FOUNDATIONONE®CDx

PATIENT
Ko, Ching-Jen

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
08 Dec 2021
ORDERED TEST #
ORD-1243579-01

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

PATIENT

DISEASE Brain glioblastoma (GBM)
NAME Ko, Ching-Jen
DATE OF BIRTH 15 July 1952
SEX Male
MEDICAL RECORD # 47589946

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 S110-24819A (PF21050)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 27 August 2021
SPECIMEN RECEIVED 30 November 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 9 Muts/Mb

Genomic Findings

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

FBXW7 E113D
KIT amplification
PDGFRA amplification
CDKN2A/B CDKN2A loss, CDKN2B loss
CRKL amplification
MTAP loss

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

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

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 9 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)**
***FBXW7* -** E113D	none	Everolimus
10 Trials *see p. 11*		Temsirolimus
***KIT* -** amplification	none	Imatinib
		Nilotinib
		Sorafenib
10 Trials *see p. 13*		Sunitinib
***PDGFRA* -** amplification	none	Imatinib
2 Trials *see p. 15*		

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.

Electronically signed by Erik Williams, M.D. | 08 December 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 Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

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

BIOMARKER

Tumor Mutational Burden

RESULT
9 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

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

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GENE
FBXW7

ALTERATION
E113D

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
339G>T

VARIANT ALLELE FREQUENCY (% VAF)
25.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[47-48]. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung adenocarcinoma[49], renal cell carcinoma[50], and cervical squamous cell carcinoma[51]. 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.

— Nontargeted Approaches —

FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[52].

FREQUENCY & PROGNOSIS

FBXW7 mutations have been reported in <2% of glioblastoma samples analyzed in the TCGA datasets[53-54]. Significant decreases in FBXW7 expression have been reported in more than 80% of glioblastoma samples studied[55]. Lower FBXW7 expression has been reported to be associated with reduced survival in patients with glioblastoma, and may correlate with tumor aggressiveness[55]. FBXW7 loss has been reported to be important for glioma progression by allowing its oncogenic targets to accumulate[55].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[56]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[56-57]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
KIT

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, primarily in GIST, AML, and systemic mastocytosis, KIT activating alterations are associated with sensitivity to KIT tyrosine kinase inhibitors including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, regorafenib, ponatinib, midostaurin, avapritinib, and ripretinib[58-65]. The use of mTOR inhibitors as an alternative therapeutic strategy has demonstrated limited success in KIT-mutated, imatinib-resistant melanoma, with 1 PR and 3 SD observed for 4 patients treated with everolimus[66]. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation[67]. The role of KIT amplification as a biomarker for response to mTOR inhibitors has not been investigated (PubMed, Mar 2021). Clinical benefit has been observed for patients with KIT amplified or overexpressing tumors following treatment with imatinib[68-78], nilotinib[79], sorafenib[80-83], and sunitinib[84-85], suggesting that KIT amplification may be sensitive to these inhibitors. However, evidence demonstrating clinical benefit for regorafenib, dasatinib, pazopanib, or ponatinib in the context of KIT amplified or overexpressing tumors is limited.

FREQUENCY & PROGNOSIS

In the TCGA datasets, KIT amplification has been reported in 2.5% of lower grade gliomas (grades 2 and 3)[86] and 9.2% of glioblastomas (Grade 4 astrocytoma)[53]. KIT amplification has been variously reported in 4-47% of glioblastomas in the scientific literature[87-89]. Amplification of KIT has been strongly correlated with the presence of KDR and/or PDGFRA amplification in glioblastoma[88,90-91]. One study found no correlation between KIT amplification and overall survival in patients with glioblastoma, while a separate study reported that overexpression of KIT was associated with tumor grade and shorter survival in patients with malignant glioma[87,92].

FINDING SUMMARY

KIT (also called c-KIT) encodes a cell surface tyrosine kinase receptor that, upon ligand binding and dimerization, activates the PI3K-AKT and RAS-MAPK signaling pathways[93]. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein[94]. KIT has been reported to be amplified in cancer[95] and may be biologically relevant in this context[96-97].

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GENE
PDGFRA

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence in solid tumors and hematologic cancers, PDGFRA activating alterations are associated with sensitivity to imatinib[98-135]. Sorafenib has shown clinical and preclinical activity against the FIP1L1-PDGFRA fusion in chronic eosinophilic leukemia (CEL) and mutations associated with clinical resistance to imatinib and sunitinib in both CEL and gastrointestinal stromal tumor (GIST)[136-141]. Complete responses to nilotinib have been reported in patients with CEL or hypereosinophilic syndrome with FIP1L1-PDGFRA or activating mutations[114,142-143]; preclinical evidence has reported efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[144-145]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[146] or regorafenib[147-148]. Preclinical studies have reported sensitivity of activating PDGFRA mutations and FIP1L1-PDGFRA fusion to dasatinib[138,144]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[58] and preclinical[58] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[149].

FREQUENCY & PROGNOSIS

PDGFRA amplification has been suggested to be more common in higher grade astrocytomas than in lower grade astrocytomas; studies have reported PDGFRA amplification in 16.3% (27/166) of Grade 2 astrocytomas and in 23.6% (91/386) of Grade 3 and 4 astrocytomas analyzed[90,150-151]. PDGFRA amplification has been reported in 5.2–33% of glioblastoma cases[53,87-88,150,152-153]. A retrospective analysis of TCGA glioma samples reported elevated expression of ERBB3 correlated with PDGFRA expression and co-expression of these genes was an indicator of poor prognosis in a GBM patient cohort[154]. Amplification of PDGFRA has been associated with tumor grade and poor progression-free and overall survival in patients with glioblastoma[150,152-153]. In addition, PDGFRA amplification has been reported to occur in conjunction with IDH1 mutation in glioblastoma, and both alterations in the same tumor have been associated with poor patient prognosis[150]. Amplification of PDGFRA has also been strongly correlated with the presence of KDR and/or KIT amplification in glioblastomas, as well as with EGFR amplification[88,90-91,155].

FINDING SUMMARY

PDGFRA encodes platelet-derived growth factor receptor alpha (PDGFR-alpha), a tyrosine kinase receptor that, upon binding of cognate ligands (PDGFA or PDGFB), activates several signaling pathways, including PI3K and MAPK[156]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[94]. Amplification of PDGFRA, frequently occurring with amplification of the genes KDR and KIT, has been associated with increased PDGFRA expression[89,157-159] and poor prognosis[89,150,160-161] in some subtypes of glioma.

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GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[162-165]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[166-167], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[168-174]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[175-176], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[169,171-172,177-179].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[180] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[53] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[95,181]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[152,159,182]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[183]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[184]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[185]. Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression[152,186]. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas[187-188].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[189-190]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[191-192]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[193-194]. One or more alterations observed here are predicted to result in p16INK4a loss of function[195-216]. One or more alterations seen here are predicted to result in p14ARF loss of function[199,216-219]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[220].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[221]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[222-223]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[224-226]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[227-229]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
CRKL

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target CRKL[230-231]. Preclinical studies report that some cancer cell lines with CRKL amplification are sensitive to tyrosine kinase inhibitor (TKI) dasatinib[230-232]. However, a patient with CRKL-amplified pancreatic cancer did not respond to dasatinib[233]. CRKL amplification has been shown to be a mechanism of acquired resistance to EGFR TKIs[231,234].

FREQUENCY & PROGNOSIS

CRKL amplification has been identified in various solid tumor types, including uterine carcinosarcoma (7%), pancreatic ductal adenocarcinoma (5.5%)[235], lung squamous cell carcinoma (4.5%)[236], sarcoma (4%), ovarian serous cystadenocarcinoma (3.8%), bladder urothelial carcinoma (3%)[237], and melanoma (3%)(cBioPortal, 2021)[95,181]. Increased CRKL expression has been reported in many tumor types, including lung[238-239], breast[240-241], ovarian[241-242], pancreatic[243], skin[241], colon[241,244], hepatocellular[245], and gastric cancers[230]. CRKL overexpression has been shown to significantly correlate with reduced OS for patients with NSCLC or hepatocellular carcinoma[239,245] and with tumor size and metastasis for patients with breast cancer[240].

FINDING SUMMARY

CRKL encodes an adaptor protein that has been shown to mediate growth, motility, and adhesion in solid tumor cells[246]. Studies in non-small cell lung cancer (NSCLC) and pancreatic cancer cells have linked CRKL amplification and overexpression with increased cell proliferation and with tumorigenesis[231,238-239,243].

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GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[247]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[248]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[247,249-250], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[251]; dual PRMT1 and PRMT5 inhibition may be more effective[252-254]. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells[255-265]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients[266].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[267-268]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[269], gastrointestinal stromal tumors[270], mantle cell lymphoma (MCL)[271], melanoma[272-273], gastric cancer[274], myxofibrosarcoma[275], nasopharyngeal carcinoma[276], ovarian carcinoma[267] and non-small cell lung cancer[277]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[278] or in astrocytoma[279]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[280], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[281]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[282-283], esophageal cancer[284-285], osteosarcoma[286], and CRC[287].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[288-289]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[269,290-291], thereby reducing intracellular arginine methylation[247,249,292] and altering cell signaling[291,293]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

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Everolimus

Assay findings association

FBXW7
E113D

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 several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[49], renal cell carcinoma[50], and cervical squamous cell carcinoma[294], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus. 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 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[295]. 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[296]. 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[297]. 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[298]. 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[299]. 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[300], 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[301].

Imatinib

Assay findings association

KIT
amplification

PDGFRA
amplification

AREAS OF THERAPEUTIC USE

Imatinib targets the BCR-ABL fusion protein, PDGFR, and KIT. It is FDA approved for the treatment of KIT-positive gastrointestinal stromal tumors (GIST), Ph+ chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL), myelodysplastic syndrome/ myeloproliferative syndrome (MDS/MPS), aggressive systemic mastocytosis without a D816V KIT mutation, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[69-70,110,302] , KIT-amplified[68-71] , or KIT-expressing tumors[73-78,303-304] , KIT activating alterations may confer sensitivity to imatinib. PDGFRA amplification may predict sensitivity to tyrosine kinase inhibitors such as imatinib; a patient with Merkel cell carcinoma expressing PDGFRA achieved a complete response to imatinib[108].

SUPPORTING DATA

In a clinical study where patients with recurrent glioblastoma were given imatinib, 2/24 patients achieved a PR, 10 patients reported SD, and median OS and PFS was observed to be 6.2 and 3 months, respectively[305]. However, other Phase 2 clinical trials of imatinib have reported no anti-tumor activity, with a study of 231 patients with glioblastoma reporting a radiographic response rate of only 3.4%[78,306] . In another Phase 2 study, imatinib plus hydroxyurea was shown to be well tolerated among patients with recurrent/progressive low-grade glioma, but had negligible antitumor activity[307].

Nilotinib

Assay findings association

KIT
amplification

AREAS OF THERAPEUTIC USE

Nilotinib targets tyrosine kinases such as ABL (including BCR-ABL), PDGFRs, KIT, CSF1R, DDR1, and DDR2. It is FDA approved to treat newly diagnosed pediatric or adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, adults with Ph+ CML in chronic or accelerated phase with resistance or intolerance to prior therapy including imatinib, and pediatric patients with Ph+ CML in chronic phase with resistance or intolerance to prior tyrosine-kinase inhibitor therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[79,308-311] , KIT-amplified[79], or KIT-expressing tumors[312], KIT activating alterations may confer sensitivity to nilotinib.

SUPPORTING DATA

Clinical data on the efficacy of nilotinib for the treatment of CNS tumors are limited (PubMed, Jul 2021). Nilotinib has been primarily investigated as a therapeutic option for the treatment of CML or gastrointestinal stromal tumors (GIST). In the context of CML, a Phase 3 clinical trial of Ph+ patients treated with imatinib or nilotinib (300 mg or 400 mg) reported progression-free survival (PFS) rates of 93% and 97-98% and overall survival (OS) rates of 93% and 94-97%, respectively, at 4 years[313]. For imatinib-resistant Japanese patients with CML, a Phase 2 trial reported a 47.8% major medical response rate to treatment with nilotinib at 12 months[314]. A Phase 3 clinical trial of single-agent nilotinib in 240 patients with advanced GIST who failed prior treatment with imatinib or sunitinib reported no significant difference in progression-free survival between nilotinib and the best supportive care, but did report increased overall survival for nilotinib-treated patients[315]. A Phase 2 trial has shown that nilotinib was well tolerated and suggested it may be particularly useful for treating patients with GIST harboring mutations in KIT exon 17[316]. Preclinical, cell-based assays have reported efficacy for nilotinib alone and in combination with additional therapies in the context of leiomyosarcoma and synovial sarcoma[317].

Sorafenib

Assay findings association

KIT
amplification

AREAS OF THERAPEUTIC USE

Sorafenib is a kinase inhibitor that targets the RAF kinases, KIT, FLT3, RET, VEGFRs, and PDGFRs. It is FDA approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and recurrent or metastatic differentiated thyroid carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[318-325] or KIT-expressing tumors[80-83] , KIT activating alterations may predict sensitivity to sorafenib.

SUPPORTING DATA

Phase 2 studies of sorafenib plus temozolomide report limited activity in patients with relapsed glioblastoma multiforme (GBM)[326]. A Phase 1/2 trial of temsirolimus in combination with sorafenib in patients with glioblastoma was terminated at the Phase 2 interim analysis after patients failed to meet the primary endpoint of 6 month progression-free survival[327]. A Phase 2 trial of sorafenib and erlotinib in glioblastoma also did not meet its primary endpoint, and erlotinib clearance was increased by the addition of sorafenib[328]. In a Phase 1 trial in patients with high-grade glioma, the combination of sorafenib with radiation therapy (RT) and temozolomide (TMZ) resulted in increased toxicity and did not result in significant improvement in clinical efficacy compared with RT and TMZ alone[329]. In a clinical study of sorafenib in pediatric patients with low-grade astrocytoma, one patient achieved a partial response (PR), one had stable disease (SD), and 9 patients had progressive disease; this study was terminated early due to unexpectedly high disease progression rates[330].

Sunitinib

Assay findings association

KIT
amplification

AREAS OF THERAPEUTIC USE

Sunitinib is a small-molecule tyrosine kinase inhibitor that targets PDGFRs, VEGFRs, KIT, FLT3, CSF-1R, and RET. It is FDA approved for the treatment of advanced or metastatic pancreatic neuroendocrine tumors, gastrointestinal stromal tumors (GISTs) in patients who have progressed on or are intolerant to imatinib, and advanced renal cell carcinoma (RCC) as well as for the adjuvant treatment of patients at high risk of recurrent RCC after nephrectomy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[84,331-335] or KIT-expressing tumors[84-85] , KIT activating alterations may predict sensitivity to sunitinib.

SUPPORTING DATA

Phase 2 clinical trials of sunitinib in glioblastoma have reported no significant improvement in clinical outcome[336-337] . A Phase 2 trial that examined sunitinib treatment followed by radiation therapy in patients with glioblastoma reported a median progression-free survival (PFS) of 7.7 weeks, and a median overall survival (OS) of 12.8 weeks; 83.3% (10/12) of patients experienced neurological deterioration prior to radiation therapy[338]. Another Phase 2 study that examined daily sunitinib treatment in patients with glioblastoma reported no objective response in any of the 40 patients, with a median PFS of 2.2 months and a median OS of 9.2 months; five patients in the study had stable disease for more than six months[339].

Temsirolimus

Assay findings association

FBXW7
E113D

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 several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[49], renal cell carcinoma[50], and cervical squamous cell carcinoma[294], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus. 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[340]. 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[327]. A Phase 2 study showed that addition of temsirolimus to bevacizumab therapy in patients with recurrent glioblastoma did not add clinical benefit[341]. A Phase 2 clinical trial of temsirolimus in pediatric glioma reported disease stabilization in 7/17 patients including one patient with anaplastic astrocytoma[342]. 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[343].

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.

Electronically signed by Erik Williams, M.D. | 08 December 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

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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

FBXW7

ALTERATION

E113D

RATIONALE

Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors. 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.

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

NCT03158389

PHASE 1/2

NCT Neuro Master Match - N²M² (NOA-20)

TARGETS
ALK, RET, CDK4, CDK6, mTOR, MDM2, PD-L1, SMO

LOCATIONS: Berlin (Germany), Dresden (Germany), Regensburg (Germany), Bochum (Germany), Frankfurt am Main (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Cologne (Germany), Mannheim (Germany)

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

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

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

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

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

GENE
KIT

ALTERATION
amplification

RATIONALE
KIT amplification or activating mutations may predict sensitivity to small molecule tyrosine kinase inhibitors. Also, because KIT activation leads to activation of the PI3K-AKT-mTOR pathway, PI3K and mTOR pathway inhibitors may be relevant in a tumor with KIT activation.

NCT03797326

PHASE 2

Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants With Select Solid Tumors (MK-7902-005/E7080-G000-224/LEAP-005)

TARGETS
PD-1, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia), Kazan (Russian Federation), Herston (Australia), Arkhangelsk (Russian Federation), Moscow (Russian Federation)

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)

NCT02461849

PHASE 2

Patients With Refractory, Metastatic Cancer Harboring KIT Mutation or Amplification to Investigate the Clinical Efficacy and Safety of Imatinib Therapy

TARGETS
KIT, ABL

LOCATIONS: Seoul (Korea, Republic of)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Seoul (Korea, Republic of), Tokyo (Japan), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

NCT03025893

PHASE 2/3

A Phase II/III Study of High-dose, Intermittent Sunitinib in Patients With Recurrent Glioblastoma Multiforme

TARGETS
CSF1R, FLT3, KIT, RET, VEGFRs

LOCATIONS: Groningen (Netherlands), Nijmegen (Netherlands), Amsterdam (Netherlands)

NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

TARGETS
FGFRs, KIT, PD-1, PDGFRA, RET, VEGFRs

LOCATIONS: Massachusetts

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

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

GENE
PDGFRA

RATIONALE
PDGFRA amplification may predict sensitivity to imatinib and to anti-PDGFRA antibodies.

ALTERATION
amplification

NCT04051606

PHASE 2

Regorafenib in Bevacizumab Refractory Recurrent Glioblastoma

TARGETS
BRAF, KIT, RET, VEGFRs

LOCATIONS: Ohio

NCT01738139

PHASE 1

Ipilimumab and Imatinib Mesylate in Advanced Cancer

TARGETS
KIT, ABL, CTLA-4

LOCATIONS: Texas

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.

ALK
R1264G

CARD11
S694L

CD22
amplification

CEBPA
amplification

KIT
rearrangement

KMT2A (MLL)
V3557fs*10

MSH6
H501Y

MYCN
A184S

NOTCH3
V976I

PIK3CA
C692W

POLE
G1256E

SPEN
F1309Y

WHSC1 (MMSET)
K361Q

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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*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

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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

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

MR Suite Version 5.1.1

The median exon coverage for this sample is 736x

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

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