FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Wang, Ya Chen	Lung adenocarcinoma	26 Oct 2022
	COUNTRY CODE: TW	ORDERED TEST #: ORD-1479431-01

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

PATIENT
DISEASE Lung adenocarcinoma
NAME Wang, Ya Chen
DATE OF BIRTH 01 November 1965
SEX Female
MEDICAL RECORD # 48605965

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 Lung
SPECIMEN ID S111-77378C (PF22116)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 31 August 2022
SPECIMEN RECEIVED 17 October 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

BRAF V600E
SETD2 D995fs*1

7 Disease relevant genes with no reportable alterations: *ALK, EGFR, ERBB2, KRAS, MET, RET, ROS1*

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Dabrafenib** (p. 5), **Dabrafenib + Trametinib** (p. 4), **Vemurafenib** (p. 6)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 2 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)
***BRAF* -** V600E	Dabrafenib + Trametinib 2A	Dabrafenib 2A
		Vemurafenib 2A
		Encorafenib + Binimetinib
		Vemurafenib + Cobimetinib
10 Trials see p. 8		

2A *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

***SETD2* -** D995fs*1 ..... p. 3

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.

Electronically signed by Erik Williams, M.D. | 26 October 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2022).

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[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
2 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[42]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[50]. A meta-analysis of 19 studies of immune checkpoint inhibitor-treated NSCLC (n = 2,315 patients) demonstrated that high TMB predicted a significantly longer OS than low TMB (HR = 0.70), and within the high TMB group, immunotherapy was associated with an improved PFS (HR = 0.62, P<0.001), OS (HR = 0.67, P<0.001) and a higher response rate (OR = 2.35, P<0.001) compared to chemotherapy[51]. In contrast, a large study of Chinese patients with untreated lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[44]. Another study of patients with NSCLC treated with EGFR inhibitors or platinum doublet chemotherapy found elevated TMB to be correlated with poorer prognosis, as well as finding lower TMB in combination with PD-L1 negative status to be significantly associated with longer median survival in patients with lung adenocarcinoma[52]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[52-53].

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[54-55] and cigarette smoke in lung cancer[32,56], treatment with temozolomide-based chemotherapy in glioma[57-58], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[59-63], and microsatellite instability (MSI)[59,62-63]. 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[22-23,26-28,32-39,64].

GENE
BRAF

ALTERATION
V600E

TRANSCRIPT ID
NM_004333.4

CODING SEQUENCE EFFECT
1799T>A

VARIANT CHROMOSOMAL POSITION
chr7:140453136

VARIANT ALLELE FREQUENCY (% VAF)
14.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Patients with BRAF V600E-mutated metastatic non-small cell lung cancer achieved clinical benefit from the combination of the BRAF V600 inhibitor dabrafenib and MEK inhibitor trametinib. In the first-line setting, patients achieved an ORR of 64% (23/36), a median PFS (mPFS) of 10.9 months, and a median OS (mOS) of 24.6 months[65]. Patients with previously treated metastatic disease achieved an ORR of 67% (38/57), an mPFS of 10.2 months, and an mOS of 18.2 months[66]. The BRAF V600 inhibitors vemurafenib and dabrafenib have also demonstrated efficacy as monotherapies for patients with BRAF V600E-mutated non-small cell lung cancer[67-70]. The ERK1/2 kinase inhibitor ulixertinib was evaluated for patients with BRAF-mutated lung cancer; 3 out of 12 patients achieved a PR, including 2 responses for patients with BRAF V600E mutations[71]. In 2 Phase 1 studies evaluating the MEK-pan-RAF dual inhibitor CH5126766, 3 patients harboring BRAF V600E mutations experienced PRs, including 2 patients with melanoma[72] and 1 patient with low-grade serous ovarian carcinoma[73].

FREQUENCY & PROGNOSIS

BRAF mutations have been reported in up to 4% of non-small cell lung cancer (NSCLC) cases in various studies[74-78], with a large-scale meta-analysis suggesting a frequency of 3%[79]. BRAF mutations are significantly more prevalent in lung adenocarcinoma than non-adenocarcinoma NSCLC[76,79]. BRAF mutations can co-occur with alterations in other known oncogenic drivers of NSCLC, including EGFR, KRAS, and ALK[76,78]. Although one retrospective study in Europe observed shorter OS for patients with BRAF-mutated metastatic or recurrent NSCLC (HR=1.38 compared with patients with KRAS mutations or no drivers)[80], other studies did not detect a prognostic effect of BRAF mutations overall[79,81]. Comparing survival for patients with different BRAF mutation classes (I-III), retrospective studies reported similar OS between classes on non-targeted treatments[80,82-83]. Patients with BRAF-mutated metastatic NSCLC may benefit from PD-1/L1 immune checkpoint inhibitors (ORR of 24-29% [9/37-4/14])[80,84], irrespective of the BRAF mutation class[85].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[86-87]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[88-89]. Among the V600 mutations, V600E accounts for 70-80% of observations, V600K for 10-30%, and V600R for 5-7%, with V600D comprising the majority of the rest[88,90-91]. Mutations at V600 are Class 1 BRAF alterations that have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[88,92]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M, exhibited sensitivity to V600-targeted therapies[91,93-103]; other mutations at this position are predicted to behave similarly.

GENE
SETD2

ALTERATION
D995fs*1

TRANSCRIPT ID
NM_014159.6

CODING SEQUENCE EFFECT
2982_2983insT

VARIANT CHROMOSOMAL POSITION
chr3:47163143

VARIANT ALLELE FREQUENCY (% VAF)
23.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS

Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[104]. SETD2 has been associated with favorable prognosis in gastric cancer[105]. SETD2 has also been associated with poor prognosis in RCC and MDS[106-107], while data in other tumor types is limited (PubMed, Jun 2022).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[108] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[109]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[110]. SETD2 alterations such as observed here have been shown to be inactivating[111-116].

Dabrafenib + Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600 selective inhibitor and trametinib is a MEK inhibitor. These 2 therapies are FDA approved in combination to treat metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation, advanced anaplastic thyroid cancer (ATC) with BRAF V600E mutation, and advanced solid tumors with BRAF V600E mutation in adult and pediatric patients 6 years of age and older. This combination is also approved to treat patients with melanoma with BRAF V600E/K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in various solid tumors and hematologic malignancies, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as dabrafenib and trametinib[65,117-127] .

SUPPORTING DATA

In a Phase 2 trial for patients with previously treated BRAF V600E-mutated metastatic non-small cell lung cancer (mNSCLC), dabrafenib in combination with trametinib achieved an ORR of 68% (39/57), median PFS (mPFS) of 10.2 months, median OS (mOS) of 18.2 months, and 5-year survival rate of 19%[128]; dabrafenib plus trametinib demonstrated similar activity as first-line therapy for patients with BRAF V600E-mutated mNSCLC, with an ORR of 64% (23/36), mPFS of 10.8 months, mOS of 17.3 months, and 5-year survival rate of 22%[65,128] . In one retrospective study, 40 patients with BRAF V600E-mutated NSCLC treated with dabrafenib plus trametinib achieved a mPFS of 17.5 months and mOS of 25.5 months[129], whereas in another, 100% (9/9, including 5 newly diagnosed) of patients with BRAF-mutated NSCLC achieved disease control and 6-month mPFS on dabrafenib plus trametinib[130]. Multiple case studies have also reported clinical benefit for patients with NSCLC harboring either a BRAF V600E mutation[131-141] or a non-V600E mutation[142-144] following treatment with dabrafenib plus trametinib. Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wildtype BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutated thyroid cancer[93,145-146] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[118-119,147-149] .

Dabrafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600-selective inhibitor that is FDA approved as a monotherapy to treat melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Mutations at BRAF V600, including V600E, V600K, V600R, V600D, and V600M, have been reported to exhibit clinical sensitivity to V600-targeted therapies[91,93-102,150] ; therefore, this tumor may be sensitive to V600-targeted therapy such as dabrafenib.

SUPPORTING DATA

In a Phase 2 trial for BRAF V600E-mutated metastatic non-small cell lung cancer (NSCLC), dabrafenib monotherapy resulted in PRs for 33% (26/78) and disease control for 58% (45/78) of previously treated patients; 4/6 treatment-naive patients achieved PRs[70]. The median PFS and OS were 5.5 months and 12.7 months, respectively[70]. Similar median PFS (5.0 months) and OS (10.8 months) were reported in a retrospective study of BRAF-targeted therapy outcomes for BRAF-mutated metastatic NSCLC; 44% (4/9) of patients responded to dabrafenib in this study[151]. A patient with BRAF V600E-mutated lung adenocarcinoma experienced a PR to dabrafenib of 8 months and subsequently had progressive disease that coincided with the acquisition of a secondary KRAS mutation[152]. Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[91,93-102,150] . Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wildtype BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutated thyroid cancer[93,145-146] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[118-119,147-149] .

Encorafenib + Binimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

The combination of the BRAF inhibitor encorafenib and MEK inhibitor binimetinib is FDA approved to treat patients with melanoma with BRAF V600E or BRAF V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical efficacy in the treatment of patients with BRAF V600-mutated melanoma[153-156] , and activity in colorectal, thyroid, and lung cancer[156-158] , activating alterations affecting BRAF predict sensitivity to the combination of encorafenib and binimetinib.

SUPPORTING DATA

A case study observed improved responses in leptomeningeal and brain metastases for a patient with BRAF V600E-mutated lung adenocarcinoma following combination treatment with encorafenib and binimetinib[158]. The combination of encorafenib and binimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF V600 activating alterations[153,156-158] , and has been studied primarily in the context of BRAF V600-mutated melanoma where patients treated with this combination achieved greater PFS and OS compared with encorafenib or vemurafenib monotherapy[153-154,159] . A combination of encorafenib, binimetinib, and the CDK4/6 inhibitor ribociclib in a Phase 1b trial for patients with BRAF V600-mutant cancers elicited responses in melanoma, astrocytoma, unknown carcinoma, and in 1 of 3 patients with colorectal cancer; a Phase 2 study of this combination in V600-mutant melanoma reported an ORR of 52.4% (22/42), including 5 CRs, median PFS of 9.2 months, and median OS of 19.4 months[160].

Vemurafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and is FDA approved to treat melanoma as monotherapy for patients with the BRAF V600E mutation. It is also approved to treat patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data, BRAF V600E mutations may confer sensitivity to V600-targeted therapies such as vemurafenib[67-68,94-95,100,161-165] .

SUPPORTING DATA

Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[91,93-102,150] . Single-agent vemurafenib has been examined in Phase 2 basket trials including cohorts with BRAF-mutated NSCLC. In the VE-BASKET study for patients with BRAF V600 mutation, vemurafenib elicited an ORR of 37% (23/62 PRs), a median PFS of 6.5 months, a median OS of 15.4 months, and a median response duration of 7.2 months in the overall NSCLC cohort; similar ORRs were achieved by treatment-naïve and previously-treated patients[68,166] . In the AcSé study, patients with BRAF V600-mutated NSCLC and progression on 1 or more standard treatments achieved an ORR of 44.8% (43/96), with a median PFS, OS, and duration of response of 5.2, 10, and 6.4 months, respectively; patients with BRAF non-V600 mutations did not experience a response (0/15) and achieved a median PFS of 1.8 months and a median OS of 5.2 months[67]. Similarly, in the MyPathway study, patients with advanced BRAF V600E-mutated NSCLC experienced an ORR of 43% (6/14, 1 CR), while the response rate was low for diverse tumor types with BRAF non-V600 mutation (4%, 1/23)[69]. A retrospective study reported an ORR of 54% (13/24, 2 CR) and a DCR of 96% (23/24) for patients with V600E-mutated advanced NSCLC treated with vemurafenib following prior BRAF inhibitor therapy[151]. Case reports support the activity of vemurafenib against BRAF V600E-mutated metastatic NSCLC[167-168] , including patients with intracranial disease[169] or pulmonary sarcomatoid carcinoma[170]. One patient with NSCLC, low TMB, and TRIM24-BRAF fusion experienced a PR with vemurafenib treatment[171]. Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wildtype BRAF and leading to paradoxical activation of the MAPK pathway[94,145] . In a Phase 1b trial, patients with BRAF V600E-mutated melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[172].

Vemurafenib + Cobimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and cobimetinib is a MEK inhibitor. The combination is FDA approved 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 in melanoma and colorectal carcinoma, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as vemurafenib and cobimetinib[173-175] .

SUPPORTING DATA

One patient with BRAF V600E-positive NSCLC experienced a 15-month SD on vemurafenib plus cobimetinib after switching from dabrafenib plus trametinib due to toxicity[176]; a basket trial reported no responses for 2 patients with NSCLC[177]. The combination of vemurafenib and cobimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF alterations[175-178] . The Phase 2 TAPUR basket study reported an ORR of 57% (2 CRs, 14 PRs, n=28), median PFS of 5.8 months, and median OS of 15.2 months for patients with BRAF mutations in various non-melanoma solid tumors, including 1 PR for a patient with an unspecified malignant neoplasm. Vemurafenib with cobimetinib has been studied primarily in the context of BRAF V600-mutated melanoma, where patients treated with this combination achieved greater PFS and OS compared with vemurafenib alone[173-174,179] . Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wildtype BRAF and leading to paradoxical activation of the MAPK pathway[94,145] . In a Phase 1b trial, patients with BRAF V600E-mutated melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[172].

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
BRAF

ALTERATION
V600E

RATIONALE
BRAF V600 mutation may predict sensitivity to inhibitors of BRAF, MEK, or ERK. BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK. Limited clinical and preclinical studies indicate BRAF mutations may predict sensitivity to MEK-pan-RAF dual inhibitors.

NCT03178552

PHASE 2/3

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

TARGETS
MEK, PD-L1, BRAF, KRAS

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Kaohsiung (Taiwan), Shatin (Hong Kong), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Bangkok (Thailand), Hat Yai (Thailand), Singapore (Singapore), St Leonards (Australia)

NCT03337698

PHASE 1/2

A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)

TARGETS
PD-L1, MEK, CEA, CXCR4, EZH2, MDM2, ADORA2A

LOCATIONS: Taipei City (Taiwan), Seoul (Korea, Republic of), Blacktown (Australia), Haifa (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Newcastle upon Tyne (United Kingdom), Dijon (France), London (United Kingdom), Sutton (United Kingdom)

NCT04585815

PHASE 1/2

Umbrella Study of Sasanlimab Combined With Targeted Therapies in Participants With Non Small Cell Lung Cancer

TARGETS
VEGFRs, PD-1, TIGIT, BRAF, MEK

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taichung (Taiwan), Concord (Australia), St Leonards (Australia), Camperdown (Australia), Heidelberg (Australia), Edegem (Belgium), Newcastle upon Tyne (United Kingdom), London (United Kingdom)

NCT04913285

PHASE 1

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

TARGETS
BRAF, MEK

LOCATIONS: Taipei (Taiwan), Perth (Australia), Villejuif (France), Lyon (France), Nantes (France), Bordeaux (France), Barcelona (Spain), California, Valencia (Spain)

NCT04452877

PHASE 2

A Study of Dabrafenib in Combination With Trametinib in Chinese Patients With BRAF V600E Mutant Metastatic NSCLC

TARGETS
BRAF, MEK

LOCATIONS: Hangzhou (China), Shanghai (China), Guangzhou (China), Changsha (China), Tianjin (China), Beijing (China), Chengdu (China), Harbin (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT03781219

PHASE 1

A PhaseI Study of HL-085 Plus Vemurafenib in Solid Tumor With BRAF V600 Mutation

TARGETS
MEK, BRAF

LOCATIONS: Hangzhou (China), Zhengzhou (China), Beijing (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)

NCT03284502

PHASE 1

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

TARGETS
MEK, RAFs

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

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

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.

BRD4
P1012L

CIC
I155V

IRS2
G1308V

MKNK1
R35Q

MST1R
D507V

SPEN
T796S

STAG2
S823Y

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. 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) 7.3.0

The median exon coverage for this sample is 844x

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