FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
PE

REPORT DATE
28 Jan 2022
ORDERED TEST #
ORD-1285006-01

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 Lung adenocarcinoma
DATE OF BIRTH 09 February 2001
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN
MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lung
SPECIMEN ID Q21-24405-1
SPECIMEN TYPE Block
DATE OF COLLECTION 28 December 2021
SPECIMEN RECEIVED 14 January 2022

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

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

ROS1 SDC4-ROS1 fusion
CDKN2A/B p16INK4a splice site 151-1G>A and p14ARF splice site 194-1G>A

7 Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET***

† See About the Test in appendix for details.
α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Ceritinib** (p. 6), **Crizotinib** (p. 7), **Entrectinib** (p. 7), **Lorlatinib** (p. 8)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS

***ROS1* -** SDC4-ROS1 fusion

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Ceritinib	2A	Cabozantinib
Crizotinib	2A	
Entrectinib	2A	
Lorlatinib	2A	
Brigatinib		

10 Trials *see p. 10*

☐ *NCCN category*

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

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BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[1-2] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab[3-8] and PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[9-11] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[12-17], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[18-21]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[12]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 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[22]. 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[22-24]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Mutational Burden

RESULT
Cannot Be Determined

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[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-34]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[7,25-26,29-31,35-41]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[42], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[43], has been observed across all TMB levels. As the TMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[44]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[45]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[46-47], several other large studies did find a strong association with increased TMB[48-51]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[52]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[46]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[53]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[53-54].

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[55-56] and cigarette smoke in lung cancer[7,57], treatment with temozolomide-based chemotherapy in glioma[58-59], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[60-64], and microsatellite instability (MSI)[60,63-64]. Elevated TMB has been reported to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[26-28,65]. However, the TMB level in this sample could not be determined with confidence.

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GENE
ROS1

ALTERATION
SDC4-ROS1 fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The ROS1 TKIs crizotinib[66], entrectinib[67], ceritinib[68], and lorlatinib[69-70] have shown significant clinical activity for patients with ROS1-rearranged non-small cell lung cancer (NSCLC). Treatment with brigatinib[71], repotrectinib[72], cabozantinib[73-76], or taletrectinib[77-78] has resulted in clinical benefit for patients with ROS1-rearranged NSCLC that developed resistance to crizotinib or ceritinib. The Phase 1/2 TRIDENT-1 study of repotrectinib reported ORRs of 91% (10/11; Phase 1) and 86% (6/7; Phase 2) for patients who are tyrosine kinase inhibitor (TKI) naive with ROS1-rearranged non-small cell lung cancer (NSCLC); for patients who are TKI pretreated, the ORRs were 28% (5/18; Phase 1) and 50% (11/22; Phase 2)[79-80] . The Phase 2 TRUST study of taletrectinib reported ORRs of 87% (13/15) and 60% (3/5) for patients who are crizotinib naive and patients who have been pretreated with crizotinib with ROS1-rearranged NSCLC, respectively[81]. Two Phase 1 studies reported ORRs of 58% (7/12) and 33% (2/6) for patients with ROS1-rearranged NSCLC, respectively[77-78].

FREQUENCY & PROGNOSIS

ROS1 rearrangements or fusions have been reported in 1-2% of non-small cell lung carcinoma (NSCLC) tumors[82-85], including in 1-3.4% of lung adenocarcinoma cases[84,86-89]. CD74-ROS1 fusions accounted for 23% (3/13) to 27% (5/18) of the ROS1 rearrangements identified in two studies of lung cancer[83,87]. Elevated ROS1 protein levels have been observed in 22% of NSCLC samples evaluated in one study[90]. A study of 1,137 patients with lung adenocarcinoma showed that Stage 4 patients with ROS1 rearrangement had significantly better overall survival (OS) compared to other genetically defined Stage 4 subgroups, with an estimated mean OS of 5.3 years for patients who were treated with chemotherapy and crizotinib[85]. Positive kinase fusion status (ALK, ROS1, or RET) was associated with improved prognosis in lung adenocarcinoma, independently of other prognostic factors[83], although never-smokers with surgically resected lung adenocarcinoma and ALK or ROS1 fusion had significantly shorter disease-free survival (hazard ratio, 2.11)[89]. A study of 208 never-smokers observed an improved objective response rate and longer median progression-free survival (PFS) for ROS-fusion-positive patients treated with pemetrexed but a reduced PFS for ROS1-positive patients treated with EGFR-targeted kinase inhibitors[88].

FINDING SUMMARY

The ROS1 oncogene encodes a tyrosine kinase of the insulin receptor family that plays a role in regulating cellular growth and differentiation by activating several signaling pathways, including those involving mitogen-activated protein kinase ERK1/2, phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), STAT3, and VAV3[91]. ROS1 fusions involving a 5' partner joined with the 3' kinase domain (exons 36-42) of ROS1 have been characterized as activating and oncogenic[82-84,87,91-96] and clinically sensitive to ROS1-targeted therapies[67,70,97-99]. Rearrangements, such as observed here, are predicted to be activating and oncogenic.

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GENE
CDKN2A/B

ALTERATION
p16INK4a splice site 151-1G>A and p14ARF splice site 194-1G>A

TRANSCRIPT ID
NM_000077

CODING SEQUENCE EFFECT
151-1G>A

VARIANT ALLELE FREQUENCY (% VAF)
7.6%

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[100-103]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[104-105], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[106-112]; 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[113-114], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[115]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[116]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[116-122]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[119,123-125].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[126-127]. 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[118,128]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[129-130]. One or more alterations observed here are predicted to result in p16INK4a loss of function[131-152]. One or more alterations seen here are predicted to result in p14ARF loss of function[135,152-155].

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[156]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[157-158]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[159-161]. 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[162-164]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

Brigatinib

Assay findings association

ROS1
SDC4-ROS1 fusion

AREAS OF THERAPEUTIC USE

Brigatinib is a kinase inhibitor that targets ALK, ROS1, and mutant EGFR and is FDA approved to treat patients with metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical responses in patients with ROS1-fusion-positive NSCLC[71,165] and strong preclinical evidence[166-167] , ROS1 rearrangements may predict sensitivity to brigatinib.

SUPPORTING DATA

Brigatinib has been studied primarily for the treatment of ALK-rearranged NSCLC[168-170] . Brigatinib was associated with an ORR of 17% (3/18 patients) in other solid tumors with ALK/ROS1/EGFR alterations[71]. A patient with ROS1-rearranged non-small cell lung cancer (NSCLC) that had previously progressed on crizotinib and then ceritinib exhibited a PR following treatment with brigatinib[165]. In another study for 3 patients with NSCLC and ROS1 rearrangements treated with brigatinib, 2 previously treated with crizotinib experienced SD and PD, whereas the single patient who was crizotinib-naive experienced a PR lasting >21 months[71]. A case study of 4 patients with ROS1-rearranged NSCLC who had progressed on crizotinib reported a 25% (1/4) ORR[171].

Ceritinib

Assay findings association

ROS1
SDC4-ROS1 fusion

AREAS OF THERAPEUTIC USE

Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is FDA approved to treat metastatic non-small cell lung cancer (NSCLC) in patients whose tumors are positive for ALK rearrangements, as detected by an FDA-approved test. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of Phase 2 clinical studies demonstrating benefit to patients with ROS1-rearranged NSCLC[68,172] , ROS1 rearrangements may predict sensitivity to ceritinib.

SUPPORTING DATA

Ceritinib has been shown to confer clinical benefit in patients with ALK/ROS1-rearranged NSCLC[68,173] . In a Phase 2 study for patients with advanced ROS1-rearranged NSCLC, ceritinib achieved an ORR of 67% (20/30) and a median progression-free survival of 19.3 months for crizotinib-naive patients[68]. The median OS among all patients was 24 months, and 5/8 (63%) patients with brain metastases experienced intracranial disease control[68]. Another Phase 2 study of ceritinib treatment in ALK- or ROS1-rearranged advanced lung adenocarcinoma reported confirmed PRs in 73% (19/26) of patients, a DCR of 92% (24/26), and a median PFS of 14.4 months[172]. In patients with ROS1-rearranged NSCLC that have progressed on crizotinib, the clinical evidence for ceritinib is limited and mixed[68,174-175] . Among the two patients previously treated with crizotinib included in a Phase 2 study of ceritinib, neither responded to treatment[68]; however, in a separate case study, a patient with ROS1-rearranged NSCLC that progressed on crizotinib was treated with ceritinib and exhibited a PR for 8 months before a pause due to toxicity followed by an additional 17 months of clinical benefit when ceritinib was resumed[165,175] .

Crizotinib

Assay findings association

ROS1
SDC4-ROS1 fusion

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Crizotinib has shown clinical and preclinical evidence of activity in ROS1-rearranged NSCLC[66,84-85,87,98-99,176-181] and IMT[96].

SUPPORTING DATA

Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[81,182-185] , ROS1 rearrangements[85,98-99,186-187] , an NTRK1 fusion[188], or MET activation[189-205] . The Phase 2 METROS trial for pretreated patients with ROS1-rearranged NSCLC treated with crizotinib reported an ORR of 65% (n=26; 1 CR, 16 PRs, 6 SDs), and with median follow-up of 21 months, median PFS was 22.8 months and median OS was not reached[206]. Similarly, the Phase 1 PROFILE 1001 trial for patients with ROS1-rearranged NSCLC treated with crizotinib reported an ORR of 72% (n= 53; 6 CRs, 32 PRs and 10 SD)[66]. High ORR to crizotinib in ROS1-rearranged NSCLC is observed in other studies[186-187] . In the AcSé trial, patients with ROS1-translocated NSCLC treated with crizotinib achieved an ORR of 67.6% (1 CR and 24 PRs) and a DCR of 86% (32/37) with a median PFS and OS of 5.5 months and 17.2 months, respectively[186]. In retrospective studies, crizotinib therapy was associated with an ORR of 80% (24/30) or higher (5/5) and a median PFS of 9.1 months for patients with ROS1-rearranged advanced lung adenocarcinoma[85,99] .

Entrectinib

Assay findings association

ROS1
SDC4-ROS1 fusion

AREAS OF THERAPEUTIC USE

Entrectinib is a TKI that targets TRKA/B/C (NTRK1/2/3), ROS1, and ALK. It is FDA approved to treat adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) and adult and pediatric patients with NTRK fusion-positive solid tumors that lack a known acquired resistance mutation and are metastatic or likely to result in severe morbidity after surgical resection, have no satisfactory alternative treatments, or have progressed following treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[67,207-209] and clinical benefit in other solid tumor types[210-213] , ROS1 fusions may predict sensitivity to entrectinib.

SUPPORTING DATA

Combined analysis of Phase 1 and Phase 2 trials of entrectinib in ROS1-inhibitor-naive NSCLC with ROS1 gene fusion with and without CNS metastases reported an ORR of 77.4% (41/53, 3 CRs), a median response duration of 24.6 months, and a median PFS of 19.0 months[214]. The ORR was similar for patients with (73.9%, 17/23) and without (80.0%, 24/30) CNS disease at baseline, and the intracranial ORR was 55.0% (11/20)[214]. A real-world study in ROS1-rearranged NSCLC reported median PFS of 19.0 and 8.5 months to entrectinib and crizotinib, respectively[207]. Clinical benefit with entrectinib monotherapy has been achieved for adult and pediatric patients with various solid tumors with and without CNS metastases and with NTRK, ROS1, or ALK fusions[67,207-210,215] , and preclinical sensitivity has been observed in NTRK fusion-positive AML cell lines[216]. In a Phase 1 trial, responses were restricted to patients harboring NTRK, ROS1, or ALK rearrangements, with the exception of ALK-mutant neuroblastoma, and were observed for patients with ALK or ROS1 rearrangements who had not received prior ALK TKI or crizotinib, respectively[67].

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Lorlatinib

Assay findings association

ROS1
SDC4-ROS1 fusion

AREAS OF THERAPEUTIC USE

Lorlatinib is a tyrosine kinase inhibitor that targets ALK and ROS1. It is FDA approved to treat patients with ALK-positive metastatic non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[69-70,217-220] and preclinical[220-222] evidence, ROS1 activation may predict sensitivity to lorlatinib.

SUPPORTING DATA

Lorlatinib has primarily been investigated for ALK- and ROS1-positive NSCLC as an approach to overcome resistance to prior TKIs[69,223] . A Phase 1 study evaluating lorlatinib for the treatment of NSCLC reported an ORR of 50% (6/12) and a median duration of response (mDOR) of 12 months for ROS1-positive patients[69]. In the follow-up Phase 2 trial, patients who were crizotinib-naive and -treated achieved ORRs of 62% (13/21; 2 CRs, 11 PRs) and 35% (14/40; 2 CRs, 12 PRs) and a mPFS of 21 and 8.5 months, respectively; intracranial (IC) activity was seen irrespective of prior treatment, with crizotinib-naive and -treated patients achieving an IC-ORR of 64% (7/11; 5 CRs, 2 PRs) and 50% (12/24; 9 CRs, 3 PRs), respectively[70]. In case studies, a patient with metastatic NSCLC harboring an EZR–ROS1 fusion and S1986Y/F dual mutations responded to lorlatinib[220], and a patient with lung adenocarcinoma and EZR-ROS1 fusion experienced a PR from second-line crizotinib and an ongoing reduction in serum CEA from third-line lorlatinib[218].

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Cabozantinib

Assay findings association

ROS1
SDC4-ROS1 fusion

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Cabozantinib has shown clinical efficacy in ROS1-rearranged NSCLC after disease progression on at least one prior ROS1 TKI[73-76,224] and preclinical activity in wild-type and mutant ROS1-fusion cell lines[73-74,166,225] .

SUPPORTING DATA

A Phase 2 study of cabozantinib for ROS1-rearranged lung adenocarcinoma previously treated with at least 1 ROS1 TKI reported 1 PR lasting 9.1 months until resistance due to an emergent MET D1228N mutation, 1 unconfirmed PR, and 4 SDs[224]. Other case studies of patients with ROS1-rearranged NSCLC previously treated with at least 1 ROS1 TKI have reported 4 PRs[73-76] , 3 SDs (duration of 2.2–7.4 months)[75], and 1 PD[226]. A Phase 2 randomized discontinuation trial of cabozantinib reported a 10.0% (6/60) ORR and a 58.3% (35/60) DCR, with median PFS of 4.2 months, for patients with genomically unselected, heavily pretreated NSCLC[227]. Patients with EGFR wild-type non-squamous NSCLC who had progressed after previous treatment experienced longer median PFS with cabozantinib alone or combined with erlotinib (4.3 and 4.7 months, HR=0.39 and 0.37, respectively) compared with single agent erlotinib (1.8 months) in a randomized Phase 2 trial[228]. A Phase 1 study of cabozantinib for advanced solid tumors reported an ORR of 20.0% (4/20; 4 PRs, all in EGFR-mutated tumors) and DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[229].

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

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ORDERED TEST # ORD-1285006-01

CLINICAL TRIALS

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
ROS1

RATIONALE
Activating ROS1 fusions may predict sensitivity to inhibitors of ROS1.

ALTERATION
SDC4-ROS1 fusion

NCT03178552

PHASE 2/3

A Study to Evaluate Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)

TARGETS
ALK, RET, MEK, PD-L1, BRAF, TRKB, TRKC, ROS1, TRKA

LOCATIONS: San Isidro (Peru), Lima (Peru), La Rioja (Argentina), Panama City (Panama), Recoleta (Chile), San Jose (Costa Rica), Ijui (Brazil), Buenos Aires (Argentina), Porto Alegre (Brazil), Sao Paulo (Brazil)

NCT03155620

PHASE 2

Pediatric MATCH: Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Advanced Refractory Solid Tumors or Lymphomas

TARGETS
TRKC, TRKA, TRKB, FGFRs, EZH2, mTOR, PI3K, MEK, AXL, ROS1, ALK, MET, ABL, BRAF, PARP, Farnesyl transferase, CDK4, CDK6, ERK2, ERK1, RET

LOCATIONS: San Juan (Puerto Rico), Florida

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

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Pennsylvania, Indiana

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Florida, Louisiana, Texas

NCT03093116

PHASE 1/2

A Study of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements

TARGETS
TRKA, ALK, ROS1, TRKB, TRKC

LOCATIONS: Florida, Georgia, Texas, Virginia, District of Columbia, Maryland, Pennsylvania

NCT04310007

PHASE 2

Testing the Addition of the Pill Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer

TARGETS
MET, ROS1, RET, VEGFRs, PD-1

LOCATIONS: Florida, Louisiana, Georgia, South Carolina, Alabama, Texas, North Carolina

NCT02795156

PHASE 2

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

TARGETS
BRAF, VEGFRs, RET, KIT, EGFR, ERBB4, ERBB2, MET, ROS1

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, PD-L1, ERBB2, PI3K-alpha, RET, AKTs

LOCATIONS: Florida, Louisiana, Tennessee, Texas, New Jersey, Missouri

NCT02568267

PHASE 2

Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA

LOCATIONS: Florida, Texas, North Carolina, Virginia, Maryland, Ohio, New York

NCT04302025

PHASE 2

A Study of Alectinib, Entrectinib, Vemurafenib Plus Cobimetinib, or Pralsetinib in Patients With Resectable Stages II-III Non-Small Cell Lung Cancer With ALK, ROS1, NTRK, BRAF V600, or RET Molecular Alterations

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, MEK, BRAF, RET

LOCATIONS: Florida, Tennessee, District of Columbia, Missouri, New York, Ohio, Massachusetts, Michigan, California

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ALK
N941S

FANCG
P385T

SMARCA4
E882Q

Electronically signed by Erik Williams, M.D. | 28 January 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

Electronically signed by Erik Williams, M.D. | 28 January 2022
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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

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

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

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cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

MR Suite Version 5.2.0

The median exon coverage for this sample is 970x

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