FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Lu, Wei-Ming	Brain glioblastoma (GBM)	16 Jan 2024
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1793429-01

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 Lu, Wei-Ming
DATE OF BIRTH 26 August 1965
SEX Male
MEDICAL RECORD # 50109905

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 S112-68613A (PF24002)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 26 December 2023
SPECIMEN RECEIVED 08 January 2024

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

KIT **amplification, FIP1L1-KIT fusion**
PDGFRA **amplification, deletion exons 8-9**
CDK4 **amplification**
PIK3CA **E542K**
TERT **promoter -124C>T**
TP53 **V197M, R248W**

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

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***TERT*** **promoter -124C>T** (p. 7)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Imatinib** (p. 9), **Nilotinib** (p. 9), **Sorafenib** (p. 10), **Sunitinib** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***TERT*** **promoter -124C>T** (p. 7)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 4 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)**
KIT **-** amplification, FIP1L1-KIT fusion	none	Imatinib
		Nilotinib
		Sorafenib
10 Trials see p. 13		Sunitinib
PDGFRA **-** amplification, deletion exons 8-9	none	Imatinib
9 Trials see p. 15		Sorafenib
CDK4 **-** amplification	none	none
10 Trials see p. 11		
PIK3CA **-** E542K	none	none
10 Trials see p. 17		

Electronically signed by Erik Williams, M.D. | 16 January 2024
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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

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.

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[4-5]. 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)[6].

— Nontargeted Approaches —

Preclinical and clinical evidence suggests that acquired MMR deficiency may be a resistance mechanism to temozolomide treatment for glioma, displaying lack of T cell infiltration and increased tumor mutational burden[7-9]. Patients with MMR-deficient and hypermutated glioma showed worse treatment outcomes to immune checkpoint inhibitors[10-11].

FREQUENCY & PROGNOSIS

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[12-14]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[12], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[15]. The frequency of microsatellite instability (MSI) has been reported to be increased in relapsed compared with primary glioblastoma (GBM)[12], in GBMs with a previous lower-grade astrocytoma[13], and in giant cell GBM compared with classic GBM[14]. Acquired MMR deficiency has been reported as a potential resistance mechanism to temozolomide, and patients with glioma and MMR deficiency showed poor survival outcomes[10-11].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA MMR in the tumor[16]. 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[16-18]. 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[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
4 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[22-25], anti-PD-1 therapies[23-27], and combination nivolumab and ipilimumab[28-36]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[7,23,37-38]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[39-40] or anti-PD-L1[41] 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 Muts/Mb, and 4.2% of cases have high TMB (>20 Muts/Mb)[42]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in MMR or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[43-44]. Increased TMB has been reported to correlate with higher tumor grade in glioma[45] and glioblastoma (GBM) tissue samples with germline biallelic MMR deficiency[39] and with shorter OS for patients with diffuse glioma[46]. Increased TMB has also been associated with acquired MMR deficiency following temozolomide treatment for glioma, and patients with MMR-deficient glioma showed poor survival outcomes[7,11].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions 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[47-48] and cigarette smoke in lung cancer[49-50], treatment with temozolomide-based chemotherapy in glioma[51-52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[53-57], and microsatellite instability[53,56-57]. 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[7,23,37-41].

GENE
KIT

ALTERATION
amplification, FIP1L1-KIT fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, primarily in gastrointestinal stromal tumor (GIST), melanoma, AML, and systemic mastocytosis, KIT activating alterations are associated with sensitivity to TKIs including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, regorafenib, ponatinib, midostaurin, apatinib, avapritinib, and ripretinib[58-72]. 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[73-74]. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation[75]. The role of KIT amplification as a biomarker for response to mTOR inhibitors has not been investigated (PubMed, Feb 2023). Clinical benefit has been observed for patients with KIT amplified or overexpressing tumors following treatment with imatinib[76-86], nilotinib[87], sorafenib[88-91], and sunitinib[92-93], 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)[94] and 9.2% of glioblastomas (Grade 4 astrocytoma)[95]. KIT amplification has been variously reported in 4-47% of glioblastomas in the scientific literature[96-98]. Amplification of KIT has been strongly correlated with the presence of KDR and/or PDGFRA amplification in glioblastoma[97,99-100]. In the glioblastoma multiforme TCGA dataset, KIT mutation has been observed in 1.1% of cases[95]. KIT alterations have been correlated with lower median OS compared with KIT wildtype for patients with gliomas (21.6 vs. 37.6 months), including astrocytomas (33.2 vs. 58.6 months)[101]. One study found no correlation between KIT amplification and OS for patients with glioblastoma (GBM), while a separate study reported that overexpression of KIT was associated with tumor grade and shorter survival for patients with malignant glioma[96,102].

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[103]. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein[104]. KIT has been reported to be amplified in cancer[105] and may be biologically relevant in this context[106-107]. 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
PDGFRA

ALTERATION
amplification, deletion exons 8-9

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Based on extensive clinical evidence in gastrointestinal stromal tumor (GIST)[108-116] and limited preclinical evidence[117-119], PDGFRA activating mutations are associated with sensitivity to imatinib. Sorafenib has shown clinical and preclinical activity against PDGFRA mutations associated with clinical resistance to imatinib and sunitinib both in GIST and in the context of FIP1L1-PDGFRA fusion in chronic eosinophilic leukemia (CEL)[120-126]. Clinical benefit from nilotinib has been reported for individual patients with CEL with activating PDGFRA mutations[127]; preclinical evidence has also suggested efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[128-129]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[130-131] or regorafenib[132-133]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[59,63] and preclinical[63] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[134]. Preclinical and limited clinical evidence support sensitivity of PDGFRA mutations to crenolanib[135-139]. Preclinical evidence suggests sensitivity of PDGFRA mutations to dasatinib[123,128] and midostaurin[140-142] in the context of GIST and FIP1L1-PDGFRA fusions in CEL. On the basis of limited evidence of clinical benefit for patients with increased PDGFR expression, PDGFRA amplification may be associated with sensitivity to imatinib[143-144].

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[99,145-146]. PDGFRA amplification has been reported in 5.2-33% of glioblastoma cases[95-97,145,147-148]. PDGFRA mutations have been reported in 0-6% of low-grade glioma, high-grade glioma, and glioblastoma samples[51,94-95,149-158]. 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[159]. PDGFRA amplification has been associated with tumor grade and poor PFS and OS for patients with glioblastoma[145,147-148]. In addition, PDGFRA amplification has been reported to occur in conjunction with IDH1 mutations in glioblastoma, and both alterations in the same tumor have been associated with poor patient prognosis[145]. 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[97,99-100,160].

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[161]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[104]. Amplification of PDGFRA, frequently occurring with amplification of the genes KDR and KIT, has been associated with increased PDGFRA expression[98,162-164] and poor prognosis[98,145,165-166] in some subtypes of glioma. The PDGFRA rearrangement in this tumor results in deletion of exons 8-9. The PDGFRA exon 8-9 deletion mutation was demonstrated to be active in the absence of ligand and has been characterized as transforming[117,167]. This mutation was sensitive to imatinib and the kinase inhibitor vatalanib[117].

GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[168-171]. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib[172], palbociclib[168,173], and ribociclib[174].

FREQUENCY & PROGNOSIS

CDK4 amplification has been observed in 9.4% of glioma cases[175]. A study has reported amplification of the 12q14-15 region, where CDK4 and MDM2 reside, in 4.8% (2/42) of glioblastomas[176]. CDK4 alterations have been correlated with lower mOS compared with CDK4 wildtype in patients with gliomas (22.9 vs. 43.3 months), including oligodendrogliomas (37.1 vs. 60.0 months) and glioblastomas (10.0 vs. 18.5 months)[101]. Amplification of CDK4 and corresponding increased CDK4 protein expression has been reported to be associated with a poorer patient outcome in anaplastic astrocytoma and glioblastoma[177-180].

FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[181]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[182-183]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[168,184-190].

GENE
PIK3CA

ALTERATION
E542K

HGVS VARIANT
NM_006218.2:c.1624G>A (p.E542K)

VARIANT CHROMOSOMAL POSITION
chr3:178936082

VARIANT ALLELE FREQUENCY (% VAF)
11.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[191-200], AKT[201-202], or mTOR[203-210]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[199]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[198]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[196-197]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[211]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[212]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[213]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[191], but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)[193].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 9% of glioblastoma (GBM) samples analyzed in the TCGA dataset[95], and other studies report the incidence of PIK3CA mutations in primary GBMs as 5-18%[214-216]. One study detected PIK3CA mutation in 16% (36/232) of IDH-wildtype GBM samples analyzed[217]. PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)[149,214-216,218]. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity[216]. One study found that PIK3CA mutation in glioblastoma (GBM) was associated with shorter median PFS in both a discovery cohort (6.9 vs. 12.4 months, HR=2.89, p=0.01) and in the TCGA cohort (6.1 vs. 9 months, p=0.008), but was not consistently associated with median OS[219]. In a study of IDH-wildtype GBM, patients with alterations in PI3K class I genes (PIK3CA, PIK3R1, PIK3CG, and PIK3R2) had significantly longer OS (20.0 months altered vs. 16.9 months wildtype, HR=0.62, p=0.002) and PFS (11.0 months altered vs. 7.4 months wildtype, p=0.0043); patients with PIK3CA alterations experienced an improved OS but this association was not highly significant (20.0 months altered vs. 18.1 months wildtype, p=0.0407)[217].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[220-221]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[222-243].

GENE
TERT

ALTERATION
promoter -124C>T

HGVS VARIANT
NM_198253.2:c.-124C>T

VARIANT CHROMOSOMAL POSITION
chr5:1295228

VARIANT ALLELE FREQUENCY (% VAF)
40.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[244]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[245]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[246].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[247-248], most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas[247-251]. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)[247,249]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[217]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[252]. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM[247,249,252-253]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v2.2022).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[254]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[255-257]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[258-260], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[258].

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v1.2023)[261]. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2022)[262].

GENE
TP53

ALTERATION
V197M, R248W

HGVS VARIANT
NM_000546.4:c.589G>A (p.V197M),
NM_000546.4:c.742C>T (p.R248W)

VARIANT CHROMOSOMAL POSITION
chr17:7578260, chr17:7577539

VARIANT ALLELE FREQUENCY (% VAF)
60.0%, 14.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data suggest that solid tumors with TP53 mutations, such as R175H, Y220C, G245S, and R248W, may benefit from adoptive cell therapy targeting these specific TP53 mutations[263-264]. Clinical benefit has been reported for patients with breast cancer (2 PRs)[264], ovarian cancer (1 PR)[264], and colorectal cancer (CRC; 1 SD)[263] treated with tumor infiltrating lymphocyte-based or modified T-cell receptor-based adoptive cell therapy. 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[265-268] or p53 gene therapy such as SGT53[269-274]. 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[275]. Phase 2 studies of adavosertib in combination with chemotherapy reported ORRs of 32% (30/94) and 41% (12/29) for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[276-277]. For patients with platinum-sensitive TP53-mutated ovarian cancer, the combination of adavosertib with paclitaxel and carboplatin significantly increased PFS compared with paclitaxel and carboplatin alone (9.9 vs. 8.0 months)[278]. 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[279]. 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[280]. 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[281]. 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[274]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[282]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[283].

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[149,284]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[217]. 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[285-290]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[291]. 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[217]. 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[292].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[293]. Alterations such as seen here may disrupt TP53 function or expression[294-298].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2023)[299]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[300-302], including sarcomas[303-304]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[305] to 1:20,000[304]. 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[306]. 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[307-312]. 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[307-308]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[313]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[311,314-315]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Imatinib

Assay findings association

KIT
amplification, FIP1L1-KIT fusion

PDGFRA
amplification, deletion exons 8-9

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[77-78,112,316] , KIT-amplified[76-79] , or KIT-expressing tumors[81-86,317-318] , KIT activating alterations may confer sensitivity to imatinib. On the basis of strong clinical evidence, PDGFRA activating mutations[108,110-112,116] , fusions[319-328] , and expression[143] may predict sensitivity to imatinib. PDGFRA amplification may predict sensitivity to TKIs such as imatinib; a patient with Merkel cell carcinoma expressing PDGFRA achieved a CR to imatinib[143].

SUPPORTING DATA

In a clinical study where patients with recurrent glioblastoma (GBM) were given imatinib, 8.3% (2/24) of patients achieved a PR, 10 patients reported SD, and median OS and median PFS were observed to be 6.2 and 3 months, respectively[329]. However, other Phase 2 clinical trials of imatinib have reported no antitumor activity, with a study of 231 patients with GBM reporting a radiographic response rate of only 3.4%[86,330-331] . 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[332].

Nilotinib

Assay findings association

KIT
amplification, FIP1L1-KIT fusion

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[87,333-336] , KIT-amplified[87], or KIT-expressing tumors[337], 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 2024). Nilotinib has been primarily investigated as a therapeutic option for the treatment of chronic myeloid leukemia (CML) or gastrointestinal stromal tumors (GIST). In the context of CML, a Phase 3 clinical trial for patients who are Philadelphia chromosome (Ph) positive treated with imatinib or nilotinib (300 or 400 mg) reported PFS rates of 93% and 97-98% and OS rates of 93% and 94-97%, respectively, at 4 years[338]. For Japanese patients with CML who are resistant to imatinib, a Phase 2 trial reported a 49% major medical response rate to treatment with nilotinib at 12 months[339]. 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 PFS between nilotinib and the best supportive care but did report increased OS for patients treated with nilotinib[340]. 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[341].

Sorafenib

Assay findings association

KIT
amplification, FIP1L1-KIT fusion

PDGFRA
amplification, deletion exons 8-9

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[342-349] or KIT-expressing tumors[88-91] , KIT activating alterations may predict sensitivity to sorafenib. On the basis of clinical responses in patients with GIST, PDGFRA activating mutations may predict sensitivity to sorafenib[120,125].

SUPPORTING DATA

Phase 2 studies of sorafenib plus temozolomide report limited activity for patients with relapsed glioblastoma multiforme (GBM)[350]. A Phase 1/2 trial of temsirolimus in combination with sorafenib for patients with glioblastoma was terminated at the Phase 2 interim analysis after patients failed to meet the primary endpoint of 6-month PFS[351]. 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[352]. In a Phase 1 trial for 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[353]. In a clinical study of sorafenib for pediatric patients with low-grade astrocytoma, 1 patient achieved a PR, 1 had SD, and 9 patients had progressive disease; this study was terminated early due to unexpectedly high disease progression rates[354].

Sunitinib

Assay findings association

KIT
amplification, FIP1L1-KIT fusion

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[92,355-359] or KIT-expressing tumors[92-93] , KIT activating alterations may predict sensitivity to sunitinib.

SUPPORTING DATA

Phase 2 clinical trials of sunitinib in glioblastoma (GBM) have reported no significant improvement in clinical outcome[360-361] . A Phase 2 trial that examined sunitinib treatment followed by radiation therapy for patients with GBM reported a median PFS of 7.7 weeks and a median OS of 12.8 weeks; 83% (10/12) of patients experienced neurological deterioration prior to radiation therapy[362]. Another Phase 2 study that examined daily sunitinib treatment for patients with GBM reported no objective response for any of the 40 patients, with a median PFS of 2.2 months and a median OS of 9.2 months; 5 patients in the study had SD for >6 months[363].

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.

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
CDK4

ALTERATION
amplification

RATIONALE
CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

NCT04557449

PHASE 1/2

Study to Test the Safety and Tolerability of PF-07220060 in Participants With Advance Solid Tumors

TARGETS
CDK4, Aromatase, ER

LOCATIONS: Hangzhou (China), Wuhan (China), Zhengzhou (China), Xi'an (China), Beijing (China), Kashiwa (Japan), Poprad (Slovakia), Bratislava (Slovakia), Nove Zamky (Slovakia), Olomouc (Czechia)

NCT05262400

PHASE 1/2

A Study to Learn About the Study Medicine (Called PF-07220060 in Combination With PF-07104091) In Participants With Breast Cancer and Solid Tumors

TARGETS
CDK2, Aromatase, CDK4, ER

LOCATIONS: Hangzhou (China), Shanghai (China), Tianjin (China), Chengdu (China), Vratsa (Bulgaria), Haskovo (Bulgaria), Plovdiv (Bulgaria), Sofia (Bulgaria), Olomouc (Czechia), Praha 2 (Czechia)

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT05953350

PHASE 1/2

A Phase Ib/II Study Confirmed Inhibition of Autophagy Synergizes Anti-tumor Effect of High Dose CDK4/6i

TARGETS
CDK4, CDK6

LOCATIONS: Guangzhou (China)

NCT05538572

PHASE 1

A Phase 1 Study of PRT3645 in Participants With Select Advanced or Metastatic Solid Tumors

TARGETS

LOCATIONS: Singapore (Singapore), Ohio, Connecticut, New York, Pennsylvania, Tennessee, Texas, Virginia, Georgia, Florida

NCT04391595

PHASE NULL

LY3214996 Plus Abemaciclib in Recurrent Glioblastoma Patients

TARGETS
CDK4, CDK6, ERK1, ERK2

LOCATIONS: Arizona

NCT05432518

PHASE NULL

GBM Personalized Trial

TARGETS
CDK4, CDK6, DDR2, ABL, SRC, KIT, EGFR, ERBB4, ERBB2, mTOR

LOCATIONS: Calgary (Canada)

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: London (United Kingdom), California, Illinois, Michigan, Oklahoma, Massachusetts, Arkansas, New York, Pennsylvania, Maryland

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

GENE
KIT

ALTERATION
amplification, FIP1L1-KIT fusion

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.

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: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kurume (Japan), Matsuyama (Japan), Seongnamsi Bundang (Korea, Republic of), Songpa-gu (Korea, Republic of), Seoul (Korea, Republic of), Seodaemun (Korea, Republic of)

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

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

LOCATIONS: Shanghai (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: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of), New York, North Carolina

NCT05740215

PHASE 1/2

Efficacy and Safety Study of F520 Combined With Lenvatinib in the Treatment of Patients With Advanced Solid Tumors

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

LOCATIONS: Chongqing (China)

NCT03970447

PHASE 2/3

A Trial to Evaluate Multiple Regimens in Newly Diagnosed and Recurrent Glioblastoma

TARGETS
BRAF, VEGFRs, RET, KIT

LOCATIONS: Waratah (Australia), St Leonards (Australia), Heidelberg (Australia), Regensburg (Germany), Frankfurt (Germany), Heidelberg (Germany), Tübingen (Germany), Zürich (Switzerland), Lausanne (Switzerland), Washington

NCT05554341

PHASE 2

Testing the Use of Nilotinib and Paclitaxel as a Treatment for Patients With Prior Taxane Treatment, A ComboMATCH Treatment Trial

TARGETS
ABL, KIT

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT05064280

PHASE 2

Phase II Study of Pembrolizumab in Combination With Lenvatinib in Patients With TNBC, NSCLC, and Other Tumor Types and Brain Metastases

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

LOCATIONS: Texas

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

GENE
PDGFRA

ALTERATION
amplification, deletion exons 8-9

RATIONALE
PDGFRA amplification may predict sensitivity to imatinib and to anti-PDGFRA antibodies. PDGFRA activating mutations may predict sensitivity to certain PDGFRA-targeted therapies.

NCT03970447

PHASE 2/3

A Trial to Evaluate Multiple Regimens in Newly Diagnosed and Recurrent Glioblastoma

TARGETS
BRAF, VEGFRs, RET, KIT

LOCATIONS: Waratah (Australia), St Leonards (Australia), Heidelberg (Australia), Regensburg (Germany), Frankfurt (Germany), Heidelberg (Germany), Tübingen (Germany), Zürich (Switzerland), Lausanne (Switzerland), Washington

NCT05554341

PHASE 2

Testing the Use of Nilotinib and Paclitaxel as a Treatment for Patients With Prior Taxane Treatment, A ComboMATCH Treatment Trial

TARGETS
ABL, KIT

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT02925234

PHASE 2

The Drug Rediscovery Protocol (DRUP Trial)

TARGETS
EGFR, PARP, BRAF, ABL, KIT, MEK, ERBB2, SMO, VEGFRs, RET, PD-1, ERBB4, MET, ROS1, PD-L1, VEGFA, TRKB, ALK, TRKC, TRKA, FGFRs, PDGFRA, CDK4, CDK6, AXL, FLT3, CSF1R, CTLA-4, PI3K-alpha

LOCATIONS: Groningen (Netherlands), Drachten (Netherlands), Hoogeveen (Netherlands), Leeuwarden (Netherlands), Almelo (Netherlands), Zwolle (Netherlands), Deventer (Netherlands), Apeldoorn (Netherlands), Arnhem (Netherlands), Ede (Netherlands)

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, ALK, BRAF, KIT, MEK

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

NCT02379416

PHASE 1

Combination Nilotinib and Paclitaxel in Adults With Relapsed Solid Tumors

TARGETS
ABL, KIT

LOCATIONS: Maryland

NCT04771520

PHASE 2

Avapritinib for the Treatment of CKIT or PDGFRA Mutation-Positive Locally Advanced or Metastatic Malignant Solid Tumors

TARGETS
KIT, PDGFRA

LOCATIONS: Texas

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

GENE
PIK3CA

ALTERATION
E542K

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

NCT04589845

PHASE 2

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

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

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

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04586335

PHASE 1

Study of CYH33 in Combination With Olaparib an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.

TARGETS
PARP, PI3K-alpha

LOCATIONS: Shanghai (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)

NCT05390710

PHASE 1/2

PhI to Solid Tumors and PhII to Locally Advanced or mTNBC

TARGETS
PD-L1, AKTs

LOCATIONS: Bengbu (China)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

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

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT05773326

PHASE NULL

Superselective Intra-arterial Cerebral Infusion of Temsirolimus in HGG

TARGETS
mTOR

LOCATIONS: Arizona

NCT05432518

PHASE NULL

GBM Personalized Trial

TARGETS
CDK4, CDK6, DDR2, ABL, SRC, KIT, EGFR, ERBB4, ERBB2, mTOR

LOCATIONS: Calgary (Canada)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

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.

ASXL1
NM_015338.5: c.1330T>C
(p.S444P)
chr20:31021331

CREBBP
NM_004380.2: c.4240G>A
(p.V1414I)
chr16:3789619

ERBB3
NM_001982.3: c.3941G>A
(p.R1314H)
chr12:56495751

ERBB4
NM_005235.2: c.284G>A
(p.R95H)
chr2:212812292

FGFR3
rearrangement

KDR
rearrangement and
rearrangement

KIT
rearrangement

MSH3
NM_002439.3:
c.189_190insGCAGCGCCCCCA
GCGCCC
(p.P63_P64insAAPPAP)
chr5:79950727

PARP3
NM_005485.4: c.360T>G
(p.D120E)
chr3:51978453 and
NM_005485.4: c.1223G>A
(p.R408H)
chr3:51980306

PDGFRA
rearrangement,
rearrangement and
rearrangement

PIK3C2G
rearrangement

SRC
NM_005417.3: c.811C>T
(p.R271W)
chr20:36026209

ORDERED TEST # ORD-1793429-01

APPENDIX Genes Assayed in FoundationOne®CDx

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
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*	*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*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
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	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (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*	*MRE11 (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*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*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*
PRKN (PARK2)	*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*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*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

Homologous Recombination status
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 PRINCIPLE

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® Sequencing platform (HiSeq 4000 or NovaSeq 6000), 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. 2023. 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 fraction-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. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. 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.
5. 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.
6. 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.
7. 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 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%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). 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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 7.15.0
MR Reporting Config Version Config 49
Analysis Pipeline Version v3.29.0
Computational Biology Suite Version 6.29.0

The median exon coverage for this sample is 676x

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