FOUNDATIONONE®CDx

PATIENT
Hung, Wen-Lung

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
17 Nov 2021
ORDERED TEST #
ORD-1233272-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Brain glioblastoma (GBM)
NAME Hung, Wen-Lung
DATE OF BIRTH 19 January 1959
SEX Male
MEDICAL RECORD # 47672833

PHYSICIAN

ORDERING PHYSICIAN Hsu, Pin-Chuan
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Brain
SPECIMEN ID S110-30310 A
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 12 October 2021
SPECIMEN RECEIVED 08 November 2021

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

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

EGFR R108K - subclonal, R222C, A289T, amplification, EGFRvIII†
PIK3CA G118D
CDKN2A/B CDKN2A loss, CDKN2B loss
MTAP loss exons 7-8
TERT promoter -124C>T

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

† See About the Test in appendix for details.

6 Therapies with Clinical Benefit   19 Clinical Trials
0 Therapies with Resistance

REPORT UPDATES
Corrected Report 18-Nov-2021
This Corrected Report has been issued to update PHYSICIAN NAME from "Yeh, Yi-Chen" to "Hsu, Pin-Chuan".

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
EGFR - R108K - subclonal, R222C, A289T, amplification, EGFRvIII	none	Cetuximab
		Erlotinib
		Gefitinib
10 Trials *see p. 12*		Panitumumab
PIK3CA - G118D	none	Everolimus
10 Trials *see p. 14*		Temsirolimus

Electronically signed by Erik Williams, M.D. | 17 November 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

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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.

CDKN2A/B - CDKN2A loss, CDKN2B loss............................ p. 6

MTAP - loss exons 7-8... p. 7

TERT - promoter -124C>T.. p. 8

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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BIOMARKER 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 inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

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

FINDING SUMMARY
Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[10]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[10-12]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER
Tumor Mutational Burden

RESULT
3 Muts/Mb

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

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

FINDING SUMMARY
Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[16,26-30].

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GENOMIC FINDINGS

GENE
EGFR

ALTERATION
R108K - subclonal, R222C, A289T, amplification, EGFRvIII

TRANSCRIPT ID
NM_005228, NM_005228, NM_005228

CODING SEQUENCE EFFECT
323G>A, 664C>T, 865G>A

VARIANT ALLELE FREQUENCY (% VAF)
0.91%, 23.0%, 18.9%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

In multiple glioblastoma (GBM) studies, the presence of EGFRvIII has not predicted clinical benefit from first-generation EGFR TKIs such as erlotinib[47-52] or gefitinib[50,53]. However, case reports have described patients with EGFRvIII-positive GBM responding to erlotinib[54-57]. In a retrospective study of patients with GBM treated with erlotinib or gefitinib, co-expression of EGFRvIII with PTEN protein was the strongest predictor of response (P<0.001)[58], suggesting that activity in this setting is dependent on PTEN status[59-60]. However, a prospective Phase 2 trial testing erlotinib monotherapy for patients with EGFRvIII and PTEN-positive recurrent glioblastoma reported minimal efficacy and was terminated[52]. The second-generation EGFR TKIs afatinib and dacomitinib have shown minimal efficacy for patients with EGFRvIII glioblastoma (GBM)[61-64]. A Phase 1/2 study of afatinib, temozolomide, or the combination for patients with GBM reported clinical benefit, including for patients with EGFRvIII; however, temozolomide alone and in combination exhibited better responses than afatinib monotherapy[61-62]. A Phase 2 trial of dacomitinib for patients with EGFR-amplified GBM reported a DCR of 26% (5/19) among patients with EGFR amplification and EGFRvIII; however, the trial failed to meet its primary endpoint of 6-month PFS[63]. A retrospective biomarker analysis of another Phase 2 study of dacomitinib for patients with GBM found no association between EGFRvIII and clinical benefit[64]. A patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFRvIII, experienced progression of the EGFRvIII-positive tumor during treatment with osimertinib[65]. Novel approaches that specifically target EGFRvIII in glioblastoma (GBM), such as the vaccine rindopepimut, are

under investigation in both clinical and preclinical studies. A Phase 2 trial reported significant improvement in OS for patients with EGFRvIII-positive GBM with rindopepimut in combination with bevacizumab compared to bevacizumab alone (HR=0.53, p=0.01)[66]. However, a Phase 3 study of rindopepimut combined with temozolomide compared to temozolomide alone in newly diagnosed EGFRvIII-positive GBM patients was terminated after the interim analysis, due to a lack of clinical benefit as measured by OS (20 vs. 20 months)[67]. For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[68], gefitinib[69], afatinib[70], dacomitinib[71], and osimertinib[72]; however, the data for patients with other tumor types are limited[64,73-77]. A case study of a patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFR amplification and multiple missense mutations, reported a near-CR of the EGFR-amplified and -mutated tumor to osimertinib[65]. A case series of 11 patients with bithalamic gliomas with EGFR mutations suggested that treatment with EGFR inhibitors, including osimertinib, prolonged patient survival relative to other types of treatment; however, no patients attained PR or SD[76]. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy[61,63-64,78-79]; however, a small subset of patients has experienced clinical benefit[63-64,78]. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma[58,80-82]. There are conflicting data on the efficacy of anti-EGFR antibodies for the treatment of EGFR-amplified tumors. A meta-analysis of colorectal cancer patients treated with second-line or higher cetuximab or panitumumab observed an association between EGFR copy number gain and increased OS and PFS[83]. However, studies in head and neck squamous cell carcinoma and gastric cancer found either no association or a negative association between EGFR copy number gain and survival after treatment with first-line cetuximab or panitumumab in combination with chemotherapy[84-85]. The Phase 3 INTELLANCE trial of depatuxizumab mafodotin (ABT-414), an EGFR-targeted antibody-drug conjugate with a toxic payload, in patients with EGFR-amplified glioblastoma (GBM) was stopped for futility. Interim analysis demonstrated improved median PFS (mPFS) of ABT-414 monotherapy compared with placebo (HR=0.84); however, no OS benefit

was observed (HR=1.01). Improved mPFS was also observed in patients harboring EGFRvIII (HR=0.73) but without an OS improvement (HR=0.95)[86]. The Phase 2 INTELLANCE trial demonstrated clinical benefit for EGFR-amplified GBM for the combination of ABT-414, temozolomide, and radiotherapy (HR=0.66, p=0.017), but there was no evidence of efficacy for ABT-414 monotherapy (HR=1.04, p=0.83)[87].

FREQUENCY & PROGNOSIS
Across several genomic studies of CNS tumors, EGFR amplification has been reported in 16.9% of anaplastic astrocytomas, and 39.7% of glioblastoma multiformes (GBMs)[88-91]. Across several genomic studies of CNS tumors, EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas[88-91]. In the glioblastoma (GBM) TCGA dataset, putative high-level amplification of EGFR has been found in 48% of cases and mutation has been found in 21% of cases[89]. Missense mutations in the EGFR extracellular domain have been found in 10-15% of GBMs and approximately half have a low-level amplification of the mutated allele[92-93]. One study detected EGFR alterations in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event[94]. The EGFRvIII mutation has been variously reported in 6-46% of GBM samples[58,95-102]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[103-104]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[105]. The link between EGFRvIII status and prognosis is unclear, although some studies suggest that it may be linked to improved survival and response to chemotherapy[106].

FINDING SUMMARY
EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[107]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[108-110]. A mutation of the EGFR gene, referred to as EGFRvIII, results from a gene rearrangement

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that deletes exons 2-7. This alteration causes an in-frame deletion of 801 base pairs encoding part of the extracellular ligand-binding domain[95]. This deletion has shown to result in ligand-independent (constitutive) phosphorylation and activation of EGFR, as well as consequent tumorigenesis[95,111]. EGFR mutations that have been characterized in biochemical assays to be activating, as observed here, are predicted to confer sensitivity to EGFR-targeted therapies[92,112-128]. The EGFR A289V mutation, located in the extracellular domain, has been shown to be activating[92]. Glioblastoma cell lines harboring an EGFR A289V or A289D mutation were shown to be dependent on EGFR kinase activity[93], and other mutations at this position are also likely activating. In addition, A289V is frequently associated with increased EGFR gene copy number[92].

GENE

PIK3CA

ALTERATION
G118D

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
353G>A

VARIANT ALLELE FREQUENCY (% VAF)
43.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[129-131], AKT[132-133], or mTOR[134-141]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[142]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[143]. 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)[144]. 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 tumors[145]. However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-mutated tumors[146-147].

— Potential Resistance —

Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[148-152].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 9% of glioblastoma (GBM) samples analyzed in the TCGA dataset[89], and other studies report the incidence of PIK3CA mutations in primary GBMs as 5-18%[153-155]. One study detected PIK3CA mutation in 16% (36/232) of IDH-wildtype GBM samples analyzed[94]. PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)[153-157]. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity[155]. One study found that PIK3CA mutation in glioblastoma (GBM) was associated with shorter median PFS in both a discovery cohort (6.9 vs. 12.4 months, HR=2.89, p=0.01) and in the TCGA cohort (6.1 vs. 9 months, p=0.008), but was not consistently associated with median OS[158]. 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)[94].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[159-160]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[161-181].

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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 palbociclib[182-185]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[186-187], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[188-194]; 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 inhibitors[195-196], 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[189,191-192,197-199].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of

CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[90] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[89] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[200-201]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[101,202-203]. 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 alone[204]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[94]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[205]. 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[202,206]. 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 astrocytomas[207-208].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[209-210]. 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 control[211-212]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[213-214]. One or more alterations observed here are predicted to result in p16INK4a loss of function[215-236]. One or more alterations seen here are predicted to result in p14ARF loss of function[219,236-239]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[240].

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 cancer[241]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[242-243]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[244-246]. 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 tumors[247-249]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENE
MTAP

ALTERATION
loss exons 7-8

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 inhibitors[250]. 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 loss[251]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[250,252-253], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[254]; dual PRMT1 and PRMT5 inhibition may be more effective[255-257]. 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 cells[258-268]. 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 patients[269].

FREQUENCY & PROGNOSIS
MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[270-271]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[272], gastrointestinal stromal tumors[273], mantle cell lymphoma (MCL)[274], melanoma[275-276], gastric cancer[277], myxofibrosarcoma[278], nasopharyngeal carcinoma[279], ovarian carcinoma[270] and non-small cell lung cancer[280]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[281] or in astrocytoma[282]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[283], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[284]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[285-286], esophageal cancer[287-288], osteosarcoma[289], and CRC[290].

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 activity[291-292]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[272,293-294], thereby reducing intracellular arginine methylation[250,252,295] and altering cell signaling[294,296]. 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.

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GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
41.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches are under development, including immunotherapies utilizing TERT as a tumor-associated antigen, antisense oligonucleotide- or peptide-based therapies, and TERT promoter-directed cytotoxic molecules.

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[297-298], most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas[297-301]. 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%)[297,299]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[94]. The significance of the TERT promoter mutation as an independent prognostic indicator in patients with glioma is not clear. While TERT promoter mutations significantly associate with poor prognosis in patients with GBM, this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM[297,299,302-303]. 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). TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[303].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[304]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[305-307]. 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)[308-310], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[308].

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).

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17 Nov 2021

ORDERED TEST # ORD-1233272-01

Cetuximab

Assay findings association

EGFR
R108K - subclonal, R222C, A289T,
amplification, EGFRvIII

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

GENE ASSOCIATION
For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[83].

SUPPORTING DATA
A Phase 3 trial of combined cetuximab and platinum/5-FU in patients with HNSCC demonstrated improved response compared to platinum/5-FU alone, but EGFR amplification was not shown to predict response to this treatment[84]. A Phase 3 study of patients with pancreatic adenocarcinoma did not report any improved outcome in patients treated with a combination of cetuximab plus gemcitabine vs gemcitabine alone[311]. In a Phase 1/2 trial of 36 patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cetuximab in combination with doxorubicin, stable disease was reported in approximately 63% of patients[312]. A Phase 1 study of the combination therapy of cetuximab, erlotinib, and bevacizumab reported stable disease in 21% (7/34) of patients with non-small cell lung cancer (NSCLC)[313]. A clinical trial of cetuximab with bevacizumab (an anti-VEGF monoclonal antibody) in patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone[314]. In preclinical trials, cetuximab, matuzumab, and panitumumab were reported to be ineffective at blocking EGFR dimerization and activation in GBM cells expressing EGFR extracellular domain mutations[315]. However, another study demonstrated that in patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly better progression-free survival (PFS) and numerical (although not statistically significant) improvement in overall survival (OS)[102].

Erlotinib

Assay findings association

EGFR
R108K - subclonal, R222C, A289T,
amplification, EGFRvIII

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

GENE ASSOCIATION
Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[68,316-318]. For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[319-323]. Responses to erlotinib have been reported for patients with EGFR rearrangements[324-328].

SUPPORTING DATA
In the MyPathway Phase 2a basket study for advanced solid tumors, 1 of 9 patients with EGFR activation mutations responded to erlotinib monotherapy; the responding patient had urethral adenocarcinoma[329]. A patient with EGFR-mutated metastatic lacrimal gland adenoid cystic carcinoma experienced clinical benefit from erlotinib treatment that was ongoing at 14 months[330]. A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[58]. In a Phase 2 study of 65 patients with GBM or gliosarcoma, treatment with erlotinib, temozolomide, and radiotherapy resulted in longer progression-free survival relative to a historical control study utilizing a regimen of temozolomide and radiotherapy alone (19.3 months vs. 14.1 months)[331]. However, in a Phase 1/2 trial of erlotinib monotherapy in 11 patients with relapsed or refractory GBM or anaplastic astrocytoma, all patients showed disease progression and the drug showed significant toxicity[332]. In addition, a Phase 2 trial of patients with recurrent or progressive GBM treated with erlotinib and sorafenib did not meet its objective of a 30% increase in overall survival time compared with historical controls; sorafenib was found to increase erlotinib clearance[333].

FOUNDATIONONE®CDx

PATIENT
Hung, Wen-Lung

TUMOR TYPE
Brain glioblastoma (GBM)

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THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE

ORDERED TEST # ORD-1233272-01

Everolimus

Assay findings association

PIK3CA
G118D

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 evidence[134-141] , 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[138-141,334-338] .

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 temozolomide[339-340] , and 1 adult with glioblastoma (GBM) harboring PIK3CA mutation and KRAS amplification who experienced disease progression with single-agent everolimus[79]. 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 months[341]. 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 months[342]. 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 cases[343]. 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, respectively[344]. 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 months[345]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[346], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[347].

Gefitinib

Assay findings association

EGFR
R108K - subclonal, R222C, A289T, amplification, EGFRvIII

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

GENE ASSOCIATION
Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[318,348-353] , and responses have been reported for patients with EGFR-rearranged NSCLC[326-327] . For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[319-323] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[319,354] .

SUPPORTING DATA
A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[58]. A Phase 2 clinical study of gefitinib in patients with high-grade glioma (including GBM, anaplastic astrocytoma, and oligodendroglioma) reported 18% (5/28) disease stabilization; efficacy was not correlated with EGFR expression[80]. However, a Phase 1/2 clinical trial of gefitinib combined with radiotherapy in 178 patients with GBM reported no overall survival benefit of added gefitinib, and EGFR expression was found to be of no prognostic value for patients treated with gefitinib plus radiotherapy[81]. A Phase 2 trial of preoperative gefitinib treatment in patients with recurrent GBM reported that although EGFR phosphorylation was decreased in treated patients as compared to the control group, measurement of 12 downstream molecules revealed no significant changes[82].

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THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE

Panitumumab

Assay findings association

EGFR
R108K - subclonal, R222C, A289T, amplification, EGFRvIII

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

GENE ASSOCIATION
For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[83].

SUPPORTING DATA
A Phase 1 trial of EnGeneIC delivery vehicle (EDV) targeting EGFR with panitumumab in combination with doxorubicin for 14 patients with glioblastoma (GBM) reported no responses and 28% (4/14) SDs[355]. Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer[356-358] and has been investigated in a variety of other tumor types. For patients with head and neck squamous cell carcinoma (HNSCC), data are conflicting; some trials of panitumumab in various lines and with different chemotherapy combinations have shown modest benefit[359-361] and others have reported no benefit[362-364] . A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility[365]. Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)[366-367] ; biliary tract cancers, including cholangiocarcinoma[368-369] ; and renal cell carcinoma (RCC)[370].

Temsirolimus

Assay findings association

PIK3CA
G118D

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 evidence[134-141] , 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[138-141,334-338] .

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 regimen[371]. 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 temsirolimus[372]. A Phase 2 study showed that addition of temsirolimus to bevacizumab therapy in patients with recurrent glioblastoma did not add clinical benefit[373]. A Phase 2 clinical trial of temsirolimus in pediatric glioma reported disease stabilization in 7/17 patients including one patient with anaplastic astrocytoma[374]. 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 glioma[51].

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

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CLINICAL TRIALS

ORDERED TEST # ORD-1233272-01

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

GENE
EGFR

ALTERATION
R108K - subclonal, R222C, A289T, amplification, EGFRvIII

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

NCT03239015 — PHASE 2
Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

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

LOCATIONS: Shanghai (China)

NCT03810872 — PHASE 2
An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB2, ERBB4

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

NCT03618667 — PHASE 2
GC1118 in Recurrent Glioblastoma Patients With High EGFR Amplification

TARGETS
EGFR

LOCATIONS: Seoul (Korea, Republic of)

NCT04172597 — PHASE 2
A Study of Poziotinib in Patients With EGFR or HER2 Activating Mutations in Advanced Malignancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: California

NCT02800486 — PHASE 2
Super Selective Intra-arterial Repeated Infusion of Cetuximab (Erbitux) With Reirradiation for Treatment of Relapsed/Refractory GBM, AA, and AOA

TARGETS
EGFR

LOCATIONS: New York

FOUNDATIONONE®**CDx**

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Hung, Wen-Lung

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CLINICAL TRIALS

NCT02861898   PHASE 1/2

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

TARGETS
EGFR

LOCATIONS: New York

NCT03783403   PHASE 1

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

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Heidelberg (Australia), Melbourne (Australia), Edmonton (Canada), California, Colorado, Arizona, Toronto (Canada), Oklahoma, Texas, Pennsylvania

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NCT02451553   PHASE 1

Afatinib Dimaleate and Capecitabine in Treating Patients With Advanced Refractory Solid Tumors, Pancreatic Cancer or Biliary Cancer

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Washington

NCT03829436   PHASE 1

TPST-1120 as Monotherapy and in Combination With (Nivolumab, Docetaxel or Cetuximab) in Subjects With Advanced Cancers

TARGETS
PD-1, PPARalpha

LOCATIONS: California, Michigan, Oklahoma, Pennsylvania, New York, Tennessee, Maryland, North Carolina, Florida

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NCT02303678   PHASE 1

D2C7 for Adult Patients With Recurrent Malignant Glioma

TARGETS
EGFRvIII

LOCATIONS: North Carolina

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CLINICAL TRIALS

ORDERED TEST # ORD-1233272-01

GENE
PIK3CA

ALTERATION
G118D

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

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)

NCT02688881 — PHASE 4

Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors

TARGETS
mTOR

LOCATIONS: Seoul (Korea, Republic of)

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)

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)

FOUNDATIONONE®CDx

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CLINICAL TRIALS

ORDERED TEST # ORD-1233272-01

NCT03834740

PHASE NULL

Ph0/2 Ribociclib & Everolimus

TARGETS
CDK6, CDK4, mTOR

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

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APPENDIX   Variants of Unknown Significance

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

BRCA2	*CSF3R*	*EGFR*	*EP300*
Q3036E	E591K	C628Y	N1227K
ERCC4	*FLT3*	*NFE2L2*	*NOTCH1*
C723*	Q121R	T260R	E334K
PDCD1 (PD-1)	*RAD51D*	*STK11*	*TNFAIP3*
A202_R203insGA	A52V	F354L	G456V

FOUNDATIONONE®CDx

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APPENDIX | Genes Assayed in FoundationOne®CDx

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

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

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	APC
AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2
BTK	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73
CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R
CTCF	CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1
DDR2	DIS3	DNMT3A	DOT1L	EED	EGFR	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRFI1	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	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11A	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	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	SOCS1
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	RSPO2	SDC4	SLC34A2	TERC*	TERT**	TMPRSS2

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

CE

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.

5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.

6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or

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governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

MR Suite Version 5.1.1

The median exon coverage for this sample is 744x

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APPENDIX   References

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