wildtype, HR=0.62, p=0.002) and PFS (11.0 months altered vs. 7.4 months wildtype, p=0.0043); patients with PIK3CA alterations experienced an improved OS but this association was not highly significant (20.0 months altered vs. 18.1 months wildtype, p=0.0407)⁷⁰.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K⁴⁷⁻⁴⁹, AKT⁵⁰⁻⁵¹, or mTOR⁵²⁻⁵⁹. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study⁶⁰. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 9% of glioblastoma (GBM) samples analyzed in the TCGA dataset⁶⁶, and other studies report the incidence of PIK3CA mutations in primary GBMs as 5-18%⁶⁷⁻⁶⁹. One study detected PIK3CA mutation in 16% (36/232) of IDH-wildtype GBM samples analyzed⁷⁰. PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)^{67-69,71-72}. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity⁶⁹. One study found that PIK3CA mutation

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival⁷⁴⁻⁷⁵. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic⁷⁶⁻⁹⁷.

GENE

CCND2

ALTERATION

amplification - equivocal

cancer¹⁰⁰⁻¹⁰¹.

FREQUENCY & PROGNOSIS

In the TCGA dataset, CCND2 amplification was observed in 3% of glioblastoma cases⁶⁶ and 7% of lower grade glioma cases¹⁰². CCND2 amplification has been reported in 3% of primary malignant gliomas in one study, with amplification occurring in one anaplastic astrocytoma and two glioblastoma cases¹⁰³. CCND2 mRNA expression has been reported to be increased in higher grade (3 and 4) astrocytoma tumors as compared to lower grade tumors¹⁰⁴. Cyclin D2 has been reported to be the main cyclin expressed in glioblastoma stem cells (GSCs) but was barely detectable in differentiated glioblastoma cells¹⁰⁵. Cyclin D2, in complex with CDK4/6, has been

reported to be involved in the cell cycle progression of undifferentiated GSCs, but not differentiated GSCs, and to be involved in their tumorigenicity¹⁰⁵. High CCND2 nuclear expression at the time of initial surgery for patients with glioblastoma was reported to significantly associate with early mortality in a multivariate analysis of 72 patients¹⁰⁶.

FINDING SUMMARY

CCND2 encodes the protein cyclin D2, which binds and regulates the cyclin-dependent kinases that control cell cycle progression, and is a downstream target of cancer signaling pathways including hedgehog and PI3K¹⁰⁷⁻¹⁰⁸. CCND2 has been reported to be amplified in cancer¹⁰⁹, and may be biologically relevant in this context¹¹⁰⁻¹¹¹.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although preclinical studies suggest that cyclin D2 activates CDK4/6⁹⁸⁻⁹⁹, it is unknown whether CCND2 amplification or activating mutation predicts response to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib. Clinical studies of CDK4/6 inhibitors have shown the most promise for estrogen receptor-positive breast

ORDERED TEST # ORD-1321248-01

GENOMIC FINDINGS

GENE

ATRX

ALTERATION

D1940fs*14

TRANSCRIPT ID

NM_000489

CODING SEQUENCE EFFECT

5819_5822delATAG

VARIANT ALLELE FREQUENCY (% VAF)

38.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to directly address ATRX inactivation. Based on preclinical¹¹²⁻¹¹³ and limited clinical data¹¹⁴, ATRX alterations may confer sensitivity to combination strategies involving WEE1 inhibition. In a Phase 2 study evaluating the WEE1 inhibitor adavosertib plus irinotecan for the treatment of pediatric patients with neuroblastoma, prolonged SD was reported for 44% (4/9) of patients with ATRX-deficient tumors and responses were seen in two tumors that had evidence of ALT¹¹⁴. Preclinical evidence also suggests that ATRX deficiency may impart sensitivity to synthetic lethal approaches

involving PARP inhibition and irinotecan¹¹⁵, combined PARP and ATR inhibition¹¹³, or double-strand break-induction with agents such as doxorubicin, irinotecan, and topotecan¹¹⁶; however, these approaches have not been demonstrated clinically.

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT¹¹⁷. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)¹¹⁷⁻¹¹⁹, 12.6% of pheochromocytomas and paragangliomas¹²⁰, and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma¹²¹⁻¹²⁵. ATRX loss in PNET^{118,126} and melanoma¹²⁷ and mutation in other neuroendocrine tumors¹²⁰ is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy¹¹⁶. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma¹²⁸⁻¹³¹ and has been proposed as a distinguishing biomarker¹²⁹⁻¹³¹. ATRX mutation has not been detected in concurrence with MYCN

amplification in glioma and neuroblastoma¹²²⁻¹²⁵. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation¹²⁹. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS¹³²⁻¹³³.

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance¹³⁴⁻¹³⁵. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)^{117,133,136-137}. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function¹³⁸⁻¹⁴⁰; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors^{134,141}. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)¹⁴².

ORDERED TEST # ORD-1321248-01

GENOMIC FINDINGS
GENE

CDKN2A/B

ALTERATION

p16INK4a loss exons 1-2 and p14ARF loss exon 2

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib¹⁴³⁻¹⁴⁶. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment¹⁴⁷⁻¹⁴⁸, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents^{100-101,149-153}; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors¹⁵⁴⁻¹⁵⁵, the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas¹⁵⁶ and detected more frequently in patients with glioblastoma

multiforme (GBM; 58%)⁶⁶ than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)^{109,157}. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)¹⁵⁸⁻¹⁶⁰. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone¹⁶¹. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed⁷⁰. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples¹⁶². Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression^{159,163}. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas¹⁶⁴⁻¹⁶⁵.

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b¹⁶⁶⁻¹⁶⁷. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby

maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control¹⁶⁸⁻¹⁶⁹. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition¹⁷⁰⁻¹⁷¹. One or more alterations observed here are predicted to result in p16INK4a loss of function¹⁷²⁻¹⁹³. One or more alterations seen here are predicted to result in p14ARF loss of function^{176,193-196}.

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer¹⁹⁷. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma¹⁹⁸⁻¹⁹⁹. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases²⁰⁰⁻²⁰². CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors²⁰³⁻²⁰⁵. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE

FGF23

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF23. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show

activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR²⁰⁶.

FREQUENCY & PROGNOSIS

FGF23 alterations have been reported with highest incidence in uterine carcinosarcoma (7.0%), ovarian carcinoma (6.5%), testicular germ cell cancer (5.4%), cutaneous melanoma (5.0%), low-grade glioma (4.9%), lung squamous cell carcinoma (4.5%), sarcoma (4.3%), colorectal adenocarcinoma (4.2%), lung adenocarcinoma

(3.7%), and head and neck squamous cell carcinoma (3.4%) (cBioPortal, 2022)^{109,157}.

FINDING SUMMARY

FGF23 encodes a member of the fibroblast growth factor protein family that plays a central role in phosphate homeostasis²⁰⁷. Overexpression of FGF23 by tumor cells can cause hypophosphatemia through excessive renal phosphate clearance²⁰⁸, while germline gain-of-function (protein stabilizing) mutations in FGF23 cause autosomal dominant hypophosphatemic rickets²⁰⁹.

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GENOMIC FINDINGS

GENE

FGF6

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF6. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23)

experienced a radiologic CR²⁰⁶.

FREQUENCY & PROGNOSIS

Somatic alterations affecting FGF6 are infrequently documented, with the highest rates reported in penile cancer (4%), cutaneous melanoma (1-3%), stomach carcinoma (1-3%) and colorectal cancer (1%) (cBioPortal, COSMIC, Jan 2022)^{109,157,210}. Amplification of FGF6 has been frequently observed in testicular germ cell cancer (5%) and ovarian serous cystadenocarcinoma (5%), and in 2-6% of lower-grade gliomas, glioblastomas, sarcomas, breast invasive carcinomas, uterine carcinosarcomas, lung squamous cell carcinomas (SCC), head and neck SCC, pancreatic adenocarcinomas, and esophageal carcinomas (cBioPortal, Jan 2022)^{109,157}. FGF6 is co-localized with FGF23 and CCND2 at chromosomal locus 12p13 and has been reported to be co-amplified with these genes in 1.3% of

patients with breast cancer²¹¹. FGF6 expression has been reported in 54% (14/26) of prostate cancer samples, which also frequently express FGFR4²¹². FGF6 expression has also been observed in 71% (12/17) of patients with childhood acute lymphoblastic leukemia²¹³.

FINDING SUMMARY

FGF6 (also known as HST-2) encodes a member of the fibroblast growth factor protein family and is hypothesized to play a role in muscle tissue regeneration²¹⁴ by signaling through FGFR4, and to a lesser extent FGFR1 and FGFR2²¹⁵. FGF6 expression has been observed in several cancers^{212-213,216} and was shown to be oncogenic in preclinical models²¹⁶⁻²¹⁷. FGF6 has been reported as amplified in cancer¹⁰⁹ and may be biologically relevant in this context¹¹⁰⁻¹¹¹.

GENE

KDM5A

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to directly address genomic alterations in KDM5A. However, multiple preclinical studies have identified potential targets in KDM5A amplified or activated cells that may respond to therapy. KDM5A-mediated chromatin remodeling induces CCND1 expression and represses CDKI expression²¹⁸⁻²²²; therefore, KDM5A activation or amplification may sensitize cells to CDK4/CDK6 inhibitors. Drug-resistant cell populations, characterized by elevated KDM5A expression, responded to histone deacetylase (HDAC) inhibition²²³, suggesting that HDAC inhibitors

may be a potential therapeutic option. KDM5A also induces expression of VEGF and promotes angiogenesis, oncogenic transformation, and tumorigenesis, which can be inhibited by KDM5A knockdown²²⁴⁻²²⁵, suggesting that tumors harboring KDM5A amplification may be sensitive to angiogenesis inhibitors, including kinase inhibitors that target the VEGF receptors, such as sunitinib, sorafenib, vandetanib, ponatinib, cabozantinib, regorafenib, pazopanib, and axitinib. However, these inhibitors have yet to be extensively tested in the context of KDM5A amplification or activation; therefore, it is not known if these therapeutic strategies are relevant.

FREQUENCY & PROGNOSIS

KDM5A amplification has been reported with the highest incidence in TCGA datasets in ovarian serous cystadenocarcinoma (7.2%), testicular germ cell cancer (5.8%), pancreatic adenocarcinoma (4.3%), and lung squamous cell carcinoma (3.9%) (cBioPortal, Jan 2022)^{109,157}. Elevated levels of KDM5A expression have also been reported in a

range of solid tumor types^{219-220,222,224,226-227}, and fusion of KDM5A to NUP98 has been documented in acute myeloid leukemia²²⁸⁻²²⁹. KDM5A expression is significantly correlated with HIF-1alpha and VEGF expression, as well as tumor size, angiogenesis, and poor patient prognosis in lung cancer²²⁵.

FINDING SUMMARY

KDM5A encodes a lysine-specific histone demethylase that potentiates the expression of genes involved in cellular proliferation, senescence, angiogenesis, and migration^{218-219,224,230-231}. KDM5A overexpression alters the transcriptional regulation of cell cycle genes, including CCND1, and a variety of cyclin-dependent kinase inhibitors (CDKIs), including CDKN1A, CDKN1B, and CDKN2A, and results in cell cycle progression^{218-222,224}. Additionally, elevated KDM5A expression and associated chromatin remodeling has been implicated in resistance to various tyrosine kinase inhibitors in vitro, including erlotinib and gefitinib^{223,226,232}.

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ORDERED TEST # ORD-1321248-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

R273C

TRANSCRIPT ID

NM_000546

CODING SEQUENCE EFFECT

817C>T

VARIANT ALLELE FREQUENCY (% VAF)

89.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib²³³⁻²³⁶, or p53 gene therapy and immunotherapeutics such as SGT-53²³⁷⁻²⁴¹ and ALT-801²⁴². In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype²⁴³. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer²⁴⁴. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer²⁴⁵. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone²⁴⁶. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel²⁴⁷. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations²⁴⁸. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal

cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring²⁴⁹. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage²⁴¹. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246²⁵⁰⁻²⁵². In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR²⁵³. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies²⁵⁴⁻²⁵⁵; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies²⁵⁶⁻²⁵⁷. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs^{72,258}. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations⁷⁰. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively²⁵⁹⁻²⁶⁴. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)²⁶⁵. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM⁷⁰. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1,

followed by loss of PTEN²⁶⁶.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers²⁶⁷. Alterations such as seen here may disrupt TP53 function or expression²⁶⁸⁻²⁷².

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2021)²⁷³. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers²⁷⁴⁻²⁷⁶, including sarcomas²⁷⁷⁻²⁷⁸. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000²⁷⁹ to 1:20,000²⁷⁸. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30²⁸⁰. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion²⁸¹⁻²⁸⁶. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy²⁸¹⁻²⁸². Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease²⁸⁷. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{285,288-289}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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ORDERED TEST # ORD-1321248-01

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Everolimus

Assay findings association

PIK3CA

E542V - subclonal

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence⁵²⁻⁵⁹, PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors^{56-59,290-294}.

SUPPORTING DATA

Case reports have described 2 children with PIK3CA-mutated diffuse glioma or glioneuronal tumor who benefited from treatment with everolimus alone or in combination with temozolomide²⁹⁵⁻²⁹⁶, and 1 adult with glioblastoma (GBM) harboring PIK3CA mutation and KRAS amplification who experienced disease progression

with single-agent everolimus²⁹⁷. A Phase 2 trial of radiotherapy (RT), temozolomide (TMZ), and bevacizumab followed by everolimus and bevacizumab reported that 61% (31/51) of patients with newly diagnosed glioblastoma had objective responses with a median progression-free survival (PFS) of 11.3 months and median overall survival (OS) of 13.9 months²⁹⁸. A Phase 2 study of everolimus combined with TMZ and RT for the treatment of newly diagnosed glioblastoma reported a median PFS of 6.4 months and median OS of 15.8 months²⁹⁹. A Phase 1 trial of everolimus plus TMZ for patients with newly diagnosed or progressive glioblastoma reported partial responses (PR) in 11% (3/28) and stable disease (SD) in 57% (16/28) of cases³⁰⁰. A pilot study of everolimus with gefitinib in patients with recurrent glioblastoma reported 14% (3/22) PRs, 36% (8/22) SDs, and median PFS and OS of 2.6 months and 5.8 months, respectively³⁰¹. Everolimus treatment achieved SD in 45% (5/11) of pediatric patients with heavily pretreated low-grade CNS tumors; median PFS of these responses was 14 months³⁰². Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors³⁰³, a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months³⁰⁴.

Temsirolimus

Assay findings association

PIK3CA

E542V - subclonal

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence⁵²⁻⁵⁹, PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors^{56-59,290-294}.

SUPPORTING DATA

A Phase 1, dose-escalation trial combining temsirolimus and radiation/temozolomide therapy, with or without adjuvant temozolomide monotherapy, in patients with

newly diagnosed glioblastoma reported no clinical responses but 24/25 patients experienced a period of stable disease; increased infection rates were noted with this regimen³⁰⁵. A Phase 1/2 trial of temsirolimus in combination with sorafenib in glioblastoma was terminated at the Phase 2 interim analysis after patients failed to meet the primary endpoint of 6 month progression-free survival; significant toxicity was also observed in the combination therapy, even at low doses of temsirolimus³⁰⁶. A Phase 2 study showed that addition of temsirolimus to bevacizumab therapy in patients with recurrent glioblastoma did not add clinical benefit³⁰⁷. A Phase 2 clinical trial of temsirolimus in pediatric glioma reported disease stabilization in 7/17 patients including one patient with anaplastic astrocytoma³⁰⁸. A Phase 1/2 study of temsirolimus in combination with erlotinib reported 6% (1/16) complete responses, 6% (1/16) partial responses, and 12.5% (2/16) instances of stable disease in patients with anaplastic glioma³⁰⁹.

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied

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ORDERED TEST # ORD-1321248-01

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

evidence in the patient's tumor type.

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ORDERED TEST # ORD-1321248-01

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
CCND2
RATIONALE
CCND2 amplification or activation may predict sensitivity to CDK4/6 inhibitors.

ALTERATION
amplification - equivocal

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)

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)

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ORDERED TEST # ORD-1321248-01

CLINICAL TRIALS
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

NCT03158389
PHASE 1/2

NCT Neuro Master Match - N²M² (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

NCT02896335
PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS

CDK4, CDK6

LOCATIONS: Massachusetts

NCT03310879
PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS

CDK4, CDK6

LOCATIONS: Massachusetts

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ORDERED TEST # ORD-1321248-01

CLINICAL TRIALS
GENE
PIK3CA
ALTERATION

E542V - subclonal

RATIONALE

PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of

this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT04589845
PHASE 2

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

TARGETS

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

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

NCT03239015
PHASE 2

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

TARGETS

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

LOCATIONS: Shanghai (China)

NCT04337463
PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS

mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318
PHASE 2

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

TARGETS

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

LOCATIONS: Guangzhou (China)

NCT03772561
PHASE 1

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

TARGETS

PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

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ORDERED TEST # ORD-1321248-01

CLINICAL TRIALS

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)

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

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

LOCATIONS: Alaska, Washington, Oregon, California, Idaho

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

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

NCT03158389

PHASE 1/2

 NCT Neuro Master Match - N²M² (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)

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ORDERED TEST # ORD-1321248-01

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.

ATR
D701E

BRCA2
G2528R

DAXX
E457del

EPHB4
R206Q

MAP3K1
T948_T949del

MSH6
K1358fs*2

NBN
V346M

NOTCH3
R75Q

RAD52
amplification

TBX3
A562V

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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	ATRAX	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	ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT
KMT2A (MLL)	MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA
RAF1	RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT**
TPR52								

*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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- 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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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 857x

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