FOUNDATIONONE®CDx

PATIENT
Liu, Shu-Yen

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
18 Apr 2022
ORDERED TEST #
ORD-1341404-01

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 Liu, Shu-Yen
DATE OF BIRTH 26 May 1970
SEX Female
MEDICAL RECORD # 48392161

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S111-12619F (PF22047)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 26 March 2022
SPECIMEN RECEIVED 11 April 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

EGFR EGFR-SEPT14 rearrangement, EGFR-SEPT14 fusion, amplification
PIK3CA R88Q, P104L
CDKN2A/B CDKN2A loss, CDKN2B loss
MUTYH W142*
TERT promoter -124C>T
TP53 V272L

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

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***EGFR* amplification** (p. 4), ***TERT* promoter -124C>T** (p. 7)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cetuximab** (p. 9), **Everolimus** (p. 10), **Panitumumab** (p. 10), **Temsirolimus** (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 -124C>T** (p. 7)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***MUTYH* W142*** (p. 7)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 1 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* -** EGFR-SEPT14 rearrangement, EGFR-SEPT14 fusion, amplification	none	Cetuximab
5 Trials *see p. 12*		Panitumumab
***PIK3CA* -** R88Q, P104L	none	Everolimus
10 Trials *see p. 13*		Temsirolimus

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

***MUTYH* -** W142* ..... p. 7

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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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.

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

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

BIOMARKER

Tumor Mutational Burden

RESULT
1 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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GENE
EGFR

ALTERATION
EGFR-SEPT14 rearrangement, EGFR-SEPT14 fusion, amplification

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]. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy[61,63-64,66-67]; however, a small subset of patients has experienced clinical benefit[63-64,66]. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma[58,68-70]. 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[71]. 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[72-73]. 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)[74]. 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)[75].

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)[76-79]. EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas in several genomic studies of CNS tumors[76-79]. In GBMs, Missense mutations in the EGFR extracellular domain have been found in 10-15% of cases and approximately half have a low-level amplification of the mutated allele[80-81]. In a study of IDH-wildtype GBM samples, EGFR alterations were detected in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event[82]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[83-84]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[85].

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[86]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[87-89]. Disruption of the EGFR C-terminal region through deletion[90-92], truncation[90-91,93], splicing errors[90,93], or gene fusion[94-95], has been demonstrated to be activating and is likely to be oncogenic. These mutations have been shown to cause cellular transformation and tumor formation and to be sensitive to EGFR-targeting therapies, including erlotinib, lapatinib, and cetuximab[90-92,94-95]. One or more of the alterations observed here are predicted to be activating.

POTENTIAL DIAGNOSTIC IMPLICATIONS

The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2021)[96].

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GENE
PIK3CA

ALTERATION
R88Q, P104L

TRANSCRIPT ID
NM_006218, NM_006218

CODING SEQUENCE EFFECT
263G>A, 311C>T

VARIANT ALLELE FREQUENCY (% VAF)
26.4%, 59.3%

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[97-100], AKT[101-102], or mTOR[103-110]. 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[111]. 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)[112]. 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)[113]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[114] but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)[115]. The PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-mutated tumors[116-117].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 9% of glioblastoma (GBM) samples analyzed in the TCGA dataset[77], and other studies report the incidence of PIK3CA mutations in primary GBMs as 5-18%[118-120]. One study detected PIK3CA mutation in 16% (36/232) of IDH-wildtype GBM samples analyzed[82]. PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)[118-122]. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity[120]. 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[123]. 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)[82].

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[124-125]. PIK3CA P104L, E110del, E453del and G914R have been reported to increase PI3K activity and have been reported in individuals with megalencephaly syndromes, suggesting they promote cell growth[126]. In addition, missense mutations of E453 and a short deletion including this residue have been shown to be activating[127-129]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[126-127,130-149].

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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[150-153]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[154-155], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[156-162]; 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[163-164], 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[157,159-160,165-167].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[78] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[77] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[168-169]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[170-172]. 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[173]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[82]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[174]. 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[171,175]. 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[176-177].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[178-179]. 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[180-181]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[182-183]. One or more alterations observed here are predicted to result in p16INK4a loss of function[184-205]. One or more alterations seen here are predicted to result in p14ARF loss of function[188,205-208]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[209].

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[210]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[211-212]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[213-215]. 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[216-218]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENE
MUTYH

ALTERATION
W142*

TRANSCRIPT ID
NM_001048171

CODING SEQUENCE EFFECT
425G>A

VARIANT ALLELE FREQUENCY (% VAF)
48.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2022)[219]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[220-221]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[222-224]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[225].

FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[226]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[220-221,227-229]. Numerous other MUTYH mutations have also been shown to result in loss of function[227-230].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH 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 MUTYH-associated polyposis (ClinVar, Sep 2021)[231]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[220,232-234]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[220]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[235-239]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[221]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
48.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[240]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[241]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[242].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[243-244], 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[243-247]. 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%)[243,245]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[82]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[248]. 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[243,245,248-249]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v2.2021).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[250]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[251-253]. 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)[254-256], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[254].

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v2.2021)[257]. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2021)[96].

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GENE
TP53

ALTERATION
V272L

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
814G>T

VARIANT ALLELE FREQUENCY (% VAF)
65.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[258-261], or p53 gene therapy and immunotherapeutics such as SGT-53[262-266] and ALT-801[267]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[268]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[269]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[270]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[271]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[272]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[273]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[274]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[266]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[275-277]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[278]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[279-280]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[281-282]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs[122,283]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[82]. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively[284-289]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[290]. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM[82]. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN[291].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[292]. Alterations such as seen here may disrupt TP53 function or expression[293-297].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[298-300], including sarcomas[301-302]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[303] to 1:20,000[302]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[304]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[305-310]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[305-306]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[311]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[309,312-313]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Cetuximab

Assay findings association

EGFR
EGFR-SEPT14 rearrangement, EGFR-SEPT14 fusion, amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[71].

SUPPORTING DATA

A clinical trial of cetuximab with bevacizumab (an anti-VEGF monoclonal antibody) in patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab 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)[316]. 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[72]. 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[317]. 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[318]. 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)[319].

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Everolimus

Assay findings association

PIK3CA
R88Q, P104L

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[103-110] , 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[107-110,320-324] .

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[325-326] , and 1 adult with glioblastoma (GBM) harboring PIK3CA mutation and KRAS amplification who experienced disease progression with single-agent everolimus[67]. 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[327]. 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[328]. 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[329]. 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[330]. 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[331]. 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[332], 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[333].

Panitumumab

Assay findings association

EGFR
EGFR-SEPT14 rearrangement, EGFR-SEPT14 fusion, amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[71].

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[334]. Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer[335-337] 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[338-340] and others have reported no benefit[341-343] . A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility[344]. Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)[345-346] ; biliary tract cancers, including cholangiocarcinoma[347-348] ; and renal cell carcinoma (RCC)[349].

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Temsirolimus

Assay findings association

PIK3CA
R88Q, P104L

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[103-110] , 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[107-110,320-324] .

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[350]. 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[351]. A Phase 2 study showed that addition of temsirolimus to bevacizumab therapy in patients with recurrent glioblastoma did not add clinical benefit[352]. A Phase 2 clinical trial of temsirolimus in pediatric glioma reported disease stabilization in 7/17 patients including one patient with anaplastic astrocytoma[353]. 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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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

EGFR-SEPT14 rearrangement, EGFR-SEPT14 fusion, amplification

RATIONALE

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

NCT03618667

PHASE 2

GC1118 in Recurrent Glioblastoma Patients With High EGFR Amplification

TARGETS EGFR

LOCATIONS: Seoul (Korea, Republic of)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

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

LOCATIONS: Utah

NCT02800486

PHASE 2

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

TARGETS EGFR

LOCATIONS: New York

NCT02861898

PHASE 1/2

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

TARGETS EGFR

LOCATIONS: New York

NCT03783403

PHASE 1

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

TARGETS CD20, EGFR, SIRP-alpha

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

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GENE
PIK3CA

ALTERATION
R88Q, P104L

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT04589845

PHASE 2

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

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

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

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

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)

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NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04632992

PHASE 2

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

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

LOCATIONS: Alaska, Washington, Oregon, California, Idaho

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

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

ARID1A
A183T

ASXL1
V1092M

CDK6
rearrangement

EGFR
rearrangement and rearrangement

LTK
G213_A214insGGG and R575W

MSH6
K1358fs*2

PTCH1
E44G and S827G

RAD51D
G265R

SPEN
N2999K

ZNF217
I211V

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*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*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*
KMT2A (MLL)	*MSH2*	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*
RAF1	*RARA*	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***
TMPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

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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%.

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
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 6.1.0

The median exon coverage for this sample is 697x

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