FOUNDATIONONE®CDx

PATIENT
Hung, I-Ting

TUMOR TYPE
Brain anaplastic oligodendroglioma

COUNTRY CODE
TW

REPORT DATE
21 Mar 2022

ORDERED TEST #
ORD-1321264-01

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 oligodendroglioma
NAME Hung, I-Ting
DATE OF BIRTH 14 January 1974
SEX Female
MEDICAL RECORD # 41190196

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 S111-07110A (PF22038)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 22 February 2022
SPECIMEN RECEIVED 14 March 2022

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.

IDH1 R132H
CIC S734fs*28
FUBP1 Q608*
HDAC1 E398K
TERT promoter -146C>T

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***IDH1* R132H** (p. 3), ***TERT* promoter -146C>T** (p. 5)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: Ivosidenib (p. 6)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***IDH1* R132H** (p. 3)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***IDH1* R132H** (p. 3), ***TERT* promoter -146C>T** (p. 5)

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)**
***IDH1* -** R132H	none	Ivosidenib
10 Trials *see p. 7*		

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]. A pediatric patient with Lynch syndrome but MSS was reported to develop anaplastic oligodendroglioma[10]. 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]. A case study of a pediatric patient with glioblastoma with an oligodendroglioma component was reported to harbor MSI-high, which was proposed to be a possible mechanism of resistance to temozolomide treatment[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[12]. 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[12-14]. 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[15-17]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[12,14,16-17].

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[18-20], anti-PD-1 therapies[18-21], and combination nivolumab and ipilimumab[22-27]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[18,28-29]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[30-31] or anti-PD-L1[32] 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

The median TMB of oligodendrogliomas is 2.7 mutations per megabase (muts/Mb), and 8.4% of cases have high TMB (>20 muts/Mb)[33]. 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[34-35]. Increased TMB has been reported to correlate with higher tumor grade in glioma[36] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[30], as well as with shorter OS of patients with diffuse glioma[37].

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[38-39] and cigarette smoke in lung cancer[40-41], treatment with temozolomide-based chemotherapy in glioma[42-43], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[44-48], and microsatellite instability (MSI)[44,47-48]. 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[18,28-32].

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GENE
IDH1

ALTERATION
R132H

TRANSCRIPT ID
NM_005896

CODING SEQUENCE EFFECT
395G>A

VARIANT ALLELE FREQUENCY (% VAF)
44.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib[49]. A Phase 1b/2 study of the IDH1 inhibitor olutasidenib for patients with IDH1-mutated glioma reported a DCR of 50% (n=24) with 1 PR[50]. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18.2% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)[51]. Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors[52-55]. In a Phase 1 trial of the PD-L1 inhibitor atezolizumab in patients with glioblastoma (GBM), 2 of the 3 patients with IDH1-mutant tumors experienced clinical benefit (1 PR and 1 long-term SD; the third patient experienced short-term SD), whereas none of the 8 patients with IDH1-wild-type GBM experienced benefit (8/8 PD); significantly longer PFS and a trend toward longer OS were observed in the patients with IDH1-mutated tumors compared to the patients with IDH1-wild-type tumors[32]. Preclinical data indicate that IDH1-mutated glioma may be sensitive to the glutaminase inhibitor telaglenastat in combination with radiotherapy[56].

— Nontargeted Approaches —

IDH1/2 mutations are associated with improved survival outcomes for patients with glioma treated with radiation or alkylating chemotherapy (NCCN CNS Cancers Guidelines, v2.2021).

FREQUENCY & PROGNOSIS

IDH1 mutation is characteristic of low-grade gliomas and secondary glioblastoma, and is relatively rare in primary glioblastoma[57-61]. In the TCGA datasets, IDH1 mutation has been found in 77% of lower grade glioma cases and in 5% of glioblastoma cases[62-63]. IDH1 mutations are highly prevalent in grade 2 and grade 3 astrocytoma, oligodendroglioma, and oligoastrocytoma, reported in 43-100% of grade 2 tumors and 45-93% of grade 3 tumors[64-67]. Studies have reported that IDH mutation (IDH1 or IDH2) was associated with improved overall survival in glioma, including oligodendroglioma[68-70]. This improvement in overall survival may be due to increased radiation sensitivity in gliomas with IDH mutation[71]. In the context of IDH-mutated gliomas, TERT mutations are associated with improved OS (NCCN CNS Cancers Guidelines, v2.2021)[72]. IDH1/2 mutations are a strong favorable prognostic marker for OS in Grade 2-3 glioma, particularly in combination with 1p/19q codeletion (NCCN CNS Cancers Guidelines, v2.2021). Several studies have found IDH1 mutations to be associated with improved prognosis and longer PFS and OS in patients with various types of glioma including anaplastic astrocytoma and GBM[61,69,73-78]. Co-occurrence of IDH1/2 mutation and chromosome 1p/19q co-deletion is associated with oligodendroglial features and the best patient prognosis, while co-occurrence of IDH1/2 mutation and ATRX mutation, without 1p/19q co-deletion, is associated with astrocytic features and intermediate prognosis, worse than that of patients with IDH1/2 mutation and 1p/19q co-deletion but significantly better than that of patients without IDH1/2 mutation[66].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis[79]. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer[79-83]. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)[81-85], which promotes tumorigenesis[81,86-89].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Co-occurring TERT mutation, IDH mutation, and 1p/19q co-deletion is indicative of oligodendroglioma (NCCN CNS Cancers Guidelines, v2.2021)[90]. IDH1/2 mutation is associated with Grade 2 and 3 astrocytomas and oligodendrogliomas, and distinguishes secondary glioblastoma (GBM) from primary GBM (NCCN CNS Cancers Guidelines, v2.2021).

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GENE
CIC

ALTERATION
S734fs*28

TRANSCRIPT ID
NM_015125

CODING SEQUENCE EFFECT
2199_2201GTC>A

VARIANT ALLELE FREQUENCY (% VAF)
81.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

CIC mutations have been described in various solid tumors, including 1–10% of sequenced gastric, endometrial, and colorectal carcinomas and melanoma tumors (cBioPortal, COSMIC, Jan 2022)[91-93], although the consequences of CIC mutations in these tumor types have not been studied. CIC mutations have been observed in 58–69% of oligodendrogliomas but are less common in other gliomas, such as astrocytoma or oligoastrocytoma[94-96]. Published data investigating the prognostic implications of CIC alterations are generally limited (PubMed, Jun 2021). Conflicting data have been reported regarding the prognostic significance of CIC mutation in oligodendroglioma[95,97-98].

FINDING SUMMARY

CIC encodes a transcriptional repressor that plays a role in central nervous system (CNS) development[99]. CIC inactivation has been reported in various malignancies, and is highly recurrent in oligodendroglioma[94-95].

GENE
FUBP1

ALTERATION
Q608*

TRANSCRIPT ID
NM_003902

CODING SEQUENCE EFFECT
1822C>T

VARIANT ALLELE FREQUENCY (% VAF)
85.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapies targeting FUBP1 mutation directly or downstream effectors have not been tested preclinically or clinically in tumors that harbor FUBP1 mutations.

FREQUENCY & PROGNOSIS

FUBP1 alteration has been reported in 1.5% of samples analyzed in COSMIC, with the highest incidences reported in tumors of the meninges (5%), endometrium (3%), central nervous system (3%), large intestine (3%), stomach (3%), liver (3%), and skin (2%) (COSMIC, 2022)[93]. One study reported higher expression of FUBP1 in colorectal carcinoma tissues compared to adenoma and normal colon epithelial tissues[100]. A genetic signature defined by concomitant alterations in IDH1, CIC, and FUBP1 is associated with longer survival in patients with glioma[97]. FUBP1 has been shown to activate the expression of MYC[101-104], activate p27KIP1[105], and regulate the splicing of MDM2[106].

FINDING SUMMARY

FUBP1 encodes far upstream element binding protein 1 (also called FBP-1), a DNA-binding protein reported to have roles in transcriptional activation and splicing regulation of target genes. It is believed to act as an oncogene in some tumor types, such as hepatocellular carcinoma and non-small-cell lung cancer[107-108], and as a tumor suppressor in others, particularly oligodendroglioma, for which mutations and/or loss of FUBP1 often co-occur with alterations in CIC or IDH1[94,96-98,109].

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GENE
HDAC1

ALTERATION
E398K

TRANSCRIPT ID
NM_004964

CODING SEQUENCE EFFECT
1192G>A

VARIANT ALLELE FREQUENCY (% VAF)
91.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The HDAC inhibitors romidepsin, belinostat, and vorinostat have been approved in T-cell lymphomas, and panobinostat has been approved in multiple myeloma[110]. Other HDAC1 inhibitors are in development, and clinical trials are underway in a variety of solid and hematologic malignancies[110]. However, HDAC1 has not been clearly established as a sensitizing biomarker for these inhibitors (PubMed, 2021).

FREQUENCY & PROGNOSIS

In the TGCA datasets, HDAC1 amplification has been most frequently observed in ovarian serous cystadenocarcinoma (3%)[111], esophagus-stomach cancer (1.9%)[112], sarcoma (1.9%)[113], uterine corpus endometrial carcinomas (3%)[44], and lung adenocarcinoma (1.7%)[114]. HDAC1 mutation has been observed less frequently in solid tumors, with the highest prevalence seen in tumors of the liver (2.2%), pancreas (2.2%), and skin (2.1%) and is rare in hematological malignancies (<1%) (COSMIC, 2021)[93]. Elevated HDAC1 protein expression has been correlated with a poor prognosis and diminished overall survival in patients with gastric, lung, pancreatic, and prostate cancer[115-118].

FINDING SUMMARY

HDAC1 encodes histone deacetylase 1, a protein that is involved in transcriptional repression[119]. Aberrant activation or overexpression of HDAC1 has been associated with transcriptional repression of tumor suppressor regulatory activity, resulting in increased cellular proliferation[120-122].

GENE
TERT

ALTERATION
promoter -146C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-146C>T

VARIANT ALLELE FREQUENCY (% VAF)
47.4%

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[123]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[124]. 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[125].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[126-127], 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[126-130]. In the context of IDH-mutated gliomas, TERT mutations are associated with improved OS (NCCN CNS Cancers Guidelines, v2.2021)[72]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[131]. 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[126,128,131-132]. 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[133]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[134-136]. 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)[137-139], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[137].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Co-occurring TERT mutation, IDH mutation, and 1p/19q co-deletion is indicative of oligodendroglioma (NCCN CNS Cancers Guidelines, v2.2021)[90]. 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)[90].

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Ivosidenib

Assay findings association

IDH1
R132H

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML) or previously treated locally advanced or metastatic cholangiocarcinoma. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML[140] and cholangiocarcinoma[141-142] and limited clinical data in myelodysplastic syndrome (MDS)[140] and glioma[49,143] , IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

In a Phase 1 study of ivosidenib for patients with IDH1-mutated advanced solid tumors, 1 patient achieved PR in the non-enhancing glioma population (ORR=2.9% [1/35]); for patients with non-enhancing glioma and enhancing glioma, SD rates were 85.7% (30/35) and 45.2% (14/31), respectively, and median PFS was 13.6 months and 1.4 months, respectively[49,143] .

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
IDH1

ALTERATION
R132H

RATIONALE
IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP inhibitors in solid tumors. Preclinical data indicate that IDH1 mutations may predict sensitivity to glutaminase inhibitors.

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), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT04740190

PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

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)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

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NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: Newcastle upon Tyne (United Kingdom), London (United Kingdom), Connecticut, Texas

NCT03830918

PHASE 1/2

Niraparib and Temozolomide in Treating Patients With Extensive-Stage Small Cell Lung Cancer With a Complete or Partial Response to Platinum-Based First-Line Chemotherapy

TARGETS
PARP

LOCATIONS: California

NCT03914742

PHASE 1/2

BGB-290 and Temozolomide in Treating Patients With Recurrent Gliomas With IDH1/2 Mutations

TARGETS
PARP

LOCATIONS: California, Michigan, Ohio, Massachusetts, Connecticut, Pennsylvania, Maryland, Virginia, North Carolina, Alabama

NCT03212274

PHASE 2

Olaparib in Treating Patients With Advanced Glioma, Cholangiocarcinoma, or Solid Tumors With IDH1 or IDH2 Mutations

TARGETS
PARP

LOCATIONS: California, Wisconsin, Missouri, Kansas

NCT03221400

PHASE 1/2

PEN-866 in Patients With Advanced Solid Malignancies

TARGETS
PARP, HSP90

LOCATIONS: Nevada, Colorado, Nebraska, Wisconsin, Michigan, Oklahoma, Arkansas, Tennessee, Pennsylvania

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.

ERBB2
P378L

IGF1R
T345A

KMT2A (MLL)
A53V

MLL2
R1709H and R3508Q

MSH6
K1358fs*2

RAD51B
H378Y

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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)

Electronically signed by Erik Williams, M.D. | 21 March 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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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-

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

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 855x

Electronically signed by Erik Williams, M.D. | 21 March 2022
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