

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 Chan, Mei-Wen		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S110-37215 B (PF21061)
	DATE OF BIRTH 01 October 1970		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Female		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 30 November 2021
	MEDICAL RECORD # 47938250		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 10 December 2021

Biomarker Findings

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

NF1 Y2285fs*5

FANCA rearrangement exon 11

PTEN loss

CDKN2A/B CDKN2A loss, CDKN2B loss

MTAP loss

RB1 splice site 1960+1G>A - subclonal[†]

SETD2 W1460*

SOX9 rearrangement exon 1

TERT promoter -146C>T

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

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

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: **TERT** promoter -146C>T (p. 10)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Selumetinib** (p. 11), **Trametinib** (p. 11)
- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 12)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: **TERT** promoter -146C>T (p. 10)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

GENOMIC FINDINGS

NF1 - Y2285fs*5

10 Trials see p. 14

FANCA - rearrangement exon 11

10 Trials see p. 12

PTEN - loss

10 Trials see p. 16

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	Selumetinib
	Trametinib
none	none
none	none

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.

CDKN2A/B - CDKN2A loss, CDKN2B loss.....	p. 7	SETD2 - W1460*.....	p. 9
MTAP - loss.....	p. 8	SOX9 - rearrangement exon 1.....	p. 9
RB1 - splice site 1960+1G>A - subclonal.....	p. 8	TERT - promoter -146C>T.....	p. 10

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.

ORDERED TEST # ORD-1255382-01

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

0 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}.

ORDERED TEST # ORD-1255382-01

GENOMIC FINDINGS
GENE
NF1
ALTERATION

Y2285fs*5

TRANSCRIPT ID

NM_001042492

CODING SEQUENCE EFFECT

6852_6855delTTAC

VARIANT ALLELE FREQUENCY (% VAF)

31.8%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma⁴⁷⁻⁵⁰, glioma or glioblastoma⁵⁰⁻⁵⁴, and non-small cell lung cancer⁵⁵, NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus, based on limited clinical data⁵⁶⁻⁵⁸ and strong preclinical data in models of malignant peripheral nerve sheath

tumor (MPNST)⁵⁹⁻⁶⁰. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST⁶¹. 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 tumors⁶², 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 months⁶³.

FREQUENCY & PROGNOSIS

NF1 mutation has been observed in 5-6% of lower grade gliomas and 9-14% of glioblastoma multiforme (GBM) cases; homozygous deletion of NF1 was observed in 1% of lower grade gliomas and 2-3% of GBMs^{40,64-66}. Among GBM subtypes, NF1 mutation and loss were reported most frequently in the mesenchymal subtype, 37% (14/28) and 38% (21/55) of cases, respectively⁶⁷. NF1 loss was significantly associated with decreased overall and disease-specific survival in patients with lower grade gliomas (II-III), but not in those with GBM⁶⁸.

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway⁶⁹. Neurofibromin acts as a tumor suppressor by repressing RAS signaling⁷⁰. Alterations such as seen here may disrupt NF1 function or expression⁷⁰⁻⁷⁹.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the NF1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with neurofibromatosis type 1 (ClinVar, Sep 2021)⁸⁰. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms⁸¹⁻⁸³. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000⁸⁴⁻⁸⁵, and in the appropriate clinical context, germline testing of NF1 is recommended.

ORDERED TEST # ORD-1255382-01

GENOMIC FINDINGS

GENE

FANCA

ALTERATION

rearrangement exon 11

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that directly target defects in the FA complex. Clinical evidence in prostate⁸⁶⁻⁸⁸, breast⁸⁹, and ovarian cancers⁹⁰, including multiple patient responses, indicates that FANCA inactivation may confer sensitivity to PARP inhibitors.

— Nontargeted Approaches —

Inactivation of the FA/BRCA pathway sensitizes cells to mitomycin C and cisplatin⁹¹⁻⁹⁴ and results in increased sensitivity of glioma cells to alkylating agents such as temozolomide⁹⁵.

FREQUENCY & PROGNOSIS

In the TCGA datasets, FANCA mutation has been seen most frequently in endometrial carcinoma (7.2%), melanoma (5.6%), urothelial carcinoma

(4.4%), colorectal adenocarcinoma (3.7%), cervical squamous cell carcinoma (2.7%), and esophagogastric adenocarcinoma (1.7%) cases (cBioPortal, Jul 2021)⁹⁶⁻⁹⁷. In some patient populations, germline polymorphisms specifically in FANCA have been linked to an increased risk of esophageal, breast, cervical, and bladder cancer⁹⁸⁻¹⁰¹. A single nucleotide polymorphism (SNP) in FANCA has been correlated with inferior PFS and OS for patients with melanoma¹⁰², whereas methylation of FANCA correlated with inferior prognosis in high-grade serous ovarian carcinoma¹⁰³. However, the link between FANCA expression and function has either not been explored, or not correlated with outcome, in these studies and other studies have failed to link FANCA polymorphisms with the risk of breast or cervical cancer¹⁰⁴⁻¹⁰⁵. Low expression of FANCA has been correlated with inferior prognosis in univariate but not multivariate analysis in breast cancer¹⁰⁶. FANCA has been reported to be downregulated in higher versus lower grade ovarian cancer, but FANCA expression did not impact OS or PFS¹⁰⁷. Gain of 16q, associated with increased copy number of FANCA, correlated with decreased PFS¹⁰⁸. Inactivation of the FA/BRCA pathway sensitizes cells to mitomycin C and cisplatin⁹¹⁻⁹⁴ and results in increased sensitivity of

glioma cells to alkylating agents such as temozolomide⁹⁵.

FINDING SUMMARY

FANCA encodes a key component of the multi-protein Fanconi anemia (FA) complex, a nuclear E3 ubiquitin ligase that is essential for preventing chromosome breakage caused by DNA damage¹⁰⁹⁻¹¹⁰. Germline mutations or deletions affecting FANCA have been reported in 26-65% of patients with Fanconi anemia (FA), a rare autosomal recessive disorder characterized by congenital abnormalities, bone marrow failure, hypersensitivity to DNA crosslinking agents, and predisposition to a subset of cancers, including acute myeloid leukemia, myelodysplastic syndrome, gynecological malignancies, and head and neck tumors^{95,111-117}. Frequency estimates suggest an incidence of 3:1,000,000 individuals in Europe and the US, and a heterozygote carrier frequency of 1:181 to 1:300 in the US and Europe, respectively, with slightly higher rates for some populations, such as the Ashkenazi Jewish population (1:89)^{114,118}. Alterations such as seen here may disrupt FANCA function or expression¹¹⁹⁻¹³².

ORDERED TEST # ORD-1255382-01

GENOMIC FINDINGS

GENE

PTEN

ALTERATION

loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway¹³³⁻¹³⁶. Clinical studies in glioblastoma have not observed an association between PTEN deficiency and response to everolimus or temsirolimus¹³⁷⁻¹³⁹. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors¹⁴⁰⁻¹⁴⁴, and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer¹⁴⁵, ovarian cancer¹⁴⁶, uterine leiomyosarcoma¹⁴⁷, and endometrial cancer¹⁴⁴ treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity¹⁴⁸⁻¹⁴⁹.

— Potential Resistance —

In a retrospective analysis of 66 patients with glioblastoma, tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations²⁶.

FREQUENCY & PROGNOSIS

Studies in the literature have indicated that PTEN alterations (mutation or homozygous deletion) occur most frequently in glioblastoma (GBM), less frequently in anaplastic astrocytoma, and rarely in lower grade glioma subtypes including low grade astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma¹⁵⁰⁻¹⁵⁷. One study detected PTEN mutation in 42% (97/232) and loss in 10% (24/232) of IDH-wildtype GBM samples analyzed¹⁵⁸. In the TCGA dataset, PTEN mutation was observed in 23% of GBM cases and PTEN deletion was reported in 7% of cases⁶⁵, while in the Lower Grade Glioma TCGA dataset, PTEN mutation was observed in 4% of cases and homozygous deletion observed in 1.2% of cases⁶⁴. Decreased PTEN expression is associated with the higher grade GBM tumors¹⁵⁹. Loss of PTEN correlated with significantly worse prognosis in all grades of gliomas^{154,160}.

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis¹³⁴. Alterations such as seen here may disrupt PTEN function or expression^{156,161-201}.

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome²⁰²⁻²⁰³. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients^{202,204}. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder²⁰². Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

ORDERED TEST # ORD-1255382-01

GENOMIC FINDINGS

GENE

CDKN2A/B

ALTERATION

CDKN2A loss, CDKN2B loss

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 palbociclib²⁰⁵⁻²⁰⁸. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment²⁰⁹⁻²¹⁰, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents²¹¹⁻²¹⁷; 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 inhibitors²¹⁸⁻²¹⁹, the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib^{212,214-215,220-222}.

— Potential Resistance —

Rb inactivation may predict resistance to CDK4/6 inhibitors such as palbociclib, abemaciclib, and

ribociclib, which act upstream of Rb²²³⁻²³².

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas²³³ and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)⁶⁵ than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)⁹⁶⁻⁹⁷. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)^{67,234-235}. 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 alone²³⁶. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed¹⁵⁸. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples²³⁷. 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^{234,238}. 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 astrocytomas²³⁹⁻²⁴⁰.

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF,

whereas CDKN2B encodes the tumor suppressor p15INK4b²⁴¹⁻²⁴². 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 control²⁴³⁻²⁴⁴. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition²⁴⁵⁻²⁴⁶. One or more alterations observed here are predicted to result in p16INK4a loss of function²⁴⁷⁻²⁶⁸. One or more alterations seen here are predicted to result in p14ARF loss of function^{251,268-271}. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b²⁷².

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 cancer²⁷³. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma²⁷⁴⁻²⁷⁵. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases²⁷⁶⁻²⁷⁸. 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 tumors²⁷⁹⁻²⁸¹. In the appropriate clinical context, germline testing of CDKN2A is recommended.

ORDERED TEST # ORD-1255382-01

GENOMIC FINDINGS

GENE

MTAP

ALTERATION

loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors²⁸². A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss²⁸³. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition^{282,284-285}, MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors²⁸⁶; dual PRMT1 and PRMT5 inhibition may be more effective²⁸⁷⁻²⁸⁹. In preclinical cancer models, MTAP inactivation showed increased

sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells²⁹⁰⁻³⁰⁰. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients³⁰¹.

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers³⁰²⁻³⁰³; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma³⁰⁴, gastrointestinal stromal tumors³⁰⁵, mantle cell lymphoma (MCL)³⁰⁶, melanoma³⁰⁷⁻³⁰⁸, gastric cancer³⁰⁹, myxofibrosarcoma³¹⁰, nasopharyngeal carcinoma³¹¹, ovarian carcinoma³⁰² and non-small cell lung cancer³¹². MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia³¹³ or in astrocytoma³¹⁴. However, MTAP has also

been reported to be overexpressed in colorectal cancer (CRC) samples³¹⁵, and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM³¹⁶. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma³¹⁷⁻³¹⁸, esophageal cancer³¹⁹⁻³²⁰, osteosarcoma³²¹, and CRC³²².

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity³²³⁻³²⁴. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment^{304,325-326}, thereby reducing intracellular arginine methylation^{282,284,327} and altering cell signaling^{326,328}. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE

RB1

ALTERATION

splice site 1960+1G>A - subclonal

TRANSCRIPT ID

NM_000321

CODING SEQUENCE EFFECT

1960+1G>A

VARIANT ALLELE FREQUENCY (% VAF)

5.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data³²⁹ and strong preclinical data³³⁰⁻³³², 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 benefit³³³. Other approaches to target RB1

inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members³³⁴ and activation of the NOTCH pathway³³⁵.

— Potential Resistance —

Rb inactivation may predict resistance to CDK4/6 inhibitors such as palbociclib, abemaciclib, and ribociclib, which act upstream of Rb²²³⁻²³².

— 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 cancer³³⁶⁻³³⁷.

FREQUENCY & PROGNOSIS

In the TCGA datasets, RB1 mutation or homozygous deletion was observed in 9% of glioblastomas⁶⁵ and 2.5% of lower grade glioma cases⁶⁴. In one study, loss of RB1 transcript expression was observed in 10.6% of glioblastomas and occurred more frequently in the proneural subtype³³⁸. One study reports that

mutation of RB1 is correlated with shorter survival in glioblastoma patients³³⁹. Several studies suggest that RB1, PTEN, and/or TP53 mutations are early events in the development of glioblastoma³⁴⁰⁻³⁴².

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle^{337,343}. Alterations such as seen here may disrupt RB1 function or expression³⁴⁴⁻³⁵⁰.

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 year³⁵¹. Germline mutations in RB1 account for approximately 40% of RB tumors³⁵² and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma³⁵³⁻³⁵⁴. In the appropriate clinical context, germline testing of RB1 is recommended.

ORDERED TEST # ORD-1255382-01

GENOMIC FINDINGS

<p>GENE SETD2</p> <p>ALTERATION W1460*</p> <p>TRANSCRIPT ID NM_014159</p> <p>CODING SEQUENCE EFFECT 4379G>A</p> <p>VARIANT ALLELE FREQUENCY (% VAF) 23.0%</p>	<p>POTENTIAL TREATMENT STRATEGIES — Targeted Therapies —</p> <p>There are no targeted therapies available to address genomic alterations in SETD2.</p> <p>FREQUENCY & PROGNOSIS Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma³⁵⁵. SETD2 has been associated with favorable prognosis in gastric cancer³⁵⁶. SETD2 has also been associated with poor prognosis in RCC and MDS³⁵⁷, while data in other tumor types is limited (PubMed, Jun 2021).</p>	<p>FINDING SUMMARY SETD2 encodes a histone lysine-36 methyltransferase³⁵⁸ that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease³⁵⁹. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role³⁶⁰. SETD2 alterations such as observed here have been shown to be inactivating³⁶¹⁻³⁶⁶.</p>
<p>GENE SOX9</p> <p>ALTERATION rearrangement exon 1</p> <p>POTENTIAL TREATMENT STRATEGIES — Targeted Therapies —</p> <p>There are no therapies available to directly address</p>	<p>genomic alterations in SOX9.</p> <p>FREQUENCY & PROGNOSIS Mutation of SOX9 in cancer is typically rare, but it has been reported in 5-9% of colorectal carcinomas, most of which were truncating or frameshift alterations, and fewer than 4% of other tumor types (cBioPortal, COSMIC, Jan 2021)^{96-97,367}. Increased expression of SOX9 has been associated with tumor development and/or increased aggressiveness of prostate cancer,</p>	<p>pancreatic ductal adenocarcinoma, ovarian cancer, glioma, and esophageal adenocarcinoma³⁶⁸⁻³⁷¹.</p> <p>FINDING SUMMARY SOX9 encodes a transcription factor important for the development and differentiation of multiple tissues, including cartilage, testis, and prostate³⁷².</p>

ORDERED TEST # ORD-1255382-01

GENOMIC FINDINGS

GENE

TERT
ALTERATION

promoter -146C>T

TRANSCRIPT ID

NM_198253

CODING SEQUENCE EFFECT

-146C>T

VARIANT ALLELE FREQUENCY (% VAF)

21.2%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials³⁷³; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth³⁷⁴. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS³⁷⁵.

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas³⁷⁶⁻³⁷⁷, most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas³⁷⁶⁻³⁸⁰. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)^{376,378}. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed¹⁵⁸. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM³⁸¹. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM^{376,378,381-382}. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS, whereas in IDH-mutated, 1p/19q co-deleted oligodendroglioma, TERT mutations are associated with improved OS (NCCN CNS Cancers Guidelines, v5.2020).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length³⁸³. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells³⁸⁴⁻³⁸⁶. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)³⁸⁷⁻³⁸⁹, as well as tandem mutations at positions -124/-125 bp and -138/-139 bp³⁸⁷.

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v5.2020). Co-occurring TERT mutation, IDH mutation, and 1p/19q co-deletion is indicative of oligodendroglioma, whereas IDH mutation in the absence of TERT mutation is suggestive of astrocytoma (NCCN CNS Cancers Guidelines, v5.2020).

ORDERED TEST # ORD-1255382-01

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Selumetinib

Assay findings association
NF1
Y2285fs*5

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma^{47-50,390-394}, glioma^{50-54,395}, and non-small cell lung cancer⁵⁵, NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of selumetinib for the treatment of glioblastoma are limited (PubMed, Sep 2021). Selumetinib has demonstrated clinical activity in low-grade glioma. A Phase 2 study of selumetinib for patients with low-grade glioma (LGG) reported 8/25 PRs for patients with BRAF alterations and 10/25 PRs for those with NF1-associated LGG⁵¹; a Phase 1 study of selumetinib reported 5/25 PRs for patients with LGG³⁹⁶. A Phase 2 study of selumetinib for patients with tumors with activating alterations in the MAPK pathway

evaluated 8 patients with high-grade glioma (HGG); 2 SDs and no objective responses were observed in this subset³⁹⁷. Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies^{48,390-391} and a Phase 1 study⁴⁷. Phase 2 studies reported clinical responses in low-grade glioma^{51,396}, melanoma³⁹⁸⁻⁴⁰², and in lung^{55,403-404} and endometrial cancer⁴⁰⁵. A Phase 2 study of selumetinib for patients with activating alterations in the MAPK pathway reported a DCR of 15% (3/20), with no objective responses observed³⁹⁷. Phase 1 studies of selumetinib to treat patients with solid tumors reported 1/15 PR for a patient with colorectal cancer (CRC) and 5/15 SDs for patients with tonsil squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and CRC⁴⁰⁶; 2/39 PRs (for patients with CRC) and 18/39 SDs were achieved when selumetinib was administered in combination with cyclosporin A⁴⁰⁷. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus⁴⁰⁸, docetaxel or dacarbazine⁴⁰⁹, AKT inhibitors⁴¹⁰, or cixutumumab (an anti-IGF-1R antibody)⁴¹¹ reported clinical responses for patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

Trametinib

Assay findings association
NF1
Y2285fs*5

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma^{47-50,390-394}, glioma^{50-54,395}, and non-small cell lung cancer⁵⁵, NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Case studies of trametinib in NF1-associated low-grade glioma have reported 7 PRs, including 2 patients with pilocytic astrocytoma, 2 patients with diffuse astrocytoma, 3 patients with low-grade glioma

experiencing PRs of over 6 months^{50,52-53,395}. A study of four pediatric patients with BRAF mutation-positive non-operable astrocytoma reported a reduction in tumor volume in response to trametinib for the 3 optic gliomas with BRAF duplication⁴¹²⁻⁴¹³. A patient with pilocytic astrocytoma harboring an NF1A-RAF1 fusion that had progressed on multiple lines of prior treatment exhibited ongoing SD following treatment with trametinib⁴¹⁴. 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 tumors⁶², 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 months⁶³.

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.

ORDERED TEST # ORD-1255382-01

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](https://www.foundationmedicine.com/genomic-testing#support-services). Or visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

GENE
FANCA
RATIONALE
 FANCA alterations may predict sensitivity to

PARP inhibitors.

ALTERATION
 rearrangement exon 11

NCT04740190
PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
 PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04123366
PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
 PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895
PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
 PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

NCT02264678
PHASE 1/2

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

TARGETS
 ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT04715620
PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
 PARP

LOCATIONS: Tianjin (China)

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Electronically signed by Erik Williams, M.D. | 27 December 2021
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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 Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531
 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-1255382-01

CLINICAL TRIALS

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)

NCT04614909
PHASE NULL

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

TARGETS
 PARP

LOCATIONS: Arizona

NCT04801966
PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04497116
PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
 ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee, Texas

NCT03967938
PHASE 2

Efficacy of Olaparib in Advanced Cancers Occurring in Patients With Germline Mutations or Somatic Tumor Mutations in Homologous Recombination Genes

TARGETS
 PARP

LOCATIONS: Brussels (Belgium)

ORDERED TEST # ORD-1255382-01

CLINICAL TRIALS

GENE
NF1
ALTERATION
 Y2285fs*5

RATIONALE

On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical

data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03239015
PHASE 2

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

TARGETS

EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, 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, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT04801966
PHASE NULL

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

TARGETS

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

LOCATIONS: Melbourne (Australia)

NCT03905148
PHASE 1/2

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

TARGETS

RAFs, EGFR, MEK

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

NCT04185831
PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS

PD-L1, MEK, mTOR

LOCATIONS: Uppsala (Sweden), Gothenburg (Sweden)

ORDERED TEST # ORD-1255382-01

CLINICAL TRIALS

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)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
 RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

NCT04800822

PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

TARGETS
 SHP2, ROS1, ALK, BRAF, EGFR, MEK

LOCATIONS: California, Michigan, New York, Tennessee, Texas

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
 IDO1, mTOR

LOCATIONS: Kansas

ORDERED TEST # ORD-1255382-01

CLINICAL TRIALS
GENE
PTEN
ALTERATION
 loss

RATIONALE
 PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors

of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04337463
PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
 mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04740190
PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
 PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04001569
PHASE 1/2

AZD8186 and Paclitaxel in Advanced Gastric Cancer

TARGETS
 PI3K-beta

LOCATIONS: Seongnam-si (Korea, Republic of)

NCT02264678
PHASE 1/2

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

TARGETS
 ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT04715620
PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
 PARP

LOCATIONS: Tianjin (China)

NCT03772561
PHASE 1

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

TARGETS
 PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

ORDERED TEST # ORD-1255382-01

CLINICAL TRIALS

NCT04614909

PHASE NULL

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

TARGETS
 PARP

LOCATIONS: Arizona

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Alaska, Washington

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
 ALK, ROS1, TRKA, TRKB, TRKC, PD-L1,
 ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Alaska, Washington, Oregon, California, Montana

ORDERED TEST # ORD-1255382-01

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.

BRIP1
R814C

EGFR
A1118V

TSC2
A678T

ORDERED TEST # ORD-1255382-01

APPENDIX
Genes Assayed in FoundationOne®CDx

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

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

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	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
BTB	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	FOXO2	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	KDMS5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	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)	NT5C2	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	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**	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)

ORDERED TEST # ORD-1255382-01

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. 2021. 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 5.2.0

The median exon coverage for this sample is 956x

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APPENDIX
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