FOUNDATIONONE®CDx

PATIENT
Chen, Chih-Cheng

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
24 Feb 2022
ORDERED TEST #
ORD-1301524-01

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 Chen, Chih-Cheng
DATE OF BIRTH 06 November 1972
SEX Male
MEDICAL RECORD # 48048824

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 S111-03914H (PF22014)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 25 January 2022
SPECIMEN RECEIVED 15 February 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 5 Muts/Mb

Genomic Findings

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

FGFR1 N546K - subclonal†
KIT amplification
MET amplification, ST7-MET fusion
PDGFRA amplification
RAD54L C391fs*1
CDKN2A/B CDKN2A loss, CDKN2B loss
KDR amplification - equivocal†
TP53 R158G

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

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cabozantinib** (p. 10), **Capmatinib** (p. 10), **Crizotinib** (p. 11), **Imatinib** (p. 11), **Infigratinib** (p. 12), **Nilotinib** (p. 12), **Sorafenib** (p. 13), **Sunitinib** (p. 13), **Tepotinib** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 5 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FGFR1 - N546K - subclonal	none	Infigratinib
10 Trials see p. 15		
KIT - amplification	none	Imatinib
		Nilotinib
		Sorafenib
10 Trials see p. 17		Sunitinib
MET - amplification, ST7-MET fusion	none	Cabozantinib
		Capmatinib
		Crizotinib
4 Trials see p. 19		Tepotinib
PDGFRA - amplification	none	Imatinib
2 Trials see p. 20		
RAD54L - C391fs*1	none	none
10 Trials see p. 21		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

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

BIOMARKER

Tumor Mutational Burden

RESULT
5 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
FGFR1

ALTERATION
N546K - subclonal

TRANSCRIPT ID
NM_023110

CODING SEQUENCE EFFECT
1638C>G

VARIANT ALLELE FREQUENCY (% VAF)
0.70%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors including erdafitinib[47-49], pemigatinib[50], infigratinib[51-52], rogaratinib[53], Debio 1347[54-55], futibatinib[56], and derazantinib[57], or multikinase inhibitors such as pazopanib[58] and ponatinib[59-61]. In the context of FGFR1 mutation, clinical responses have been reported in patients with primary brain tumors[54,56] and lung squamous cell carcinoma[62] treated with FGFR inhibitors. In a phase 1 study of futibatinib, 2 patients with FGFR1-mutated primary brain tumors exhibited PRs[56]. A patient with FGFR1-mutated glioblastoma exhibited a PR when treated with infigratinib[63]. For pediatric patients with FGFR1-mutated gliomas, a case series reported 1 sustained PR for a patient with high grade glioma, and a sustained SD and 1 PD for patients with low grade gliomas following treatment with Debio 1347[54].

FREQUENCY & PROGNOSIS

In the Brain Lower Grade Glioma TCGA dataset and the Glioblastoma Multiforme TCGA dataset, mutation of FGFR1 has been found in less than 1% of cases[64-65]. In pediatric patients, FGFR1 alterations have been identified in 18% of low-grade gliomas[33], including 5/9 pilomyxoid astrocytomas, 8% of high-grade gliomas[33], and in 6% (4/64) of thalamic gliomas[66]. FGFR1 mutation has also been reported in 5% (5/96) of pilocytic astrocytomas[67]. Mutations in the FGFR1 kinase domain have been reported in both lower-grade gliomas and glioblastomas; one of these mutations has been described as an oncogenic mutation that disrupted autophosphorylation[68-70]. FGFR fusions were identified in 3/85 IDH1 and IDH2 wild-type gliomas, but were not found in any of 126 IDH1- or IDH2-mutant gliomas[71]. Three patients with FGFR1-mutated pilocytic astrocytomas experienced relatively short survival in one study[72], although published data investigating the prognostic implications of FGFR1 alterations in gliomas are limited (PubMed, Mar 2021)[66].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[73]. The FGFR1 alteration observed here has been characterized as activating and is predicted to be oncogenic[69,74-76].

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[77-84]. 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[85]. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation[86]. 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[87-97], nilotinib[98], sorafenib[99-102], and sunitinib[103-104], 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. One patient with KIT/PDGFRA/KDR-amplified GBM experienced a PR on ripretinib[105-106] .

FREQUENCY & PROGNOSIS

In the TCGA datasets, KIT amplification has been reported in 2.5% of lower grade gliomas (grades 2 and 3)[65] and 9.2% of glioblastomas (Grade 4 astrocytoma)[64]. KIT amplification has been variously reported in 4-47% of glioblastomas in the scientific literature[107-109]. Amplification of KIT has been strongly correlated with the presence of KDR and/or PDGFRA amplification in glioblastoma[108,110-111]. 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[107,112].

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[113]. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein[114]. KIT has been reported to be amplified in cancer[115] and may be biologically relevant in this context[116-117].

GENE
MET

ALTERATION
amplification, ST7-MET fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. In a Phase 1b/2 trial for patients with MET-amplified recurrent glioblastoma, no responses were observed following treatment with capmatinib monotherapy (n=10) or capmatinib combined with buparlisib (n=33); patients in the combination therapy arm additionally harbored PTEN inactivating alterations[118]. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[119-122], gastroesophageal cancer[123], glioblastoma[124], and carcinoma of unknown primary[125]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[126-127] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[128-130]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[131] and NSCLC[132] as a monotherapy, as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[133-135] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[136] and gastric cancer either alone or in combination with docetaxel[137-138]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[139]. Patients with MET-amplified NSCLC[140] or MET-amplified gastric cancer[141] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab, as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[142]. A first-in-human Phase 1 trial of telisotuzumab vedotin (teliso-V), a MET antibody-drug conjugate, reported activity in a subset of patients with MET-positive NSCLC, with an ORR of 19% (3/16) and a DCR of 56% (9/16); no responses were observed in any other patients[143]. A subsequent Phase 2 trial of teliso-V in patients with MET-positive NSCLC reported a 35% (13/37) ORR in patients with non-squamous, EGFR-wildtype tumors, which met the prespecified criteria for transition to the next stage; lower ORRs were observed in patients with squamous (14%; 3/21) or non-squamous EGFR-mutated (13%; 4/30) tumors[144]. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, savolitinib, and foretinib have provided benefit for patients with MET-mutated papillary renal cell carcinoma (RCC)[145-148], histiocytic sarcoma[149], and non-small cell lung cancer (NSCLC) of varied histologies[150-154]. Patients with MET exon 14 mutated NSCLC who were treated with 1 of several MET inhibitors exhibited superior outcomes (median OS 24.6 vs. 8.1 months; HR=0.11, p=0.04) compared with patients who were not treated with a MET inhibitor[155]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations[156], and yielded a PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC[157]. In another study, 11 patients with hereditary papillary RCC and germline MET mutations (4 of which were H1094R) experienced 5 PRs and 5 SDs after treatment with foretinib[145]. Savolitinib yielded ORRs of 49% (30/61) in patients with MET exon 14 mutated NSCLC[158] and numerically higher ORR for patients with MET-driven papillary RCC compared to sunitinib (27% [9/33] vs. 7.4% [2/27])[148].

FREQUENCY & PROGNOSIS

A study of 53 pediatric patients with glioblastoma identified MET fusions in 11% of cases[159]. In the glioblastoma multiforme (GBM) TCGA dataset, putative amplification of MET is reported in 2.5% of cases whereas MET mutation is reported in 0.4% of cases[64]. Lower level gain of MET has been reported in 47% and 44% of primary and secondary GBM, respectively, and in 38% of diffuse astrocytomas[160]. Oncogenic fusions in receptor tyrosine kinases, including ALK, NTRK1/2/3, ROS1, and MET, are characteristic of a subset of infantile hemispheric high-grade gliomas with intermediate to good prognosis[161-162]. Multiple studies have reported MET expression to be associated with poor prognosis in patients with GBM[163-165]; however, one study reported improved overall survival in patients with GBM expressing MET relative to those negative for MET expression[166].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[167-168]. MET has been reported to be amplified in cancer[115], with amplification positively correlating with protein expression in some cancer types[169-173] and associating with therapeutic response to MET inhibitors in a variety of cancer types[119-121,123-125,174-175]. Rearrangements leading to a fusion of the MET kinase domain with a variety of partners predicted to constitutively dimerize and/or overexpress the MET portion, including the kinase domain[159,176-178], have been characterized as activating and/or tumorigenic, as well as sensitive to various MET inhibitors, including crizotinib, cabozantinib, tepotinib, and foretinib in preclinical studies[178-182]. Four patients with lung adenocarcinoma harboring MET fusions[178,183-184], a patient with lung adenocarcinoma harboring a MET kinase domain duplication[178], and a patient with glioblastoma harboring a MET fusion[159] have benefited from crizotinib.

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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[185-222]. 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)[223-228]. Complete responses to nilotinib have been reported in patients with CEL or hypereosinophilic syndrome with FIP1L1-PDGFRA or activating mutations[201,229-230]; preclinical evidence has reported efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[231-232]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[233] or regorafenib[234-235]. Preclinical studies have reported sensitivity of activating PDGFRA mutations and FIP1L1-PDGFRA fusion to dasatinib[225,231]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[77] and preclinical[77] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[106]. One patient with KIT/PDGFRA/KDR-amplified GBM experienced a PR on ripretinib[105-106] .

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[110,236-237]. PDGFRA amplification has been reported in 5.2-33% of glioblastoma cases[64,107-108,236,238-239]. 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[240]. Amplification of PDGFRA has been associated with tumor grade and poor progression-free and overall survival in patients with glioblastoma[236,238-239]. 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[236]. 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[108,110-111,241].

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[242]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[114]. Amplification of PDGFRA, frequently occurring with amplification of the genes KDR and KIT, has been associated with increased PDGFRA expression[109,243-245] and poor prognosis[109,236,246-247] in some subtypes of glioma.

GENE
RAD54L

ALTERATION
C391fs*1

TRANSCRIPT ID
NM_003579

CODING SEQUENCE EFFECT
1092_1093insCGAGACGCTGCTGCTAGTGAGGCAGACAGGC
AGCTAGGAGAGGAGCGGCTGCGGGAGCTCACCAGCATTGT
GAATAGGTAATGACCTTAAGC

VARIANT ALLELE FREQUENCY (% VAF)
37.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available that directly target RAD54L. Limited clinical evidence in ovarian cancer[248] and prostate cancer[249] indicates that RAD54L inactivation may confer sensitivity to PARP inhibitors.

FREQUENCY & PROGNOSIS

RAD54L loss or deletion has been observed in 2.8% of colon cancer, 2.3% of pheochromocytoma and paraganglioma, 2.0% of prostate adenocarcinoma cases and in fewer than 1% in other tumor types (cBioPortal, May 2021)[115,250]. RAD54L mutation is rare in cancer, with limited reports in breast cancer, squamous cell carcinomas of the cervix and skin, colorectal cancer, endometrial carcinoma, lymphoma, melanoma, and stomach adenocarcinoma (cBioPortal, COSMIC, May 2021)[251]. Loss of heterozygosity (LOH) at chromosomal region 1p32-34, in which RAD54L resides, has been reported as a frequent event in breast cancer[252], oligodendroglioma[253], nontypical meningioma[254-257], and parathyroid adenoma[258], but it is not clear whether RAD54L loss of function is pathogenic in these cases. Increased RAD54L expression was reported in NSCLC samples in response to increased mutation rate[259] and also in castration-resistant prostate cancer (CRPC) cells[260]. RAD54L polymorphisms have been associated with increased risk of developing meningioma[261], glioma[262], and decreased overall survival (P<0.004) in patients with potentially resectable pancreatic adenocarcinoma[263]. Germline mutations of RAD54L has been associated with increased risk of gastric cancer[264] but not lymphoid malignancies[265].

FINDING SUMMARY

RAD54L encodes a member of the SNF2/SWI2 superfamily and forms part of the RAD52 complex involved in recombination and DNA repair in response to ionizing radiation[266-269]. Alterations leading to disruption of critical domains with RAD54L are predicted to enhance genomic instability[270]. Alterations such as seen here may disrupt RAD54L function or expression[251,270-274].

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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[275-278]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[279-280], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[281-287]; 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[288-289], 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[282,284-285,290-292].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[293] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[64] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[115,250]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[238,245,294]. 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[295]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[296]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[297]. 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[238,298]. 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[299-300].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[301-302]. 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[303-304]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[305-306]. One or more alterations observed here are predicted to result in p16INK4a loss of function[307-328]. One or more alterations seen here are predicted to result in p14ARF loss of function[311,328-331]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[332].

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[333]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[334-335]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[336-338]. 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[339-341]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
KDR

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical benefit for patients with ccRCC[342-346] and a patient with breast angiosarcoma[347], high VEGFR-2 expression has been associated with sensitivity to sunitinib. However, because data supporting concordance between VEGFR-2 expression and KDR genomic biomarkers are limited, it is unclear whether these therapeutic strategies would be beneficial in this case. On the basis of extensive clinical evidence across multiple tumor types, expression of plasma or tumor VEGFR-1 or VEGFR-2 has not been established as a reliable biomarker to predict response to the VEGFA-targeted agent bevacizumab[348-367]. One patient with KIT/PDGFRA/KDR-amplified GBM experienced a PR on ripretinib[105-106] .

FREQUENCY & PROGNOSIS

KDR mutation has been reported in 2.0% of glioma samples analyzed in COSMIC (Jan 2022)[368]. In the TCGA datasets, KDR amplification has been reported in 2.5% of lower grade gliomas and 6.2% of glioblastomas (grade IV astrocytoma)[64-65]. In the scientific literature, KDR amplification has been reported in 3-39% of glioblastomas analyzed[107-108]. Amplification of KDR has been strongly correlated with the presence of KIT and/or PDGFRA amplification in glioblastomas[108,110-111]. The activity of VEGFR2 has been shown to be correlated with disease progression in gliomas; a study reported constitutive activity of VEGFR2 in 71% and 15% of glioblastomas and anaplastic gliomas, respectively, but not in low grade gliomas[369-370]. In addition, increased VEGFR2 expression has been associated with poor progression-free survival in recurrent high-grade gliomas[371].

FINDING SUMMARY

KDR encodes vascular endothelial growth factor receptor 2 (VEGFR2), a member of the vascular endothelial growth factor receptor (VEGFR) family. It is a receptor tyrosine kinase that transmits signals from VEGFA and is involved in both tumor angiogenesis and vasculogenesis during development[372]. KDR amplification has been reported in many tumor types and may be oncogenic[372].

GENE
TP53

ALTERATION
R158G

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
472C>G

VARIANT ALLELE FREQUENCY (% VAF)
92.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[373-376], or p53 gene therapy and immunotherapeutics such as SGT-53[377-381] and ALT-801[382]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[383]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[384]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[385]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[386]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[137]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[387]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[388]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[381]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[389-391]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[392]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[393-394]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[395-396]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs[397-398]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[296]. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively[399-404]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[405]. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM[296]. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN[406].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[407]. Alterations such as seen here may disrupt TP53 function or expression[408-412].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[413-415], including sarcomas[416-417]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[418] to 1:20,000[417]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[419]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[420-425]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[420-421]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[426]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[424,427-428]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Cabozantinib

Assay findings association

MET
amplification, ST7-MET fusion

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[151,429] , as well as by extensive preclinical data[176,430-435] . A patient with infantile fibrosarcoma-like tumor harboring an RBMS-MET fusion benefited from cabozantinib treatment[436].

SUPPORTING DATA

In a Phase 2 study, cabozantinib treatment achieved objective responses in 7 of 31 patients with glioblastoma (GBM) without prior antiangiogenic therapy and tumor shrinkage in 3 of 9 patients with prior antiangiogenic therapy, including bevacizumab[437]. In a preclinical study, cabozantinib treatment reduced GBM tumor growth in 3 xenograft mouse lines, and increased survival in two of these lines, while showed no effect on the overall survival in the third line; however, combination treatment with cabozantinib resulted in sensitization of these xenografts to TMZ treatment[438]. A Phase 1 ascending dose study of cabozantinib in patients with advanced solid tumors has reported early indications of drug response and prolonged stable disease, with no dose-limiting toxicities or serious adverse events[439]. Another Phase 1 study of cabozantinib in high-grade gliomas included 1 patient with anaplastic astrocytoma who had stable disease for >900 days[440]. A Phase 1 study examining the combination of cabozantinib and temozolomide for patients with high-grade gliomas reported that the combination was safe; however, dose reductions were common and 62% of patients experienced treatment-related grade 3/4 adverse events[441]. The combination of cabozantinib and crizotinib has been found to result in an increase in overall survival in a glioblastoma xenograft model[432]. Cabozantinib treatment has also been reported to result in decreased endothelial cell proliferation, increased apoptosis, and an inhibition of tumor growth in mouse models of breast, glioma, and lung tumors[430].

Capmatinib

Assay findings association

MET
amplification, ST7-MET fusion

AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[126,132-135,442] , hepatocellular carcinoma[131], renal cell carcinoma[136], and gastric cancer[137], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of capmatinib for the treatment of CNS tumors are limited (PubMed, Sep 2021). A Phase 1b/2 study of capmatinib with or without buparlisib did not result in CR or PR for patients with recurrent PTEN-deficient glioblastoma[118]. Capmatinib has been investigated primarily for the treatment of NSCLC, demonstrating efficacy as monotherapy for patients with MET amplification[127,443-444] or MET exon 14 skipping alterations[444-445] as well as in combination with EGFR inhibitors for patients with MET amplification[128-130] . Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with MET-amplified glioblastoma (n=10)[118], MET-overexpressing gastric cancer (n=9)[446], or other advanced solid tumors with MET amplification or overexpression (n=11)[446-447] .

Crizotinib

Assay findings association

MET
amplification, ST7-MET fusion

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), and to treat pediatric and young adult patients with ALK rearrangement-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[119-121,448-449] , gastric cancer[174], gastroesophageal cancer[123], glioblastoma[124], and carcinoma of unknown primary[125], as well as in patients with MET-mutated cancers, including NSCLC[149,151-154,450] , renal cell carcinoma (RCC)[147], and histiocytic sarcoma[149]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[149,151-155] . Four patients with lung adenocarcinoma harboring MET fusions[178,184,451] , a patient with lung adenocarcinoma harboring a MET kinase domain duplication[178], and a pediatric patient with glioblastoma harboring a MET fusion[159] have benefited from crizotinib.

SUPPORTING DATA

Case reports describe 2 patients with glioblastoma who benefited from crizotinib: 1 patient with MET amplification experienced a rapid radiographic regression[124] and another patient with overexpression of MET and ALK showed prolonged SD[452]; another patient with MET amplification did not respond to crizotinib[452]. A Phase 1 study of crizotinib combined with temozolomide and radiotherapy reported a median PFS of 16.8 months and a median OS of 31.4 months for patients with glioblastoma[453]. A Phase 1 study of crizotinib in pediatric patients with solid tumors or lymphoma reported intratumoral hemorrhage in 2 patients with primary central nervous system (CNS) tumors, and patients with CNS lesions were subsequently excluded from the study[454].

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[88-89,197,455] , KIT-amplified[87-90] , or KIT-expressing tumors[92-97,456-457] , 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[195].

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[458]. 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%[97,459] . 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[460].

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Infigratinib

Assay findings association

FGFR1
N546K - subclonal

AREAS OF THERAPEUTIC USE

Infigratinib is a TKI that inhibits FGFR1, FGFR2, and FGFR3. It is FDA approved for the treatment of patients with unresectable locally advanced or metastatic cholangiocarcinoma who have FGFR2 rearrangements or fusions and have progressed after prior therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on individual responses in patients with FGFR1-mutated glioblastoma[63] and lung squamous cell carcinoma[62], FGFR1 mutation may predict sensitivity to infigratinib.

SUPPORTING DATA

A Phase 2 study of infigratinib for patients with recurrent high-grade gliomas harboring FGFR alterations, reported a 9.5% (2/21) ORR, 1.7 month median PFS, and 6.7 month median OS[63]. Disease control greater than one year was observed in 4 patients, including a PR in a patient with FGFR1-mutated glioma, and SD in patients with glioma harboring FGFR1 mutation, FGFR3 mutation, or FGFR3-TACC3 fusion[63].

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[98,461-464] , KIT-amplified[98], or KIT-expressing tumors[465], 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, Jan 2022). 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[466]. 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[467]. 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[468]. 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[469]. Preclinical, cell-based assays have reported efficacy for nilotinib alone and in combination with additional therapies in the context of leiomyosarcoma and synovial sarcoma[470].

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[471-478] or KIT-expressing tumors[99-102] , 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)[479]. 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[480]. 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[481]. 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[482]. 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[483].

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[103,484-488] or KIT-expressing tumors[103-104] , 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[489-490] . 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[491]. 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[492].

Tepotinib

Assay findings association

MET
amplification, ST7-MET fusion

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with metastatic non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[126,132-135,442] , hepatocellular carcinoma[131], renal cell carcinoma[136], and gastric cancer[137], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of tepotinib for the treatment of CNS tumors are limited (PubMed, Sep 2021). Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[132] and MET exon 14-skipping alterations[156,493] . Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[134-135] . In advanced hepatocellular carcinoma, Phase 2 studies of tepotinib reported improved ORR and PFS for both treatment-naive and previously treated patients with MET protein overexpression[131,494-496] . In a Phase 1 study of advanced solid tumors, tepotinib monotherapy yielded an ORR of 1.3% and a DCR of 24%, with 2 confirmed PRs observed for patients with esophageal or lung cancer and 2 unconfirmed PRs for patients with colorectal or nasopharyngeal cancer[497]. In another Phase 1 study of solid tumors, tepotinib yielded a DCR of 17% (2/12), with 2 SD of ≥12 weeks observed in a patient with gastric cancer and another with urachal cancer[498].

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
FGFR1

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

ALTERATION
N546K - subclonal

NCT04169672

PHASE 2

Study of Surufatinib Combined With Toripalimab in Patients With Advanced Solid Tumors

TARGETS
FGFR1, CSF1R, VEGFRs, PD-1

LOCATIONS: Shanghai (China), Beijing (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Suwon-si (Korea, Republic of), 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, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Seoul (Korea, Republic of), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington, Hospitalet de Llobregat (Spain)

NCT03547037

PHASE 1

A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of JNJ-63723283, an Anti-Programmed Cell Death (PD)-1 Monoclonal Antibody, as Monotherapy or in Combination With Erdafitinib in Japanese Participants With Advanced Solid Cancers

TARGETS
PD-1, FGFRs

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

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NCT04008797

PHASE 1

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

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

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

NCT04424966

PHASE NULL

Infigratinib in Recurrent Glioblastoma Patients

TARGETS
FGFR3, FGFR1, FGFR2

LOCATIONS: Arizona

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Macquarie Park (Australia), Melbourne (Australia), Clayton (Australia), Frankston (Australia), Colorado, Minnesota, Arizona, Ohio, Florida

NCT02549937

PHASE 1/2

A Multi-Center, Open-Label Study of Sulfatinib(HMPL-012) in Patients With Advanced Solid Tumors

TARGETS
FGFR1, CSF1R, VEGFRs

LOCATIONS: Milano (Italy), California, Colorado, Texas, New York, Tennessee, Virginia, Florida

NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

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

LOCATIONS: Massachusetts

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. KIT/PDGFRA/KDR amplification in GBM may predict sensitivity to ripretinib.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Suwon-si (Korea, Republic of), 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, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Seoul (Korea, Republic of), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington, Hospitalet de Llobregat (Spain)

NCT04008797

PHASE 1

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

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

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
FLT3, VEGFRs, CSF1R, KIT, RET

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

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

NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

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

LOCATIONS: Massachusetts

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

NCT02379416

PHASE 1

Combination Nilotinib and Paclitaxel in Adults With Relapsed Solid Tumors

TARGETS
ABL, KIT

LOCATIONS: Maryland

GENE
MET

RATIONALE
Activating MET alterations may confer sensitivity to MET inhibitors.

ALTERATION
amplification, ST7-MET fusion

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), Saransk (Russian Federation), North Adelaide (Australia), Bedford Park (Australia)

NCT04647838

PHASE 2

Tepotinib in Solid Tumors Harboring MET Alterations

TARGETS
MET

LOCATIONS: Cheonan (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Nice (France), Lyon (France), Marseille (France), Toulouse (France), Bordeaux (France)

NCT04693468

PHASE 1

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

TARGETS
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

LOCATIONS: Texas

Electronically signed by Erik Williams, M.D. | 24 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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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

GENE
PDGFRA

ALTERATION
amplification

RATIONALE
PDGFRA amplification may predict sensitivity to imatinib and to anti-PDGFRA antibodies. KIT/PDGFRA/KDR amplification in GBM may predict sensitivity to ripretinib.

NCT04051606

PHASE 2

Regorafenib in Bevacizumab Refractory Recurrent Glioblastoma

TARGETS
BRAF, VEGFRs, RET, KIT

LOCATIONS: Ohio

NCT01738139

PHASE 1

Ipilimumab and Imatinib Mesylate in Advanced Cancer

TARGETS
KIT, ABL, CTLA-4

LOCATIONS: Texas

GENE
RAD54L

RATIONALE
RAD54L inactivation may predict sensitivity to PARP inhibitors.

ALTERATION
C391fs*1

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Darlinghurst (Australia), Moscow (Russian Federation), Krasnogorsk (Russian Federation)

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)

NCT04715620

PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
PARP

LOCATIONS: Tianjin (China)

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)

NCT04614909

PHASE NULL

Phase 0/2 Study of Pamiparib in Newly Diagnosed and rGBM

TARGETS
PARP

LOCATIONS: Arizona

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

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

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.

BAP1
V99M

CXCR4
amplification

MET
rearrangement

PTPRO
A689E

RICTOR
R873H

SPOP
K286R

TEK
loss

Electronically signed by Erik Williams, M.D. | 24 February 2022
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APPENDIX Genes Assayed in FoundationOne®CDx

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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 6.0.0

The median exon coverage for this sample is 627x

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