FOUNDATIONONE®CDx

PATIENT
Lin, Chung-Cheng

TUMOR TYPE
Unknown primary GIST
COUNTRY CODE
TW

REPORT DATE
14 Sep 2021
ORDERED TEST #
ORD-1182590-01

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 Unknown primary GIST
NAME Lin, Chung-Cheng
DATE OF BIRTH 01 April 1968
SEX Male
MEDICAL RECORD # 41619038

PHYSICIAN

ORDERING PHYSICIAN Teng, Hao-Wei
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Omentum
SPECIMEN ID S110-24967 A
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 27 August 2021
SPECIMEN RECEIVED 07 September 2021

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.

KIT W557_K558del, V654A
ATRX R1342W
CDKN2A/B p16INK4a loss and p14ARF loss exons 2-3

1 Disease relevant genes with no reportable alterations: ***PDGFRA***

8 Therapies with Clinical Benefit
1 Therapies with Resistance
10 Clinical Trials

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 5 Muts/Mb

GENOMIC FINDINGS

***KIT* -** W557_K558del, V654A

10 Trials *see p. 12*

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)	
Regorafenib	1	Nilotinib	2A
Ripretinib	1	Sorafenib	2A
Sunitinib	1	Dasatinib	
Avapritinib	2A	Ponatinib	
Imatinib	⊗		

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

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.

ATRX - R1342W ..... p. 5 exons 2-3 ..... p. 6

CDKN2A/B - p16INK4a loss and p14ARF loss

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

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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

MSI is generally rare in GIST[6], although conflicting data have been published[7]. The prognostic significance of MSI in GIST has not been an active area of investigation (PubMed, Feb 2021).

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[8]. 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[8-10]. 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[11-13]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[8,10,12-13].

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[14-16], anti-PD-1 therapies[14-17], and combination nivolumab and ipilimumab[18-23]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[14-17,24]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[14]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[25] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[15]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[17,24]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Gastrointestinal stromal tumors (GIST) harbor a median TMB of 2.5 mutations per megabase (muts/Mb), and 0% of cases have high TMB (>20 muts/Mb)[26]. Published data investigating the prognostic implications of TMB in GIST are limited (PubMed, Sep 2021).

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[27-28] and cigarette smoke in lung cancer[29-30], treatment with temozolomide-based chemotherapy in glioma[31-32], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[33-37], and microsatellite instability (MSI)[33,36-37]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[15-16,24].

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GENE
KIT

ALTERATION
W557_K558del, V654A

TRANSCRIPT ID
NM_000222, NM_000222

CODING SEQUENCE EFFECT
1669_1674delTGGAAG, 1961T>C

VARIANT ALLELE FREQUENCY (% VAF)
31.8%, 39.7%

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[38-45]. 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[46]. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation[47]. The role of KIT amplification as a biomarker for response to mTOR inhibitors has not been investigated (PubMed, Mar 2021). In a dose escalation study of GIST patients who developed KIT resistant mutations, most commonly in exons 11 and 17 after progressing on imatinib, treatment with the higher dosage of PLX9486 alone and in the lower dosage in combination with pexidartinib reported clinical benefit rates of 64% (7/11) and 67% (6/9), respectively[48].

— Potential Resistance —

However, the KIT V654A mutation has been associated with resistance to imatinib in patients and cell-based models[49-57] and was shown to reduce sensitivity to regorafenib and ponatinib in preclinical studies; although this mutation still may be inhibited at clinically achievable doses[51]. Additional clinical and preclinical data suggest that KIT V654A may confer reduced sensitivity to avapritinib.[38,58].

FREQUENCY & PROGNOSIS

KIT mutation has been reported in 54-72% of GIST cases, and the majority of these mutations affect exon 9 or exon 11[59-61]. It is estimated that up to 95% of GISTs overexpress the KIT protein, and KIT mutation has been reported to be an early event in the development of GIST[59,62]. Mutations in exon 11 of KIT are associated with a significantly greater response rate to imatinib, compared to individuals with mutations in exon 9 or without mutations in KIT[63-64]. Studies comparing patients with GIST treated with imatinib to those treated with placebo indicate that the presence of exon 11 in-frame deletions is associated with a significantly longer recurrence-free survival in univariate analysis; similar results were not observed for patients with exon 11 insertions, exon 11 point mutations, exon 9 mutations, or no KIT mutation[65]. Overall, patients with exon 11 mutations experienced a benefit from adjuvant imatinib therapy, which is in agreement with several previous studies[63-66], but although the reported effect on overall survival is favorable, it does not always reach statistical significance[65-66]. However, patients that develop imatinib resistance have a poorer prognosis than those without including a reduced 5 year survival rate[67].

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[68]. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein[69]. KIT alterations in exon 11 leading to disruption of the autoinhibitory domain (amino acids 545-579)[70-77] or internal tandem duplication (ITD) proximal to the kinase domain (amino acids 569-591)[78], such as observed here, are predicted to be activating and sensitive to imatinib[64,79-80]. KIT exon 11 deletions are frequently observed in the context of gastrointestinal stromal tumor (GIST)[63,72,81] and KIT-ITDs in acute myeloid leukemia (AML)[79,82-85]. The V654A mutation is located within the kinase domain of KIT and promotes increased proliferation of cells in the presence of c-KIT ligand and is therefore also considered to be activating[86]. It is also a common secondary KIT mutation, acquired in addition to an existing activating mutation in KIT; this mutation has been associated with resistance to imatinib[51-57] and avapritinib[38,58] in patients and cell-based models and was shown to lead to decreased sensitivity to regorafenib and ponatinib in 1 preclinical study[51]. Activating alterations in KIT, or the related gene PDGFRA, are known to underlie inherited predisposition to gastrointestinal stromal tumor (GIST) development[87-88].

POTENTIAL DIAGNOSTIC IMPLICATIONS

KIT mutations are characteristic drivers of GIST and may aid in guiding targeted therapy approaches in this setting (NCCN GIST Guidelines, v1.2021)[89].

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GENE
ATRX

ALTERATION
R1342W

TRANSCRIPT ID
NM_000489

CODING SEQUENCE EFFECT
4024C>T

VARIANT ALLELE FREQUENCY (% VAF)
94.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to directly address ATRX inactivation. Based on preclinical[90-91] and limited clinical data[92], ATRX alterations may confer sensitivity to combination strategies involving WEE1 inhibition. In a Phase 2 study evaluating the WEE1 inhibitor adavosertib plus irinotecan for the treatment of pediatric patients with neuroblastoma, prolonged SD was reported for 44% (4/9) of patients with ATRX-deficient tumors and responses were seen in two tumors that had evidence of ALT[92]. Preclinical evidence also suggests that ATRX deficiency may impart sensitivity to synthetic lethal approaches involving PARP inhibition and irinotecan[93], combined PARP and ATR inhibition[91], or double-strand break-induction with agents such as doxorubicin, irinotecan, and topotecan[94]; however, these approaches have not been demonstrated clinically.

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT[95]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[95-97], 12.6% of pheochromocytomas and paragangliomas[98], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[99-103]. ATRX loss in PNET[96,104] and melanoma[105] and mutation in other neuroendocrine tumors[98] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy[94]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[106-109] and has been proposed as a distinguishing biomarker[107-109]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[100-103]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation[107]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[110-111].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[112-113]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[95,111,114-115]. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function[116-118]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[112,119]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[120].

GENE
CDKN2A/B

ALTERATION
p16INK4a loss and p14ARF loss exons 2-3

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[121-124]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[125-126], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[127-133]; 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[134-135], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

Putative concurrent homozygous deletion of CDKN2A and CDKN2B was seen in 3/22 (14%) gastrointestinal stromal tumors (GISTs) in the Sarcoma Genome Project dataset[136]. Loss of at least part of chromosomal region 9p21, which contains the CDKN2A/B loci, was reported in 63% of patient GISTs[137]. Loss of expression of p16INK4a has been found in up to 50% of GISTs, and numerous studies have shown that loss of expression of p16INK4a and p14ARF correlates with aggressive disease, worse prognosis, and shorter survival in GIST patients[137-142].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[143-144]. 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[145-146]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[147-148]. One or more alterations observed here are predicted to result in p16INK4a loss of function[149-170]. One or more alterations seen here are predicted to result in p14ARF loss of function[153,170-173].

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[174]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[175-176]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[177-179]. 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[180-182]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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Avapritinib

Assay findings association

KIT
W557_K558del, V654A

AREAS OF THERAPEUTIC USE

Avapritinib is a selective kinase inhibitor of PDGFRA and KIT activating mutations. It is FDA approved for the treatment of unresectable or metastatic gastrointestinal stromal tumor (GIST) that is positive for PDGFRA mutation in exon 18, including the resistance mutation D842V. It is also approved to treat advanced systemic mastocytosis. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective Phase 1 and Phase 2 studies in KIT-mutated GIST[38,183] and systemic mastocytosis (SM)[184-185] , as well as a case report in metastatic vulvar melanoma[186], KIT mutation may predict sensitivity to avapritinib. On the basis of a clinical study in patients with GIST[58], as well as preclinical data[38], KIT V654A or T670I mutations may confer reduced sensitivity to avapritinib.

SUPPORTING DATA

Avapritinib has primarily been studied in the context of PDGFRA- and KIT-mutated GIST[187-188] and KIT-mutated mastocytosis[189-191] . For previously treated patients with GIST and PDGFRA exon 18 mutations, avapritinib treatment was associated with an ORR of 86% (37/43; 3 CRs, 34 PRs) and a clinical benefit rate (CBR) of 95% in the Phase 1 NAVIGATOR trial[188]. A similar cohort treated in the ≥4th-line setting with no approved treatment options achieved an ORR of 22% (24/111; 1 CR, 23 PRs) and duration of response of 10.2 months from avapritinib in this trial; patients with PDGFRA exon 18 mutations other than D842V experienced an ORR of 17%[188].

Regorafenib

Assay findings association

KIT
W557_K558del, V654A

AREAS OF THERAPEUTIC USE

Regorafenib is a small-molecule inhibitor of multiple kinases, including RET, VEGFRs, PDGFRs, KIT, and RAF family proteins. It is FDA approved to treat hepatocellular carcinoma that has been previously treated with sorafenib, metastatic colorectal cancer (CRC), or advanced gastrointestinal stromal tumors (GISTs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in gastrointestinal stromal tumor, activating KIT alterations may confer sensitivity to regorafenib[192]. Preclinical and limited clinical data indicate that secondary imatinib-resistant mutations, including V654A and A-loop alterations at residues D816, D820, N822, and A829, remain sensitive to regorafenib[51,193] . Limited preclinical data has shown that KIT V654A may reduce sensitivity to regorafenib[51].

SUPPORTING DATA

A Phase 2 follow-up study of regorafenib treatment for patients with advanced GIST and a KIT exon 11 mutation reported a longer median PFS (13.4 months) compared to patients with KIT/PDGFRA wild-type, non-SDH-deficient tumors (1.6 months)[194]. Regorafenib is approved in the third line for advanced gastrointestinal stromal tumors (GISTs) based on a Phase 3 randomized study comparing regorafenib to placebo; patients who had progressed on imatinib and sunitinib demonstrated significantly longer median PFS when treated with regorafenib (4.8 vs. 0.9 months)[41]. A Phase 2 study of regorafenib in the second-line setting for patients with imatinib-resistant advanced GIST reported a median PFS of 36.3 weeks[195].

Ripretinib

Assay findings association

KIT
W557_K558del, V654A

AREAS OF THERAPEUTIC USE

Ripretinib is a selective kinase inhibitor of PDGFRA and KIT. It is FDA approved for the treatment of patients with advanced gastrointestinal stromal tumor (GIST). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in KIT-mutated GIST[196] as well as strong preclinical evidence[197], KIT mutation may predict sensitivity to ripretinib.

SUPPORTING DATA

The Phase 3 INVICTUS study comparing ripretinib with placebo for patients with previously treated advanced gastrointestinal stromal tumor (GIST) reported improved median PFS (6.3 vs. 1.0 months, HR=0.15), median OS (15.1 vs. 6.6 months, HR=0.36), and ORR (9.4% vs. 0%)[198]. A Phase 1 study evaluating ripretinib in previously treated GIST also reported ORRs of 24%, 24%, or 9% as second-line, third-line or fourth-or-later-line therapies, respectively[196].

Sunitinib

Assay findings association

KIT
W557_K558del, V654A

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[57,199-203] or KIT-expressing tumors[199,204] , KIT activating alterations may predict sensitivity to sunitinib. On the basis of retrospective analyses[57,205] , case studies[206], and preclinical evidence in GIST[51,57,206] , KIT V654A is predicted to be sensitive to sunitinib.

SUPPORTING DATA

The median time to progression in patients with imatinib-refractory or -intolerant GIST treated with sunitinib was 27.3 weeks, as compared with 6.4 weeks for patients treated with placebo[207]. Patients with imatinib-resistant GIST harboring KIT exon 11 mutations exhibited worse progression-free survival (12.3 months) and clinical benefit rate (34%) than patients with exon 9 mutations (26.9 months; 58%) or wild type KIT (30.5 months; 56%) during treatment with sunitinib in a Phase 1/2 trial[57]. However, these data were from pooled exon 11 mutations, and the presence of secondary mutations may have impaired the response of these patients; KIT V560D was potently inhibited by sunitinib in vitro in the absence of secondary mutations[57].

Imatinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

KIT
W557_K558del, V654A

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[80,208-210] , KIT-amplified[208,210-212] , or KIT-expressing tumors[85,213-219] , KIT activating alterations may confer sensitivity to imatinib. The KIT V654A mutation is predicted to confer resistance to imatinib based on strong clinical evidence in GIST[49-50,53,55,81,220-224] .

SUPPORTING DATA

Clinical studies in GIST have reported that imatinib treatment results in significantly longer recurrence-free survival (RFS) and OS[66,213] . A meta-analysis of imatinib clinical trials suggests that patients with GIST harboring KIT exon 11 mutations respond better to imatinib than those without[225]. Several Phase 3 trials of imatinib, including a 10 -year outcomes study, reported significantly increased OS in patients with GIST harboring KIT exon 11 mutations relative to those with KIT exon 9 mutations[226-227] . A case study has reported a PR and 5-year disease stabilization upon treatment with imatinib in a patient with GIST harboring a PDGFRA exon 12 mutation[228].

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Dasatinib

Assay findings association

KIT
W557_K558del, V654A

AREAS OF THERAPEUTIC USE

Dasatinib is a kinase inhibitor that targets the BCR-ABL fusion protein, SRC family kinase receptors, KIT, EPHA2, and PDGFR-beta. It is FDA approved for the treatment of certain subtypes of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in melanoma[229-230] and preclinical evidence in other cancer types[231-232] , activating KIT alterations may confer sensitivity to dasatinib. Preclinical and limited clinical data indicate that secondary imatinib-resistant mutations, including V654A and A-loop alterations at residues D816, D820, N822, and A829, remain sensitive to dasatinib[232-237] .

SUPPORTING DATA

A Phase 2 trial of dasatinib treatment in patients with kinase inhibitor-naïve gastrointestinal stromal tumors (GIST) reported an overall response rate of 67% (29/43), with 13 complete responses and 16 partial responses[238]. A Phase 2 trial of dasatinib in patients with GIST who were refractory to imatinib and sunitinib reported a partial response rate of 32% (15/47), with 21% (10/47) of patients demonstrating progression-free survival for greater than six months[239]. Preclinical studies of a mouse model of GIST showed that combined treatment with imatinib and dasatinib resulted in the arrest of tumor cell growth and an increase in cell death, and also a decrease in KIT and AKT phosphorylation[240].

Nilotinib

Assay findings association

KIT
W557_K558del, V654A

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[241-245] , KIT-amplified[241], or KIT-expressing tumors[246], KIT activating alterations may confer sensitivity to nilotinib. Additionally, imatinib-resistant KIT mutations such as V654A and A-loop alterations at residues D816, D820, N822, and A829 maintain sensitivity to nilotinib as demonstrated in multiple clinical and preclinical studies[86,233-234,237,243,247-248] .

SUPPORTING DATA

A Phase 3 trial of nilotinib in 240 patients with advanced gastrointestinal stromal tumors (GIST) who had failed prior imatinib and sunitinib treatment showed no significant difference in progression-free survival between nilotinib and best supportive care, but overall survival was increased in nilotinib-treated patients[249]. A Phase 2 study has shown that nilotinib as a single agent third-line therapy (after imatinib and sunitinib treatment) for GIST had an objective response rate of 3% (1/35) and stable disease at six-weeks in 66% (23/35) of patients[250]. A Phase 2 study of nilotinib in patients with GIST resistant to both imatinib and sunitinib reported responses in 10% (5/52) of patients[251]. A Phase 2 clinical trial showed that nilotinib was well tolerated and suggested that it may be particularly useful in treating a subset of GIST with KIT exon 17 mutations[252].

Ponatinib

Assay findings association

KIT
W557_K558del, V654A

AREAS OF THERAPEUTIC USE

Ponatinib is a multikinase inhibitor targeting BCR-ABL, RET, KIT, FLT-3, PDGFRs, VEGFRs, FGFRs, and other tyrosine kinases. It is FDA approved for the treatment of advanced, T315I-mutated chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), as well as for CML and Ph+ ALL patients for whom no other tyrosine kinase inhibitor is indicated. Please see the drug label for full prescribing information.

GENE ASSOCIATION

KIT exon 9 and 11 activating mutations have demonstrated sensitivity to ponatinib in several preclinical cell models[253-258] , with clinical efficacy demonstrated in patients with GIST exhibiting exon 11 mutations[51,259] and imatinib resistance[260]. KIT V654A has been shown to result in decreased sensitivity to ponatinib in a preclinical study[51].

SUPPORTING DATA

Data from a Phase 2 trial in GIST indicated that ponatinib induced a clinical benefit rate (CBR; patients exhibiting complete response, partial response, or stable disease for at least 16 weeks) in 55% of patients with KIT exon 11 mutations compared with a CBR of 27% in patients lacking mutations in exon 11[260]. Ponatinib has also demonstrated robust preclinical activity in patient-derived gastrointestinal stromal tumor (GIST) cell lines against multiple imatinib-resistant KIT mutations, including the gatekeeper residue, T670I, and secondary mutations within the activation loop, including those at residues D816, D820, N822, and A829[51]. Moreover, ponatinib displayed clinical activity in 2 out of 3 patients with refractory GIST, all of whom had been previously treated with, at a minimum, imatinib, sunitinib, and regorafenib[51].

Sorafenib

Assay findings association

KIT
W557_K558del, V654A

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[237,261-267] or KIT-expressing tumors[268-271] , KIT activating alterations may predict sensitivity to sorafenib.

SUPPORTING DATA

Phase 2 studies of sorafenib in patients with gastrointestinal stromal tumors (GIST) previously treated with imatinib and sunitinib have reported partial responses in 10-13% of patients and stable disease in 52-57% of patients[265,272] . A retrospective analysis of sorafenib in 124 patients with GIST previously treated with imatinib and sunitinib reported that 57% (70/124) of patients achieved disease stabilization and 10% (12/124) achieved partial response[273].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

Electronically signed by Naomi Lynn Ferguson, M.D. | 14 September 2021
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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
KIT

ALTERATION
W557_K558del, V654A

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. The KIT V654A mutation is associated with resistance to imatinib and decreased sensitivity to avapritinib, regorafenib, and ponatinib.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03564691

PHASE 1

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

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

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

NCT04633122

PHASE 2

A Study to Assess the Efficacy and Safety of DCC-2618 and Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumors After Treatment With Imatinib

TARGETS
CSF1R, FLT3, KIT, RET, VEGFRs, PDGFRA

LOCATIONS: Beijing (China)

NCT04193553

PHASE 2

Multicentre Placebo-controlled Double-blinded Phase II Study of Lenvatinib Efficacy in Patients With Locally Advanced or Metastatic GIST (Gastrointestinal Stromal Tumor) After Imatinib/Sunitinib Failure

TARGETS
FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Reims (France), Dijon (France), Villejuif (France), Lyon (France), Marseille (France), Saint-Herblain (France), Bordeaux (France)

ORDERED TEST # ORD-1182590-01

CLINICAL TRIALS

NCT04200404

PHASE 1/2

A Study of CS1001 in Subjects With Advanced or Refractory Solid Tumors

TARGETS
BRAF, KIT, RET, VEGFRs, PD-L1

LOCATIONS: Kurralta Park (Australia)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT03475953

PHASE 1/2

A Phase I/II Study of Regorafenib Plus Avelumab in Digestive Tumors

TARGETS
PD-L1, BRAF, KIT, RET, VEGFRs

LOCATIONS: Villejuif (France), Lyon (France), Montpellier (France), Toulouse (France), Brest (France), Bordeaux (France)

NCT04138381

PHASE 1/2

Selinexor in Combination With Imatinib in Patients With Metastatic and/or Unresectable Gastrointestinal Stromal Tumors.

TARGETS
KIT, ABL, XPO1

LOCATIONS: Barcelona (Spain), Zaragoza (Spain), Madrid (Spain), Murcia (Spain), Sevilla (Spain), Tenerife (Spain)

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.

BRCA2 G2901D	***CREBBP*** Q278P	***CSF1R*** T75I	***DAXX*** R117W
DNMT3A G800C	***FANCC*** A325T	***KIT*** Y823H	***MSH3*** A65_A68>P and F203S
NTRK1 R220W	***PDGFRB*** P269S	***TNFAIP3*** I207L and T108A	***ZNF703*** A514del

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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)

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics

of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating

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physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

The median exon coverage for this sample is 303x

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