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 Thyroid medullary carcinoma

DATE OF BIRTH 11 January 1959
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Lymph Node
SPECIMEN ID Q18-10176-14
SPECIMEN TYPE Block
DATE OF COLLECTION 15 December 2018
SPECIMEN RECEIVED 15 July 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 8 Muts/Mb

Genomic Findings

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

RET A883F

7 Therapies with Clinical Benefit
0 Therapies with Lack of Response
10 Clinical Trials

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 8 Muts/Mb

GENOMIC FINDINGS

***RET* -** A883F

10 Trials *see p. 8*

ACTIONABILITY

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)	
Cabozantinib	1	Lenvatinib	2A
Vandetanib	1	Sorafenib	2A
Pralsetinib	2A	Sunitinib	2A
Selpercatinib	2A		

NCCN category

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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 has been reported in 17-65% (n = 17-76) of thyroid cancer cases[6-9]. One study reported MSI positivity in 84% (59/70) of papillary thyroid carcinoma (PTC) cases, with 64% (38/59) being MSI-H and 46% (21/59) being MSI-low (MSI-L), and MSI positivity in 92% (11/12) of follicular thyroid carcinoma (FTC) cases, with 82% (9/11) being MSI-H and 18% (2/11) being MSI-L; MSI-H was not observed in benign thyroid samples[10]. MSI was significantly associated with low risk characteristics in patients with malignant thyroid tumors[9], and MSI positivity at one or more marker sites was significantly associated with improved survival in patients with thyroid cancer[8]. One study reported an increased incidence of MSI in pediatric and adult patients with radiation-associated thyroid cancer, as compared with spontaneous thyroid carcinomas without radiation history[11].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[12]. 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[12-14]. 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[15-17]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[12,14,16-17].

BIOMARKER

Tumor Mutational Burden

RESULT
8 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[18-20], anti-PD-1 therapies[18-21], and combination nivolumab and ipilimumab[22-27]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[18-21,28]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[18]. 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[29] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[19]. 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[21,28]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Median TMB is relatively low in thyroid carcinomas, with 1.8 mutations per megabase (muts/Mb) reported in papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and medullary thyroid carcinoma (MTC) and 2.5 muts/Mb reported in anaplastic thyroid carcinoma (ATC)[30]. High TMB (>20 muts/Mb) has been reported in 1% of MTCs and 1.4% of ATCs, but not in any of the PTCs or FTCs analyzed[30]. A whole exome study of 39 follicular thyroid carcinoma tissue samples reported a worse prognosis for those with higher mutational burden (hazard ration 1.4, p=0.02), independent of histopathological classification[31].

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[32-33] and cigarette smoke in lung cancer[34-35], treatment with temozolomide-based chemotherapy in glioma[36-37], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[38-42], and microsatellite instability (MSI)[38,41-42]. 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[19-20,28].

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GENE
RET

ALTERATION
A883F

TRANSCRIPT ID
NM_020975

CODING SEQUENCE EFFECT
2647_2648GC>TT

VARIANT ALLELE FREQUENCY (% VAF)
39.5%

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, RET activating alterations may predict response to selective RET inhibitors such as pralsetinib[43-45] and selpercatinib[46-47] and the multikinase inhibitors cabozantinib[48-55], lenvatinib[56], sorafenib[57], sunitinib[57-58], and vandetanib[59-65]. It is notable that tumor markers commonly evaluated in patients with MTC, including calcitonin levels and tumor dimensions, have been seen to fluctuate considerably in response to treatment with RET inhibitors in patients with MTC, but these fluctuations do not seem to correlate with the overall, longer-term response to therapy[66]. In the context of RET mutation, these therapies have primarily been investigated for the treatment of patients with medullary thyroid carcinoma (MTC) where pralsetinib[45,67] , selpercatinib[47], cabozantinib[51,55,68], lenvatinib[69], sorafenib[70], sunitinib[71], and vandetanib[64] were reported to achieve clinical benefit. However, small studies of lenvatinib showed no significant difference in efficacy between patients with RET-mutated and RET-wild-type MTC[56] or melanoma[72]. In a Phase 1/1b study of RXDX-105 for advanced solid tumors, a patient with MTC harboring RET M918T experienced an ongoing PR[73]. Preclinical studies have shown that RET mutation may confer sensitivity to ponatinib[74-75].

FREQUENCY & PROGNOSIS

RET mutations have been reported in 45-88% of MTCs (COSMIC, Feb 2021)[76-78]. MTC is more commonly sporadic (80% of cases) as opposed to being associated with the inherited MEN2 syndrome[79]. In sporadic MTC, M918T is the most commonly identified RET mutation, accounting for 70-79% of RET-altered cases[76-77]. RET mutations are adverse prognostic markers in patients with medullary thyroid cancer (NCCN Thyroid Carcinoma Guidelines, v1.2021). RET mutation has been associated with a more aggressive clinical course in patients with sporadic MTC[76]. In one study, the 10-year survival rate was 56% for patients with RET M918T-positive tumors compared to 87% for those without M918T mutation, although the presence of the RET alterations was not determined in this study[80]. In contrast, RET M918T and A883F mutations were associated with multifocal disease and higher prevalence of lymph node metastases in another study of MTC, but presence or absence of any RET mutation was not associated with any differences in survival[81].

FINDING SUMMARY

RET (Rearranged during transfection) encodes a receptor tyrosine kinase primarily expressed in cells of the nervous system. It has been identified as a proto-oncogene that results in transformation of cells upon recombination with a partner gene[82]. The RET A883F activating mutation has been associated with the inherited disorder multiple endocrine neoplasia type 2B (MEN2B) syndrome and, when present as a germline alteration, this mutation is considered to confer a high risk for medullary thyroid cancer (MTC)[83-84]. Reports suggest that the A883F mutation may be associated with less aggressive MTC as compared with the common RET M918T mutation[83].

POTENTIAL DIAGNOSTIC IMPLICATIONS

RET mutations, particularly those at codons 634, 883, and 918, are a hallmark of medullary thyroid cancer (NCCN Thyroid Carcinoma Guidelines, v1.2021).

POTENTIAL GERMLINE IMPLICATIONS

Activating heterozygous germline mutations in RET may be associated with multiple endocrine neoplasia type 2 (MEN2), an uncommon autosomal dominant disorder with an estimated prevalence of 1:30,000-1:200,000[85-88]. MEN2 is comprised of 3 subtypes, MEN2A, MEN2B and familial medullary thyroid carcinoma (FMTC). Additionally, inactivating germline mutations of RET have been associated with Hirschsprung disease, which has an estimated prevalence of 1:5,000-1:10,000[89-90]. Subtypes of MEN2 and Hirschsprung disease may result in medullary thyroid cancer (MTC), pheochromocytomas, neuroganglionomas, and other tumors[91]. Therefore, in the appropriate clinical context, germline testing of RET is recommended.

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Cabozantinib

Assay findings association

RET
A883F

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved to treat patients with advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) after prior treatment with sorafenib, or progressive, metastatic medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

RET activating mutations may predict sensitivity to cabozantinib. In a Phase 3 study for patients with medullary thyroid carcinoma (MTC), median progression-free survival (PFS) on cabozantinib was longer for patients with RET mutation than for patients with wild-type RET (60 weeks vs. 25 weeks, p=0.0001)[51,92].

SUPPORTING DATA

In the randomized Phase 3 EXAM study for patients with advanced medullary thyroid cancer (MTC), cabozantinib was associated with improved PFS compared with placebo (11.2 vs. 4.0 months, HR=0.28) and a higher ORR (28% vs. 0%), with PFS improvement observed regardless of RET mutation status[51]. EXAM patients with RET M918T-mutated tumors displayed improved OS with cabozantinib over placebo (44.3 vs. 18.9 months, HR=0.60); OS benefit was not observed for patients without RET M918T mutation (20.2 vs. 21.5 months, HR=1.12)[68]. For patients with radioiodine-refractory differentiated thyroid carcinoma, Phase 2 studies have reported ORRs of 62.9% (22/35) for first-line cabozantinib[93] and 40.0% (10/25) as salvage therapy following other VEGFR-targeted therapies[94]. A Phase 1 study of cabozantinib for relapsed/refractory solid tumors, primarily MTC, reported an ORR of 28.6% (10/35) for patients with MTC and an SD for the single patient with papillary thyroid carcinoma included in the cohort[95].

Pralsetinib

Assay findings association

RET
A883F

AREAS OF THERAPEUTIC USE

Pralsetinib is a RET inhibitor that is FDA approved to treat adult patients with RET fusion-positive non-small cell lung cancer (NSCLC) and adult and pediatric patients with RET fusion-positive thyroid cancer or RET-mutated medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of a Phase 1/2 study in RET-mutated medullary thyroid carcinoma[96], RET mutations may predict sensitivity to pralsetinib.

SUPPORTING DATA

In the Phase 1/2 ARROW study, patients with RET-mutated medullary thyroid cancer (MTC) treated with the recommended Phase 2 dose of pralsetinib exhibited a 71% (15/21) ORR and 100% (21/21) DCR in the first-line setting, and a 60% (33/55) ORR and 93% (51/55) DCR in the previously treated setting; neither median duration of response nor median PFS were reached in either setting[96]. The 1-year PFS and OS rates were estimated to be 81% and 91% for treatment-naive patients and 75% and 89% for previously treated patients, respectively[96]. Pralsetinib has demonstrated clinical benefit in patients with various tumor types harboring RET rearrangements[43-44] , as well as in patients with RET-mutated medullary thyroid carcinoma (MTC)[96].

Selpercatinib

Assay findings association

RET
A883F

AREAS OF THERAPEUTIC USE

Selpercatinib is a RET inhibitor that is FDA approved to treat adult patients with RET fusion-positive non-small cell lung cancer (NSCLC) and adult and pediatric patients with RET fusion-positive thyroid cancer or RET-mutated medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of a Phase 1/2 study in RET-mutated MTC[97], RET mutations may predict sensitivity to selpercatinib.

SUPPORTING DATA

Selpercatinib has demonstrated activity for patients with various tumor types harboring RET rearrangements[97-100] , and in RET-mutated medullary thyroid cancer[47]. In the Phase 1/2 LIBRETTO-001 study of selpercatinib, patients with RET-mutated MTC naive to cabozantinib or vandetanib exhibited an ORR of 73% (64/88, 10 CRs), median duration of response (DOR) of 22.0 months, and 1-year PFS rate of 92%, whereas those who had previously progressed on cabozantinib and/or vandetanib exhibited an ORR of 69% (38/55, 5 CRs), unreached median DOR, and 1-year PFS rate of 82%[97].

Vandetanib

Assay findings association

RET
A883F

AREAS OF THERAPEUTIC USE

Vandetanib is a multikinase inhibitor that targets RET, VEGFRs, SRC family kinases, and EGFR. It is FDA approved for the treatment of medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

RET activating alterations may predict sensitivity to vandetanib[52,59-60,64,101-103] . Retrospective analysis of a Phase 3 trial evaluating vandetanib for patients with locally advanced or metastatic sporadic medullary thyroid cancer reported a higher ORR for patients with RET M918T mutation (54.5% mutation-positive vs. 30.9% mutation-negative)[64].

SUPPORTING DATA

Vandetanib has been studied most extensively for treatment of MTC. In a Phase 3 study of patients with advanced MTC, progression-free survival was prolonged by 12 months in patients treated with vandetanib compared with placebo[64]. A study of children and adolescents with MEN2B-associated MTC reported partial response in 62.5% (10/16) and stable disease in 37.5% (6/16) of patients with germline RET M918T mutations; in these patients, the median progression-free survival was 6.7 years and the 5- and 7-year overall survival was 88.2% and 72.3%, respectively[103-104] . One patient with RET M918T-positive MTC and acquired resistance to vandetanib achieved a 25% tumor volume reduction for 8 months when everolimus was added to continued vandetanib treatment[77].

Lenvatinib

Assay findings association

RET
A883F

AREAS OF THERAPEUTIC USE

Lenvatinib is a TKI that targets several kinases, including the VEGFRs, FGFRs, PDGFRs, RET, and KIT. It is FDA approved to treat differentiated thyroid cancer (DTC) and hepatocellular carcinoma (HCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating RET mutations or fusions may predict sensitivity to lenvatinib[105-107] . Lenvatinib benefited patients with medullary thyroid carcinoma and RET mutations (6 PR, 8 SD, 1 PD), as well as patients without detected RET mutations (3 PR, 2 SD, 2 PD), with a trend for higher PFS in patients with RET mutations[69].

SUPPORTING DATA

In the Phase 3 SELECT trial, which enrolled patients with iodine-131-refractory, differentiated thyroid carcinoma (RR-DTC), lenvatinib treatment increased progression-free survival (PFS; 19.4 vs. 3.7 months), objective response rates (ORRs; 64.8% vs. 1.2%) and duration of response (30.0 vs. 14.7 months), compared with the placebo arm; 2 patients have ongoing responses after 46-48 months[108-109]. No differences in ORRs to lenvatinib were observed for patients with RR-DTC who had received prior VEGF-targeting therapy (59%, 10/17) as compared to those who were treatment-naive (46%, 19/41)[110]. PFS following lenvatinib treatment was similar for European (18.7 months)[111] and North American (18.3 months)[112] patients with RR-DTC as for those in the collective international cohort (18.3 months)[109]. In a subgroup analysis comparing outcomes for patients with follicular thyroid carcinoma (FTC) versus papillary thyroid carcinoma (PTC), PFS for those with PTC was 16.4 months, whereas PFS was not yet achieved for those with FTC[113]. A Phase 2 trial of lenvatinib for the treatment of advanced thyroid carcinoma reported ORRs of 68% (17/25), 22% (2/9), and 24% (4/17); median PFS of 25.8, 9.2, and 7.4 months; and median OS of 31.8, 12.1, and 10.6 months for patients with RR-DTC, medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC), respectively[93]. In a Phase 2 study of lenvatinib for MTC, 36% (21/59) of patients achieved PRs, and 29% (17/59) achieved durable stable disease (SD) lasting 23 weeks or longer[56]; similar rates of PR (3 out of 6) and SD (2 out of 6) were reported for MTC in a Phase 1 study of lenvatinib for patients with solid tumors[114]. Lenvatinib benefited patients with MTC and RET mutations (6 PR, 8 SD, 1 PD) as well as patients without detected RET mutations (3 PR, 2 SD, 2 PD), with a trend for higher PFS in patients with RET mutations[69]; 2 patients with MTC and dual PIK3CA and RET mutations experienced PRs in response to lenvatinib[56]. A case study of 3 patients with ATC reported durable (7-30 months) clinical benefit in response to lenvatinib[115].

Sorafenib

Assay findings association

RET
A883F

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

RET activating alterations may predict sensitivity to sorafenib[57,70,116-120] . A study of sorafenib for the treatment of patients with medullary thyroid carcinoma reported 1 PR and 9 SDs in 10 cases with sporadic RET mutation and 1 PR and 4 SDs in 5 patients with germline RET mutation[70].

SUPPORTING DATA

Sorafenib is approved to treat locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI) treatment based on the Phase 3 DECISION trial that showed an improvement in progression-free survival (PFS) for patients treated with sorafenib relative to those receiving placebo (10.8 months vs. 5.8 months)[121]. Meta-analyses of clinical trials evaluating sorafenib in patients with DTC and medullary thyroid carcinoma (MTC) have shown clinical benefit in the majority of patients; however, high rates of adverse events leading to either dose reduction or discontinuation have also been noted[122-125] . Phase 2 trials evaluating sorafenib have reported a 71% (29/41) disease control rate (DCR) and a median PFS of 15 months in patients with metastatic papillary thyroid carcinoma[126] and a 77% (23/30) DCR and a median PFS of 19.8 months in a cohort primarily composed of patients with RAI-refractory DTC (27/30)[127]. For patients with MTC, response rates to treatment with sorafenib have ranged from 6 to 47%[70,122,128-129] . Post hoc analysis of a Phase 2 study evaluating sorafenib in 10 patients with recurrent sporadic MTC reported 1 (10%) durable partial response and a median PFS of 17.9 months[70]. A Phase 2 clinical study reported durable partial responses in 10% (2/20) and stable disease in 25% (5/20) of patients with anaplastic thyroid carcinoma treated with sorafenib; the overall median PFS and OS were 1.9 months and 3.9 months, respectively[130].

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Sunitinib

Assay findings association

RET
A883F

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

RET activating alterations may predict sensitivity to sunitinib[52,58,71,117,131] . A Phase 2 study of sunitinib for the treatment of patients with medullary thyroid carcinoma reported PR or SD >24 weeks in 78% (7/9) of cases harboring RET M918T and a 1-year PFS probability of 88%[71]. Treatment of a patient with pheochromocytoma harboring a RET germline mutation with sunitinib resulted in a PR that was ongoing at 7 years[132].

SUPPORTING DATA

A Phase 2 study of sunitinib in patients with medullary thyroid cancer (MTC) or well-differentiated thyroid cancer reported a 31% objective response rate (ORR) in 33 evaluable patients, including 1 complete response, 10 partial responses (PRs), and 16 patients experiencing stable disease (SD)[133]. Another study of sunitinib in patients with advanced thyroid epithelial cancer showed PRs in 56% (5/9) and 67% (6/9) of patients at 3 and 6 months, respectively[134]. In a Phase 1 study of patients with advanced solid tumors treated with a combination of bortezomib and sunitinib, a clinical benefit rate of 30% was reported for the 30 evaluable patients; anticancer activity was frequently observed in patients with thyroid cancer, and 6 patients with thyroid cancer achieved PRs or SD[135].

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-1144481-01

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
RET

ALTERATION
A883F

RATIONALE
RET amplification, activating mutations, or activating fusions may confer sensitivity to kinase inhibitors targeting RET.

NCT04211337

PHASE 3

A Study of Selpercatinib (LY3527723) in Participants With RET-Mutant Medullary Thyroid Cancer

TARGETS
MET, RET, ROS1, VEGFRs, EGFR, SRC

LOCATIONS: Londrina (Brazil), Barretos (Brazil), Ribeirão Preto (Brazil), Porto Alegre (Brazil), Campinas (Brazil), São Paulo (Brazil), Sao Paulo (Brazil), Sao Paolo (Brazil), Rio de Janeiro (Brazil), Rio De Janeiro (Brazil)

NCT03037385

PHASE 1/2

Phase 1 Study of BLU-667 in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer, and Other Advanced Solid Tumors

TARGETS
RET

LOCATIONS: Florida, Texas, District of Columbia, Maryland, Pennsylvania, Missouri

NCT03157128

PHASE 1/2

Phase 1 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET-Fusion Lung Cancer and Medullary Thyroid Cancer

TARGETS
RET

LOCATIONS: Florida, Bordeaux (France), Louisiana, Texas, Georgia, North Carolina, Tennessee, Virginia

NCT04079712

PHASE 2

Testing the Combination of XL184 (Cabozantinib), Nivolumab, and Ipilimumab for Poorly Differentiated Neuroendocrine Tumors

TARGETS
PD-1, CTLA-4, MET, RET, ROS1, VEGFRs

LOCATIONS: Florida, Alabama, North Carolina, Tennessee, Virginia, Kentucky, District of Columbia

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

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NCT04759911

PHASE 2

Selpercatinib Before Surgery for the Treatment of RET-Altered Thyroid Cancer

TARGETS
RET

LOCATIONS: Texas

NCT04197310

PHASE 2

Cabozantinib and Nivolumab for Carcinoid Tumors

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

LOCATIONS: Massachusetts

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

NCT04400474

PHASE 2

Trial of Cabozantinib Plus Atezolizumab in Advanced and Progressive Neoplasms of the Endocrine System. The CABATEN Study

TARGETS
PD-L1, MET, RET, ROS1, VEGFRs

LOCATIONS: Tenerife (Spain), Sevilla (Spain), Málaga (Spain), Oviedo (Spain), Madrid (Spain), Santander (Spain), Murcia (Spain), Alicante (Spain), Zaragoza (Spain), L'Hospitalet de Llobregat (Spain)

NCT04116541

PHASE 2

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

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

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

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.

ATM F763L	***CEBPA*** G223S	***FH*** P18L	***HNF1A*** P379R
IDH2 A395V	***IRS2*** G1263V	***MST1R*** T1261I	***NBN*** E471G
NOTCH3 P2209L	***RNF43*** L647P	***ROS1*** V546F	***TSC1*** K587R

Electronically signed by Claire Edgerly, M.D. | 20 July 2021
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FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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.

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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

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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 4.2.0

The median exon coverage for this sample is 1,049x

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