FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

COUNTRY CODE
TW

REPORT DATE
21 Sep 2021

ORDERED TEST #
ORD-1185248-01

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 anaplastic astrocytoma
NAME Wang, Hsiao-Lung
DATE OF BIRTH 03 January 1960
SEX Male
MEDICAL RECORD # 47439963

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 S110-21615 A (PF21012)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 27 July 2021
SPECIMEN RECEIVED 14 September 2021

Biomarker Findings
Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

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

NF1 loss exons 2-58
PIK3CA E103_P104ins22
PTEN loss exon 7
SETD2 rearrangement intron 5
TERT promoter -146C>T

4 Therapies with Clinical Benefit   **21** Clinical Trials
0 Therapies with Resistance

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 6 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)
NF1 **-** loss exons 2-58	none	Selumetinib
10 Trials *see p. 8*		Trametinib
PIK3CA **-** E103_P104ins22	none	Everolimus
10 Trials *see p. 10*		Temsirolimus
PTEN **-** loss exon 7	none	none
10 Trials *see p. 12*		

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 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

MSI-High has been reported in 3-8% of adult or pediatric astrocytomas and was generally not associated with Lynch syndrome[6-8]. Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[9-11]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[9], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[12]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[9], in GBMs with a previous lower grade astrocytoma[10], and in giant cell GBM compared to classic GBM[11].

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[13]. 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[13-15]. 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[16-18]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[13,15,17-18].

BIOMARKER
Tumor Mutational Burden

RESULT
6 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[19-21], anti-PD-1 therapies[19-22], and combination nivolumab and ipilimumab[23-28]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[19,29-30]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[31-32] or anti-PD-L1[33] 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

Anaplastic astrocytoma harbors a median TMB of 1.8 mutations per megabase (muts/Mb), and 2% of cases have high TMB (>20 muts/Mb)[34]. 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[35-36]. Increased TMB has been reported to correlate with higher tumor grade in glioma[37] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[31], as well as with shorter OS of patients with diffuse glioma[38].

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[39-40] and cigarette smoke in lung cancer[41-42], treatment with temozolomide-based chemotherapy in glioma[43-44], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[45-49], and microsatellite instability (MSI)[45,48-49]. 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[19,29-33].

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GENOMIC FINDINGS

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GENE
NF1

ALTERATION
loss exons 2-58

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —
On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[50-53], glioma or glioblastoma[53-57], non-small cell lung cancer[58], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including the approved agents everolimus and temsirolimus, based on limited clinical data[59-61] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[62-63]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[64]. 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[65], 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[66].

FREQUENCY & PROGNOSIS
NF1 mutation has been observed in 5-6% of lower grade gliomas and 9-14% of glioblastoma multiforme (GBM) cases; homozygous deletion of NF1 was observed in 1% of lower grade gliomas and 2-3% of GBMs[43,67-69]. NF1 loss was significantly associated with decreased overall and disease-specific survival in patients with lower grade gliomas (II-III), but not in those with GBM[70].

FINDING SUMMARY
NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[71]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[72]. Alterations such as seen here may disrupt NF1 function or expression[72-81].

POTENTIAL GERMLINE IMPLICATIONS
Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[82-84]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[85-86], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
PIK3CA

ALTERATION
E103_P104ins22

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
309_310insTTTTTTGATGAAACAAGACGACTTTGTGACCTT CGGCTTTTTCAACCCTTTTTAAAAGTAATTGAA

VARIANT ALLELE FREQUENCY (% VAF)
14.4%

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[87-89], AKT[90-91], or mTOR[59,92-98]. Results from the Phase 2 MATCH trial for patients with PIK3CA-altered solid tumors found that 27% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[99]. 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)[100]. The PI3K inhibitor alpelisib demonstrated an ORR of 6.0% (8/134) and a DCR of 58% (78/134) in a study of PIK3CA-mutated solid tumors[101]. However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-altered tumors[102-103]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

— 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[104-108].

FREQUENCY & PROGNOSIS
PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)[69,109-112]. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity[109]. 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[113]. 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)[114].

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[115-116]. Although alterations such as seen here have not been fully characterized, they have been associated with sensitivity to targeted therapies or have shown cancer association, which may indicate biological relevance[117-123].

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GENE
PTEN

ALTERATION
loss exon 7

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[103,124-126]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[127-130], renal cell carcinoma[131], breast cancer[132-133], and colorectal cancer[134] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[135-139], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[140], ovarian cancer[141], uterine leiomyosarcoma[142], and endometrial cancer[139] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[143-144].

— Potential Resistance —

Limited clinical evidence in glioblastoma[29], leiomyosarcoma[145], and melanoma[146] suggests that PTEN alterations may predict a lack of response to anti-PD-1 therapy. In an analysis of 39 patients with metastatic melanoma treated with pembrolizumab or nivolumab, patients with PTEN-expressing tumors achieved significantly greater reduction of tumor size than those with reduction or loss of PTEN expression[146]. In a retrospective analysis of 66 patients with glioblastoma, tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations[29]. In a patient with uterine leiomyosarcoma treated with pembrolizumab monotherapy, a treatment-resistant tumor arose that harbored PTEN loss[145].

FREQUENCY & PROGNOSIS

Studies in the literature have indicated that PTEN alterations (mutation or homozygous deletion) occur most frequently in glioblastoma (GBM), less frequently in anaplastic astrocytoma, and rarely in lower grade glioma subtypes including low grade astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma[147-154]. One study detected PTEN mutation in 42% (97/232) and loss in 10% (24/232) of IDH-wildtype GBM samples analyzed[114]. In the TCGA dataset, PTEN mutation was observed in 23% of GBM cases and PTEN deletion was reported in 7% of cases[68], while in the Lower Grade Glioma TCGA dataset, PTEN mutation was observed in 4% of cases and homozygous deletion observed in 1.2% of cases[67]. Loss of PTEN correlated with significantly worse prognosis in all grades of gliomas[151,155].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[125]. Alterations such as seen here may disrupt PTEN function or expression[153,156-195].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[196-197]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[196,198]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[196]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
SETD2

ALTERATION
rearrangement intron 5

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS

Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[199]. SETD2 has been associated with favorable prognosis in gastric cancer[200]. SETD2 has also been associated with poor prognosis in RCC and MDS[201], while data in other tumor types is limited (PubMed, Jun 2021).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[202] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[203]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[204]. SETD2 alterations such as observed here have been shown to be inactivating[205-210].

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GENE
TERT

ALTERATION
promoter -146C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-146C>T

VARIANT ALLELE FREQUENCY (% VAF)
21.6%

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[211-212], 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[211-215]. 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[211,213,216-217]. 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[217].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[218]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[219-221]. 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)[222-224], as well as tandem mutations at positions −124/−125 bp and −138/−139 bp[222].

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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| THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE |

Everolimus

Assay findings association

PIK3CA
E103_P104ins22

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[59,92-98], 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[95-98,225-229]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

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[230-231], and 1 adult with glioblastoma (GBM) harboring PIK3CA mutation and

KRAS amplification who experienced disease progression with single-agent everolimus[232]. 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[233]. 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[234]. 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[235]. 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[236]. 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[237]. 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[65], 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[66].

Selumetinib

Assay findings association

NF1
loss exons 2-58

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

GENE ASSOCIATION
On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[50-53,238-242], glioma[53-57,243], and non-small cell lung cancer[58], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA
Selumetinib has demonstrated clinical activity in low-grade glioma. A Phase 2 study of selumetinib for patients with low-grade glioma (LGG) reported 8/25 PRs for patients with BRAF alterations and 10/25 PRs for those with NF1-associated LGG[54]; a Phase 1 study of selumetinib reported 5/25 PRs for patients with LGG[244]. A Phase 2 study of selumetinib for patients with tumors with activating alterations in the MAPK pathway evaluated 8 patients with high-grade glioma (HGG); 2 SDs and no objective responses were observed in this subset[245].

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THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE

Temsirolimus

Assay findings association

PIK3CA
E103_P104ins22

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[59,92-98], 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[95-98,225-229]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

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[246]. 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[247]. A Phase 2 study showed that addition of temsirolimus to bevacizumab therapy in patients with recurrent glioblastoma did not add clinical benefit[248]. A Phase 2 clinical trial of temsirolimus in pediatric glioma reported disease stabilization in 7/17 patients including one patient with anaplastic astrocytoma[249]. 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[250].

Trametinib

Assay findings association

NF1
loss exons 2-58

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[50-53,238-242], glioma[53-57,243], and non-small cell lung cancer[58], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Case studies of trametinib in NF1-associated low-grade glioma have reported 7 PRs, including 2 patients with pilocytic astrocytoma, 2 patients with diffuse astrocytoma, 3 patients with low-grade glioma experiencing PRs of over 6 months[53,55-56,243]. A study of four pediatric patients with BRAF mutation-positive non-operable astrocytoma reported a reduction in tumor volume in response to trametinib for the 3 optic gliomas with BRAF duplication[251-252]. A patient with pilocytic astrocytoma harboring an NFIA-RAF1 fusion that had progressed on multiple lines of prior treatment exhibited ongoing SD following treatment with trametinib[253]. 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[65], 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[66].

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

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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
NF1

ALTERATION
loss exons 2-58

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03239015 — PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463 — PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318 — PHASE 2

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

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

LOCATIONS: Guangzhou (China)

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)

FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

REPORT DATE
21 Sep 2021

ORDERED TEST # ORD-1185248-01

CLINICAL TRIALS

NCT03905148
PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

NCT04800822
PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

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

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

NCT02070549
PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT03065062
PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT02159989
PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

REPORT DATE
21 Sep 2021

ORDERED TEST # ORD-1185248-01

GENE
PIK3CA

ALTERATION
E103_P104ins22

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. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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)

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)

NCT03834740 | PHASE NULL

Ph0/2 Ribociclib & Everolimus

TARGETS
CDK6, CDK4, mTOR

LOCATIONS: Arizona

FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

REPORT DATE
21 Sep 2021

ORDERED TEST # ORD-1185248-01

CLINICAL TRIALS

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04632992

PHASE 2

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

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

LOCATIONS: Alaska, Washington, Oregon, California, Montana

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

NCT03006172

PHASE 1

To Evaluate the Safety, Tolerability, and Pharmacokinetics of GDC-0077 Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer

TARGETS
PI3K-alpha, Aromatase, ER, CDK4, CDK6

LOCATIONS: London (United Kingdom), Surrey (United Kingdom), Bordeaux (France), Barcelona (Spain), Valencia (Spain), Toronto (Canada), Massachusetts, New York, Tennessee

FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

REPORT DATE
21 Sep 2021

CLINICAL TRIALS

ORDERED TEST # ORD-1185248-01

GENE
PTEN

ALTERATION
loss exon 7

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04337463
PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04740190
PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04001569
PHASE 1/2

AZD8186 and Paclitaxel in Advanced Gastric Cancer

TARGETS
PI3K-beta

LOCATIONS: Seongnam-si (Korea, Republic of)

NCT02264678
PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04635631
PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (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

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
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21 Sep 2021

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CLINICAL TRIALS

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04632992

PHASE 2

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

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

LOCATIONS: Alaska, Washington, Oregon, California, Montana

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

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

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NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

REPORT DATE
21 Sep 2021

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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.

CDK12 S987F	*FANCL* S112L	*IRS2* A512T	*PTPRO* P635L
RET D1042N	*XRCC2* T12I		

Electronically signed by J. Keith Killian, M.D. | 21 September 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

APPENDIX - PAGE 14 of 20

FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

REPORT DATE
21 Sep 2021

ORDERED TEST # ORD-1185248-01

APPENDIX | Genes Assayed in FoundationOne®CDx

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

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

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	APC
AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2
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

PATIENT	TUMOR TYPE	REPORT DATE
Wang, Hsiao-Lung	Brain anaplastic astrocytoma	21 Sep 2021

ORDERED TEST # ORD-1185248-01

APPENDIX   About FoundationOne®CDx

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. 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. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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

FOUNDATIONONE®CDx

PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
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APPENDIX   About FoundationOne®CDx

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 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

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PATIENT
Wang, Hsiao-Lung

TUMOR TYPE
Brain anaplastic astrocytoma

REPORT DATE
21 Sep 2021

ORDERED TEST # ORD-1185248-01

APPENDIX   About FoundationOne®CDx

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 5.0.0

The median exon coverage for this sample is 851x

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ORDERED TEST # ORD-1185248-01

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ORDERED TEST # ORD-1185248-01

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