FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Kan, Tan	Unknown primary melanoma	10 Jul 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1665269-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Unknown primary melanoma
NAME Kan, Tan
DATE OF BIRTH 12 August 1959
SEX Male
MEDICAL RECORD # 44543966

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Adrenal Gland
SPECIMEN ID S111-37085B (PF23086)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 20 September 2022
SPECIMEN RECEIVED 30 June 2023

Biomarker Findings

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

Genomic Findings

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

NRAS Q61R
FBXW7 rearrangement intron 5
ERBB4 E542K
PTPRO V98fs*30

2 Disease relevant genes with no reportable alterations: ***BRAF, KIT***

Report Highlights

- Targeted therapies with potential clinical benefit **approved in this patient's tumor type**: Trametinib (p. 5)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***NRAS* -** Q61R	Trametinib	Cobimetinib
10 Trials see p. 9		Selumetinib
***FBXW7* -** rearrangement intron 5	none	none
7 Trials see p. 7		

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.

***ERBB4* -** E542K .... p. 4
***PTPRO* -** V98fs*30 .... p. 4

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

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

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. 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 detected in 16-32% of cutaneous melanomas in several small datasets, with the majority exhibiting MSI-low[6]. A higher frequency of MSI (low and high) has been reported in metastatic tumors (20-77%) compared to primary tumors (2-30%)[7]. No association between MSI status and clinicopathological features of patients with melanoma was reported in one study[8].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[9]. 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[9-11]. 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[12-14]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[9,11,13-14].

BIOMARKER

Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[15-17], anti-PD-1 therapies[15-18], and combination nivolumab and ipilimumab[19-24]. In multiple studies of immune checkpoint inhibitors in melanoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-1 or anti-PD-L1 treatments[18,25-26]. Increased TMB has been associated with longer PFS and OS for patients with melanoma treated with nivolumab, with studies reporting increased benefit for patients with a mutational load above 162 missense mutations per tumor (~equivalency >8 Muts/Mb as measured by this assay)[27]. Increased TMB (~equivalency >10.8 Muts/Mb as measured by this assay) has also been associated with longer PFS and OS for patients with melanoma treated with combination nivolumab and ipilumumab[27]. Improved PFS and OS of patients with melanoma treated with ipilumumab has been observed across all TMB levels[28].

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that various melanoma subtypes harbored median tumor mutational burdens (TMBs) between 6.3 and 14.4 Muts/Mb, and 25%-40% of cases had elevated TMBs of greater than 20 Muts/Mb[29]. Malignant melanoma has been reported to have a high prevalence of somatic mutations compared with other tumor types[30], with desmoplastic melanoma ranking among the highest of melanoma subtypes (median TMB of 62 Muts/Mb)[31]. Higher mutational load has been reported in NF1-mutated melanoma samples compared with BRAF-mutated, NRAS-mutated, or BRAF/NRAS/NF1-wildtype samples[25]. Mucosal and acral melanomas have been reported to have a 5- to 10-fold lower somatic mutation burden compared with sun-exposed melanomas (mean 2.6-2.9 muts/Mb)[32-33], with one study of anorectal melanoma reporting a mean mutational burden of 0.3 muts/Mb[34]. In 1 study, elevated TMB correlated with PD-L1 positive status and increased OS in tissue specimens from patients with Stage 3 melanoma[35]. In another study, elevated tissue TMB (>20 Muts/Mb) was associated with longer PFS and OS in patients treated with anti-PD-1 or anti-PD-L1 immunotherapy as compared with patients with lower TMB[25]. Increased TMB has also been associated with histologic stage and cumulative sun exposure[36].

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[37-38] and cigarette smoke in lung cancer[39-40], treatment with temozolomide-based chemotherapy in glioma[41-42], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[43-47], and microsatellite instability (MSI)[43,46-47]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[15-16,18,25,48-51].

GENE
NRAS

ALTERATION
Q61R

HGVS VARIANT
NM_002524.3:c.182A>G (p.Q61R)

VARIANT CHROMOSOMAL POSITION
chr1:115256529

VARIANT ALLELE FREQUENCY (% VAF)
35.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in hematologic malignancies[52-58] and solid tumors[52,59-61], NRAS activating alterations may predict sensitivity to MEK inhibitors, such as trametinib, cobimetinib, binimetinib, and selumetinib. A Phase 3 study of the MEK inhibitor binimetinib for patients with melanoma with NRAS mutations who were previously untreated or had progressed on immunotherapy reported a significant increase in median PFS as compared with dacarbazine (2.8 vs. 1.5 months)[59]. In a nonrandomized Phase 2 study of binimetinib for 30 patients with melanoma with NRAS mutations, 20% (6/30) had a PR and 63% (19/30) had SD, and the size of brain metastases was reduced for 2 patients treated with binimetinib[60]. A Phase 1 study of the ERK1/2 inhibitor ulixertinib reported PRs in 18% (3/17) and SDs in 35% (6/17) of patients with melanoma with NRAS mutations[62]. Early-phase trials of investigational RAF inhibitors have reported benefit for individual patients with NRAS-altered melanoma. In a Phase 1 study, patients with melanoma with NRAS mutations benefited from treatment with belvarafenib, a type-2 pan-RAF inhibitor, with PRs reported in the dose-escalation (44% [4/9]) and dose-expansion (20% [2/10]) cohorts[63]. Phase 1 studies evaluating the pan-RAF inhibitor exarafenib (Spira et al., AACR Abstract CT032) and the MEK-pan-RAF dual inhibitor avutometinib[64] each reported responses for individual patients. A Phase 1a/1b trial of the RAF dimer inhibitor BGB3245 also observed PRs for 2 patients pretreated with immune checkpoint inhibitors[65]. Retrospective analysis of patients with melanoma treated with first-line nivolumab plus ipilimumab showed significantly improved survival for those with BRAF-mutated disease (9.9 months median PFS [mPFS] and median OS [mOS] not reached) relative to those with either NRAS-mutated disease (4.8 months mPFS and 14.2 months mOS) or disease lacking BRAF and NRAS mutations (5.3 months mPFS and 16.1 months mOS)[66].

FREQUENCY & PROGNOSIS

NRAS mutations have been reported in 5-33% of melanoma cases, with similar frequency in primary and metastatic samples[31,67-76]. Similar frequencies of NRAS mutations have been reported in cutaneous melanoma, mucosal melanoma, acral lentiginous melanoma (ALM), conjunctival melanoma, vulvar melanoma, vaginal melanoma, and melanoma of unknown primary[67-68,77-83]. Conflicting findings have been reported regarding the prognostic significance of NRAS mutation in the context of melanoma, with some studies noting significant adverse impact on clinico-pathological features as well as overall and/or melanoma-free survival[77,83-87], whereas other studies reported no significant impact on survival[75,79,88-91].

FINDING SUMMARY

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways[71]. NRAS alterations affecting amino acids G12, G13, G60, Q61, as well as mutations I24N, T50I, T58I, and A146T have been characterized as activating and oncogenic[71,92-107].

GENE
FBXW7

ALTERATION
rearrangement intron 5

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[108-109]. Case series reported objective responses for 2 patients with FBXW7-mutated cervical squamous cell carcinoma treated with everolimus[110].

FREQUENCY & PROGNOSIS

FBXW7 mutations have been reported in up to 2.8% of melanomas[111-112]. Loss of FBXW7 expression was reported in 13% (35/270) of primary melanomas and 22.5% (34/151) of metastatic melanomas[113]. Increased FBXW7 expression has been reported to be associated with improved 5-year OS (P=0.047, multivariate)[113]. An additional study found observed the same trend, but did not reach statistical significance (P=0.08, univariate)[114]. One study demonstrated that FBXW7 inactivation was associated with resistance to anti-PD-1 antibody therapy in melanoma[115].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[116]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[116-117]. Alterations such as seen here may disrupt FBXW7 function or expression[117-124].

GENE

ERBB4

ALTERATION
E542K

HGVS VARIANT
NM_005235.2:c.1624G>A (p.E542K)

VARIANT CHROMOSOMAL POSITION
chr2:212537981

VARIANT ALLELE FREQUENCY (% VAF)
47.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The ERBB family kinase inhibitors afatinib and lapatinib, the EGFR inhibitors erlotinib and gefitinib, and the Bruton tyrosine kinase inhibitor ibrutinib have been shown to inhibit ERBB4 at clinically achievable concentrations[125-130]. However, whether these inhibitors would be clinically effective for patients with ERBB4 mutation is unclear. Retrospective analyses of the Phase 3 LUX-Lung 8 trial reported that patients with squamous non-small cell lung cancer (NSCLC) harboring mutations in ERBB family members exhibited long-term benefit following afatinib treatment compared with patients with ERBB-wildtype tumors; there was no difference for patients treated with erlotinib[131-132]. A meta-analysis showed that patients with ERBB4-mutated NSCLC treated with immune checkpoint inhibitors exhibited longer PFS and OS compared with patients who had ERBB4-wildtype tumors (p=0.036 and p=0.0378)[133].

FREQUENCY & PROGNOSIS

ERBB4 mutations have been identified in various solid tumors, including stomach (13%), salivary gland (11%, 2/18), esophageal (9%), lung (8-9%), endometrioid (6%), colorectal (5%), head and neck (5%), and gallbladder carcinomas (3.9%, 2/51), and melanoma (1.8%)[133-138]. In hematological malignancies, ERBB4 mutations are rare, and have been reported at low frequency in diffuse large B-cell lymphoma (DLBCL)(2.2%-5.7%), chronic lymphocytic leukemia (CLL)(0.6-1.1%), and multiple myeloma (0.5%)[139-145]. ERBB4 amplification has been predominantly detected in gastric tumors (67%)[146]. ERBB4 fusions have been identified infrequently in solid tumors and peripheral T-cell lymphoma, although evidence for ERBB4 fusions as driver alterations is generally limited[147-150]. Expression of N-terminally truncated oncogenic ERBB4 variants has been reported in ALK fusion-negative anaplastic large cell lymphomas[151]. ERBB4 mutation correlates with poorer survival for patients with colorectal cancer (CRC)[152]. Increased ERBB4 expression has been associated with worse clinical outcomes for patients with CRC[153-154], bone sarcoma[155], esophageal squamous cell carcinoma (SCC)[156], oral SCC[157], metastatic Ewing sarcoma[158], gastric cancer[159], osteosarcoma[160], or triple-negative breast cancer[161]. In contrast, high ERBB4 expression has been described as a positive prognostic factor in breast cancer[162-164], ovarian cancer[165], cervical carcinomas[166], hormone-sensitive and castrate-resistant prostate cancer[167], and EGFR-negative intrahepatic cholangiocarcinoma[168].

FINDING SUMMARY

ERBB4 (also known as HER4) encodes a member of the ErbB receptor tyrosine kinase family that plays a role in cell proliferation and apoptosis[169]. Activating alterations are predicted to be oncogenic, and gain-of-function mutations have been identified throughout the gene[134,169-171]. The variants N181S, V348L, P854Q, and T926M have demonstrated similar activity as wildtype ERBB4 in limited preclinical studies[170,172]. A single-nucleotide polymorphism in ERBB4 has been associated with increased risk of non-small cell lung cancer (NSCLC) in the Chinese Han population[173].

GENE

PTPRO

ALTERATION
V98fs*30

HGVS VARIANT
NM_030667.1:c.293_294del (p.V98Gfs*30)

VARIANT CHROMOSOMAL POSITION
chr12:15637124-15637126

VARIANT ALLELE FREQUENCY (% VAF)
35.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to address genomic alterations in PTPRO. In a preclinical study of breast cancer, PTPRO expression was suppressed by estrogen but increased by tamoxifen; upregulation of PTPRO sensitized cells to this selective estrogen modulator[174]. Low PTPRO expression has been implicated in resistance to cetuximab in patients with KRAS wild-type colorectal carcinoma[175].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PTPRO mutation has been reported at highest frequency in lung squamous cell carcinoma (SCC, 6.2%)[176], uterine corpus endometrial carcinoma (5.4%)[43], and lung adenocarcinoma (3%)[177], whereas homozygous deletion was most frequently identified in cases of lung (3%)[177] or prostate (1.8%)[178] adenocarcinoma. Hypermethylation of the PTPRO promoter is also observed in breast[174,179-180], hepatocellular[181-182], colorectal[183], esophageal squamous cell[184], and lung SCC[185], as well as in some leukemias[186-187]. Promoter methylation significantly correlates with reduced PTPRO transcript levels[179-181,188-189] and is associated with poor prognosis for patients with lung SCC[185] and breast cancer[179,188,190]; in the context of the latter, epigenetic silencing of PTPRO is an independent predictor of shorter OS for patients with HER2+ disease[179,190]. Low PTPRO expression in breast cancer is also significantly associated with shorter OS and poor prognosis[188] and in lung SCC is an independent predictor of the latter[185].

FINDING SUMMARY

PTPRO, also known as GLEPP1 , encodes a protein tyrosine phosphatase that regulates podocyte function[191-192]. In the context of cancer, PTPRO is a tumor suppressor that attenuates signaling and tumorigenesis by multiple oncogenes, through dephosphorylation and/or endocytic downregulation of these substrates[180,188-189,193].

Trametinib

Assay findings association

NRAS
Q61R

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence, activating alterations of NRAS may predict sensitivity to MEK inhibitors[52-53,55,57,59-61,194-196].

SUPPORTING DATA

One retrospective study of MEK inhibitors in NRAS-mutated melanoma reported an ORR of 23% (5/22) for pretreated patients with trametinib as a single agent[197], although efficacy was limited in a Phase 1 trial of advanced melanoma (0 PRs, 29% DCR [2/7])[198]. A real-world study of trametinib with or without anti-PD1 antibodies in immune checkpoint inhibitor (ICI)-resistant melanoma reported PRs for 5% (1/20) of patients with NRAS-mutated disease and a median OS of 6.5 months for the cohort overall (n=22)[199]. The combination of trametinib with paclitaxel resulted in PRs for 50% (4/8) of patients with melanoma harboring NRAS mutations[200]. Combination approaches pairing trametinib with other agents are also under investigation in NRAS-mutated melanoma. A Phase 2 study of trametinib and the BRAF/CRAF inhibitor LXH254 reported 1 PR and a DCR of 67% (16/24) for patients with ICI-resistant disease at the expansion dose[201], building on a Phase 1b trial reporting an ORR of 47% (7/15)[202]. A study reported responses for 25% (1/4) of patients with the combination of trametinib and ICIs[197]. As a monotherapy for patients with BRAF V600E/K-mutated metastatic melanoma, trametinib improved PFS (4.9 vs. 1.5 months, HR=0.54) and median OS (15.6 vs. 11.3 months, HR=0.84) compared with patients treated with chemotherapy[203]. In a Phase 1 study, 10% (4/40) of patients with BRAF-wildtype metastatic melanoma achieved a PR[198]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[204], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[205].

Cobimetinib

Assay findings association

NRAS
Q61R

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor that is FDA approved to treat patients with histiocytic neoplasms. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence, activating alterations of NRAS may predict sensitivity to MEK inhibitors[52-53,55,57,59-61,194-196] .

SUPPORTING DATA

Significant clinical responses to various other MEK inhibitors have been documented for patients with NRAS-mutated melanoma[60,64,194,206] . Patients with metastatic melanoma and NRAS mutations experienced PRs (26% [5/19]) and SDs (42% [8/19]) in response to cobimetinib combined with the RAF inhibitor belvarafenib[207]. A Phase 1 study of cobimetinib monotherapy in solid tumors reported 1% (1/97) CR and 6% (6/97) PR, all of which were achieved by patients with melanoma (6 with BRAF V600E)[208]. Patients with metastatic melanoma treated with cobimetinib combined with the RAF inhibitor belvarafenib experienced PRs for those with BRAF V600 mutations (33% [3/9]) and non-V600 mutations (50% [3/6])[207]. In the Phase 3 IMspire170 study, the combination of atezolizumab and cobimetinib did not improve median PFS (5.5 vs. 5.7 months), ORR (26% vs. 32%) or 6-month OS (88% vs. 87%) compared with pembrolizumab for patients with previously untreated BRAF V600 wildtype melanoma[209]. Similarly, the Phase 2 TRICOTEL trial for patients with BRAF wildtype melanoma with central nervous system metastases reported an intracranial ORR of 27% following combination treatment of atezolizumab and cobimetinib[210]. A Phase 1b study evaluating the combination of atezolizumab and cobimetinib for the treatment of patients with solid tumors reported an ORR of 41% (9/22) in patients with melanoma, regardless of BRAF status; the 12-month PFS and OS rates were 50% and 85%, respectively[211].

Selumetinib

Assay findings association

NRAS
Q61R

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients with neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence, activating alterations of NRAS may predict sensitivity to MEK inhibitors[52-53,55,57,59-61,194-196] .

SUPPORTING DATA

In a Phase 2 study for patients with metastatic melanoma, selumetinib monotherapy achieved an ORR of 5.8%; among patients with BRAF mutations, the ORR was 11% (5/45)[212]. In a Phase 2 trial of first-line treatment of BRAF-mutated metastatic melanoma, the addition of selumetinib to dacarbazine increased PFS compared to dacarbazine plus placebo (5.6 vs 3.0 months, HR=0.63) but did not significantly improve OS (13.9 vs 10.5 months, HR 0.93, p=0.39)[213]. In a Phase 2 trial for patients with BRAF wildtype advanced melanoma, the addition of selumetinib to docetaxel did not improve median PFS compared to docetaxel plus placebo (4.2 vs 3.9 months) and was associated with lower OS (9.5 months vs 11.4 months); NRAS mutation was associated with inferior OS (HR=0.78)[214].

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

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
FBXW7

ALTERATION
rearrangement intron 5

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors.

NCT03239015
PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04803318
PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05125523
PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03297606
PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

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, SRC, RET, VEGFRs

LOCATIONS: Texas

GENE
NRAS

ALTERATION
Q61R

RATIONALE
Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways. NRAS activating mutations or amplification may therefore sensitize tumors to inhibitors of these downstream pathways.

NCT04913285
PHASE 1

A Study to Evaluate KIN-2787 in Subjects With BRAF Mutation Positive Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Taipei (Taiwan), Shanghai (China), Bengbu (China), Wuhan (China), Linyi (China), Gyeonggi-do (Korea, Republic of), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Beijing (China)

NCT04985604
PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Marseille (France), Barcelona (Spain), Madrid (Spain), California

NCT04803318
PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04835805
PHASE 1

A Study to Evaluate the Safety and Activity of Belvarafenib as a Single Agent and in Combination With Either Cobimetinib or Cobimetinib Plus Atezolizumab in Patients With NRAS-mutant Advanced Melanoma.

TARGETS
MEK, RAFs, NRAS, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Nedlands (Australia), Waratah (Australia), Melbourne (Australia), Oslo (Norway), Bergen (Norway), Berlin (Germany), Hamburg (Germany), Würzburg (Germany), Mannheim (Germany)

NCT03284502
PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs, NRAS

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

NCT05580770
PHASE 1/2

Mirdametinib + BGB-3245 in Advanced Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Waratah (Australia), Melbourne (Australia), California, Ohio, Massachusetts, Texas, Connecticut, Pennsylvania, Florida

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Lübeck (Germany), Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT04892017

PHASE 1/2

A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.

TARGETS
ULK1, ULK2, MEK

LOCATIONS: Oregon, Massachusetts, New York, Texas, Pennsylvania

NCT05340621

PHASE 1/2

OKI-179 Plus Binimetinib in Patients With Advanced Solid Tumors in the RAS Pathway (Phase 1b) and NRAS-mutated Melanoma (Phase 2)

TARGETS
HDACs, MEK

LOCATIONS: California, Michigan, Massachusetts, New York, Tennessee, Virginia, Texas, Georgia, Florida

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

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.

CARD11
NM_032415.4: c.2960C>T
(p.T987M)
chr7:2952980

CBL
NM_005188.2: c.10A>T
(p.N4Y)
chr11:119077137

EP300
NM_001429.3: c.923C>T
(p.P308L)
chr22:41523507

FGFR3
NM_000142.3: c.130G>A
(p.G44S)
chr4:1801001

IRS2
NM_003749.2: c.2512C>T
(p.R838C)
chr13:110435889

SETD2
NM_014159.6: c.579_587del
(p.P194_P196del)
chr3:47165538-47165547

TP53
NM_000546.4: c.155A>C
(p.Q52P)
chr17:7579532

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

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

Using an Illumina® Sequencing platform (HiSeq 4000 or NovaSeq 6000), hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI), and tumor mutational burden (TMB) will be reported.

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and

MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.10.0

The median exon coverage for this sample is 772x

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