FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Su, Chih Wen	Skin melanoma	26 Oct 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1479430-01

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 Skin melanoma
NAME Su, Chih Wen
DATE OF BIRTH 31 December 1975
SEX Male
MEDICAL RECORD # 29198149

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 Lymph Node
SPECIMEN ID S111-37492C (PF22115)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 23 September 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 amplification, SLC12A7-BRAF rearrangement
MTAP loss
CDKN2A/B CDKN2B loss, CDKN2A loss
EZH2 rearrangement exon 6

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

Report Highlights

- Targeted therapies with potential clinical benefit **approved in this patient's tumor type: Trametinib** (p. 7)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

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* -** amplification, SLC12A7-BRAF rearrangement	Trametinib	Selumetinib
10 Trials see p. 9		
***MTAP* -** loss	none	none
3 Trials see p. 11		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

Electronically signed by Erik Williams, M.D. | 26 October 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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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 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
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[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 TMBs between 6.3 and 14.4 Muts/Mb, and 25% to 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-mutant melanoma samples compared with BRAF-mutant, NRAS-mutant, or BRAF/NRAS/NF1 wild-type samples[25]. In 1 study, elevated TMB correlated with PD-L1 positive status and increased OS in tissue specimens from patients with Stage 3 melanoma[32]. 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[33].

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[34-35] and cigarette smoke in lung cancer[36-37], treatment with temozolomide-based chemotherapy in glioma[38-39], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[40-44], and microsatellite instability (MSI)[40,43-44]. 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[15-16,18,25,45-48].

GENE

BRAF

ALTERATION

amplification, SLC12A7-BRAF rearrangement

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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)[49]. In a retrospective genomic screen, 3 patients with BRAF fusions in melanomas responded to consecutive CTLA-4 inhibitor ipilimumab and immune checkpoint inhibitor pembrolizumab treatments, with 2 patients reported to be disease free following ipilimumab and pembrolizumab and 1 patient progressing on ipilimumab and then responding on pembrolizumab[50]. The MEK inhibitor trametinib has also been reported to benefit patients with BRAF fusions in melanomas in case reports and basket trials[51-53]. Individual case reports have also observed benefit for patients with the pan-RAF inhibitor sorafenib[54-56]. Second-generation BRAF inhibitors are in development; 1 patient with melanoma and a BRAF fusion treated with PLX8394 achieved a CR, which was the best overall response in a basket trial otherwise consisting of BRAF exon 15 missense mutations[57]. Targeting extracellular signal-regulated kinase (ERK) downstream of BRAF with ulixertinib resulted in 1 SD for the 1 patient with a BRAF fusion in another basket trial[58]. Single-agent BRAF V600-targeting treatments such as vemurafenib are not predicted to confer benefit in melanomas with BRAF fusions in the absence of BRAF V600 mutation; a report showed no tumor response for a patient with a BRAF fusion[59], although a combination of dabrafenib and trametinib resulted in a PR for 1 patient with a co-occurring BRAF V600 mutation[60]. Outcomes for patients with BRAF amplifications have been studied almost exclusively in the context of concurrent activating alterations and resistance mechanisms[61-63]; the evidence that BRAF amplification without a concurrent activating mutation is responsive to BRAF-pathway-targeting MEK or RAF inhibitors is very limited. A patient with triple-negative breast cancer with a high-level BRAF amplification and loss of PTEN and INPP4B achieved a major response to a combination of a MEK inhibitor and an AKT inhibitor[64]. Investigational ERK[58] and second-generation BRAF inhibitors[57] are also in development; however, it is uncertain whether these strategies would be of benefit for patients with BRAF amplifications.

FREQUENCY & PROGNOSIS

BRAF fusions have been observed in 5% of spitzoid neoplasms[65] and in 1-3% of melanomas[51,66]. A systematic review of 100 BRAF fusion-positive melanocytic tumor cases in the literature described BRAF fusions to be enriched for female patients, for young patients (median age of 33 years), and in tumors with spitzoid histopathologic features[67]; 42 different gene fusion partners were identified, with 55% of the partner genes having known dimerization domains, and AGK and AKAP9 being the most common recurrent partner genes[67]. BRAF rearrangement, leading to loss of the autoinhibitory region, has also been observed in 2 cases of large congenital melanocytic nevi[68]. BRAF mutations have been reported in 37-66% of melanoma cases[69-72], most frequently in cutaneous melanoma (41-51%)[72-73], melanoma of unknown primary (52%)[74] and conjunctival melanoma (14-29%)[75-76]. Putative high level BRAF amplification has been reported in 5% of melanomas (cBioPortal, Mar 2022)[77-78]. There are conflicting reports regarding the prognostic significance of BRAF mutation in the context of melanoma[74,79-81]. In one study of non-acral cutaneous melanoma, BRAF non-V600E mutation associated with some, but not other, clinicopathological features but did not impact OS since Stage 4 diagnosis, including OS after initiation of frontline ipilimumab treatment[82].

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[83-84]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[69,85]. BRAF amplification has been reported and correlated with overexpression of the BRAF protein in various tumor types[78,86-88]. Expression of the BRAF kinase domain without the N-terminal auto-inhibitory domain, whether with or without a fusion partner, is a BRAF class 2 subtype and has been shown to be constitutively active and to drive hyperactivation of the MAPK pathway, exhibiting transforming activity[55,89-100] in a manner sensitive to MEK inhibitors[61,99,101-104], ERK inhibitors[104], the pan-RAF inhibitor sorafenib[55,100], and second-generation BRAF inhibitors PLX8394 and PLX7904[105-106]. Some patients with BRAF fusions have been reported to benefit from MEK inhibitors[51-52,101,107-109] as well as pan-RAF inhibitor sorafenib[54-55,110-111]. Rearrangements such as observed here, those that are detected as a reciprocal fusion, are not clearly in frame, or may lack a fusion partner, may be indicative of an activating rearrangement event such as a fusion or an expression of the BRAF kinase domain without the N-terminal auto-inhibitory domain; however, it is unclear whether such rearrangements would lead to an oncogenic BRAF variant.

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— **Targeted Therapies** —

MTAP inactivation produces specific metabolic vulnerabilities that may be sensitive to MAT2A[112-113] or PRMT5 inhibition[113-115]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[116]. Preclinical data suggest that MTAP loss sensitizes cells to S-adenosyl-L-methionine (SAM)-competitive PRMT5 inhibitors[117], dual PRMT1 and PRMT5 inhibitors[118-120], and PRMT5 inhibitors that selectively bind the PRMT5 when complexed with S-methyl-5'-thioadenosine (MTA), such as MRTX1719, TNG908, and AMG193[121]. In preclinical models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA[122-132]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and SD for 24% (13/55) of patients[133]. Preclinical and limited clinical evidence suggest MTAP deficiency may confer sensitivity to pemetrexed[134].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[135-136]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[137], gastrointestinal stromal tumors[138], mantle cell lymphoma (MCL)[139], melanoma[140-141], gastric cancer[142], myxofibrosarcoma[143], nasopharyngeal carcinoma[144], ovarian carcinoma[135] and non-small cell lung cancer[145]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[146] or in astrocytoma[147]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[148], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[149]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[150-151], esophageal cancer[152-153], osteosarcoma[154], and CRC[155].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[156-157]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[137,158-159], thereby reducing intracellular arginine methylation[113-115] and altering cell signaling[159-160]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[161-164]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[165] and palbociclib treatment[166-167]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[168-174]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[175-176], the clinical relevance of p14ARF as a predictive biomarker is not clear. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[169,171-172,177-179].

FREQUENCY & PROGNOSIS

Concomitant loss of p16INK4a and p14ARF in melanoma is common, although loss of activity of either may also occur as a result of transcript-specific mutations or hypermethylation[180-186]. Homozygous deletion of CDKN2A and/or CDKN2B has been reported in 14-29% of melanoma cases (cBioPortal, Oct 2022)[77-78,187-189]. Various correlations between CDKN2A alterations and tumor histology or patient prognosis in melanoma have been reported in the literature, with some studies reporting CDKN2A deletion to be associated with adverse prognosis and other studies reporting no association between CDKN2A deletion and prognosis[187-188,190-191]. Studies suggest that deletion of CDKN2A is an early event in melanoma tumorigenesis, and loss of p16INK4a has been associated with increased DNA damage in human benign melanocytic tumors and has been suggested to contribute to tumorigenesis by promoting the proliferation of cells with genetic damage[192-193]. CDKN2A alterations affecting p16INK4a, p14ARF, or both have been strongly associated (up to a 76% risk) with familial melanoma[194-204].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[205-206]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[207-208]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[209-210]. One or more alterations observed here are predicted to result in p16INK4a loss of function[211-232]. One or more alterations seen here are predicted to result in p14ARF loss of function[215,232-235]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[236].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[237]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[238-239]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[240-242]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[243-245]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
EZH2

ALTERATION
rearrangement exon 6

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical evidence indicates that activating EZH2 alterations may predict sensitivity to EZH2 inhibitors[246-250]. Multiple Phase 2 trials of the EZH2 inhibitor tazemetostat have associated activating EZH2 mutations with improved clinical outcomes for patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma[251-253] . Additional EZH2 inhibitors have been tested in Phase 1 trials, including CPI-1205 for patients with B-cell lymphoma (1 CR and 5 SDs, n=32)[254] and GSK2816126 for patients with lymphoma (n=20; 1 PR, 6 SDs and 10 PDs) or solid tumors (n=21; 8 SDs and 11 PDs), although this study was terminated for lack of efficacy[255]. The dual EZH1/2 inhibitor valemetostat has shown promising clinical activity with a 53% response rate (1 CR, 7 PRs, n=15) for patients with non-Hodgkin lymphoma and an 80% ORR for the subset of patients with T-cell lymphoma (1 CR, 3 PRs, n=5)[256]. In preclinical studies, cells resistant to EZH2 inhibitors retain sensitivity to compounds that block EED, a core subunit of the PRC2 complex[257-260]. Other therapeutic approaches targeting EZH2 include DNA demethylation agents and histone deacetylation inhibitors[261-263]. In addition, preclinical studies in breast cancer cells have suggested that PI3K inhibition may reverse some of the effects of EZH2 overexpression[264]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

EZH2 mutations have been observed in 0-1.7% of melanoma cases[70-71,265]. Overexpression of EZH2 has been reported in 83% of metastatic melanomas[266]. EZH2 has been suggested to play a role in melanoma progression; studies have reported that EZH2 protein expression is rarely observed in benign melanocytic nevi, but is increased in invasive melanoma samples[266-269]. Increased EZH2 protein expression also correlated with overall patient survival in cutaneous melanoma[268-270]. Inactivation of EZH2 in a melanoma mouse model prolonged survival and reduced metastasis[270].

FINDING SUMMARY

EZH2 encodes histone-lysine N-methyltransferase, the catalytic subunit of the PRC2/EED-EZH2 complex, which methylates lysine 9 and 27 on histone H3, to bring about transcriptional repression of target genes[271-273]. In cancer cells, an EZH2-containing complex appears to play a role in bringing about de novo DNA methylation to target genes for repression[274]. The role of EZH2 in cancer is complex, being described as both an oncogene and a tumor suppressor in different contexts[261-262]. Alterations such as seen here may disrupt EZH2 function or expression[275-278].

Trametinib

Assay findings association

BRAF
amplification, SLC12A7-BRAF rearrangement

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

Activating BRAF fusions may predict sensitivity to MEK inhibitors such as trametinib. Clinical responses to trametinib have been achieved by patients with BRAF-fusion-positive melanoma[51-53,279] , low-grade glioma[280-282] , histiocytosis[283-284] , and prostate cancer[285].

SUPPORTING DATA

Individual patients with BRAF-fusion-positive melanoma have experienced either a PR or clinical benefit from single-agent trametinib[51-53,279] . 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[286]. In a Phase 1 study, 10% (4/40) of patients with BRAF-wildtype metastatic melanoma achieved a PR[287]. 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[288], 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[289].

Selumetinib

Assay findings association

BRAF
amplification, SLC12A7-BRAF rearrangement

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

Activating BRAF fusions may predict sensitivity to MEK inhibitors such as selumetinib. Clinical responses to selumetinib have been achieved by patients with BRAF-fusion-positive low-grade glioma[107,109] .

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)[290]. 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)[291]. 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)[292].

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

RATIONALE
BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK.

ALTERATION
amplification, SLC12A7-BRAF rearrangement

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)

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)

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT03839342

PHASE 2

Binimetinib and Encorafenib for the Treatment of Advanced Solid Tumors With Non-V600E BRAF Mutations

TARGETS
BRAF, MEK

LOCATIONS: Toronto (Canada)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), California, Texas

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

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

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

NCT04722575

PHASE 2

Combination or Sequence of Vemurafenib, Cobimetinib, and Atezolizumab in High-risk, Resectable Melanoma

TARGETS
MEK, PD-L1, BRAF

LOCATIONS: Padova (Italy), Naples (Italy), Genova (Italy)

NCT04059224

PHASE 2

TraMel-WT: A Trial of Trametinib in Patients With Advanced Pretreated BRAFV600 Wild-type Melanoma

TARGETS
BRAF, MEK

LOCATIONS: Jette (Belgium)

GENE
MTAP

ALTERATION
loss

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors, or to inhibitors that target PRMT5 when in complex with MTA.

NCT05094336

PHASE 1/2

AMG 193, Methylthioadenosine (MTA) Cooperative Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, Alone and in Combination With Docetaxel in Advanced Methylthioadenosine Phosphorylase (MTAP)-Null Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Nagoya-shi (Japan), Chuo-ku (Japan), Kashiwa-shi (Japan), Camperdown (Australia), Halle (Saale) (Germany), Salzburg (Austria), Würzburg (Germany), Ulm (Germany), Heidelberg (Germany), Edegem (Belgium)

NCT05245500

PHASE 1/2

Phase 1/2 Study of MRTX1719 in Solid Tumors With MTAP Deletion

TARGETS
PRMT5-MTA

LOCATIONS: Colorado, Massachusetts, New York, Tennessee, Texas

NCT05275478

PHASE 1/2

Safety and Tolerability of TNG908 in Patients With MTAP-deleted Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Massachusetts, Tennessee, Texas, Virginia

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.

CBL	*PALB2*	*RAD51D*
I423S	L169F	A52V

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 915x

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