FOUNDATIONONE®CDx

| PATIENT | TUMOR TYPE | REPORT DATE |
|---|---|---|
| Lin, Wei-Chun | Brain glioblastoma (GBM) | 11 Apr 2022 |
| | COUNTRY CODE | ORDERED TEST # |
| | TW | ORD-1336391-01 |

**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** Brain glioblastoma (GBM)
**NAME** Lin, Wei-Chun
**DATE OF BIRTH** 01 July 1947
**SEX** Male
**MEDICAL RECORD #** 48333717

**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** Brain
**SPECIMEN ID** S111-10514 A (PF22044)
**SPECIMEN TYPE** Slide Deck
**DATE OF COLLECTION** 15 March 2022
**SPECIMEN RECEIVED** 04 April 2022

## Biomarker Findings

**Microsatellite status** - MS-Stable
**Tumor Mutational Burden** - 3 Muts/Mb

## Genomic Findings

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

***MET*** amplification
***CDKN2A/B*** CDKN2A loss, CDKN2B loss
***EPHB4*** amplification - equivocal†
***TP53*** E285K

**3** Disease relevant genes with no reportable alterations: ***EGFR, IDH1, PDGFRA***

† See About the Test in appendix for details.

## Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cabozantinib** (p. 8), **Capmatinib** (p. 8), **Crizotinib** (p. 9), **Tepotinib** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)

| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| **Microsatellite status -** MS-Stable | **No therapies or clinical trials.** see Biomarker Findings section |
| **Tumor Mutational Burden -** 3 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) |
|---|---|---|
| ***MET* -** amplification | none | Cabozantinib |
| | | Capmatinib |
| | | Crizotinib |
| **5 Trials** *see p. 10* | | Tepotinib |

## 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.




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



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BIOMARKER

# Microsatellite status

**RESULT**
MS-Stable

## POTENTIAL TREATMENT STRATEGIES

**— 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

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[6-8]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[6], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[9]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[6], in GBMs with a previous lower grade astrocytoma[7], and in giant cell GBM compared to classic GBM[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[10]. 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[10-12]. 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[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER

# Tumor Mutational Burden

**RESULT**
3 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[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[16,26-27]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[28-29] or anti-PD-L1[30] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

## FREQUENCY & PROGNOSIS

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)[31]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[35].

## 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[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. 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[16,26-30].



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**GENE**
# *MET*

**ALTERATION**
amplification

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. In a Phase 1b/2 trial for patients with MET-amplified recurrent glioblastoma, no responses were observed following treatment with capmatinib monotherapy (n=10) or capmatinib combined with buparlisib (n=33); patients in the combination therapy arm additionally harbored PTEN inactivating alterations[47]. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[48-51], gastroesophageal cancer[52], glioblastoma[53], and carcinoma of unknown primary[54]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[55-56] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[57-59]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[60] and NSCLC[61] as a monotherapy, as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[62-64] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[65] and gastric cancer either alone or in combination with docetaxel[66-67]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[68]. Patients with MET-amplified NSCLC[69] or MET-amplified gastric cancer[70] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab, as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[71]. A first-in-human Phase 1 trial of telisotuzumab vedotin (teliso-V), a MET antibody-drug conjugate, reported activity in a subset of patients with MET-positive NSCLC, with an ORR of 19% (3/16) and a DCR of 56% (9/16); no responses were observed in any other patients[72]. A subsequent Phase 2 trial of teliso-V in patients with MET-positive NSCLC reported a 35% (13/37) ORR in patients with non-squamous, EGFR-wildtype tumors, which met the prespecified criteria for transition to the next stage; lower ORRs were observed in patients with squamous (14%; 3/21) or non-squamous EGFR-mutated (13%; 4/30) tumors[73].

## FREQUENCY & PROGNOSIS

In the glioblastoma multiforme (GBM) TCGA dataset, putative amplification of MET is reported in 2.5% of cases whereas MET mutation is reported in 0.4% of cases[74]. Lower level gain of MET has been reported in 47% and 44% of primary and secondary GBM, respectively, and in 38% of diffuse astrocytomas[75]. Multiple studies have reported MET expression to be associated with poor prognosis in patients with GBM[76-78]; however, one study reported improved overall survival in patients with GBM expressing MET relative to those negative for MET expression[79].

## FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[80-81]. MET has been reported to be amplified in cancer[82], with amplification positively correlating with protein expression in some cancer types[83-87] and associating with therapeutic response to MET inhibitors in a variety of cancer types[48-50,52-54,88-89].



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GENE
# *CDKN2A/B*

**ALTERATION**
CDKN2A loss, CDKN2B 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[90-93]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[94-95], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[96-102]; 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[103-104], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. 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[97,99-100,105-107].

## FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[108] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[74] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[82,109]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[110-112]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[113]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[114]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[115]. Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression[111,116]. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas[117-118].

## FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[119-120]. 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[121-122]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[123-124]. One or more alterations observed here are predicted to result in p16INK4a loss of function[125-146]. One or more alterations seen here are predicted to result in p14ARF loss of function[129,146-149]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[150].

## 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[151]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[152-153]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[154-156]. 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[157-159]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
# *EPHB4*

ALTERATION
amplification - equivocal

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no approved therapies available to target EPHB4 alterations in cancer. sEPHB4 is a soluble monomeric extracellular domain of EPHB4 that functions as an antagonist of EphrinB2-EPHB4 interaction[160], and fusion of sEPHB4 with human serum albumin (HSA) increases its stability[161]. Recombinant sEPHB4-HSA is under investigation in clinical trials. Preclinical studies have demonstrated that sEPHB4-HSA inhibits cell proliferation and xenograft tumor growth, including for cells expressing cancer-associated EPHB4 mutants or overexpressing wild-type EPHB4[160,162-166]. In addition, small-molecule inhibitors targeting multiple tyrosine kinases including EPHB4, such as JI-101 and XL647, have been under preclinical and clinical investigation[167-169].

## FREQUENCY & PROGNOSIS

Increased EPHB4 mRNA and/or protein expression has been reported in a variety of cancer types, including head and neck squamous cell carcinoma (HNSCC)[170-173], gastric and esophageal[174-178], colorectal carcinoma (CRC)[179-185], breast[186-190], ovarian[190-192], endometrial[193-195], thyroid[196-198], lung[199-200], glioma[201-202], and other solid tumors[162,203-210]. In several of these studies, increased EPHB4 expression has been associated with clinicopathologic features, including disease stage[162,170,186,191-192,200,203,205], histological grade[176,186,193,202], and hormone receptor status[189,194]. High EPHB4 expression has been associated with inferior survival in multivariate analyses for patients with CRC treated with bevacizumab [hazard ratio (HR) = 5.95][184], HNSCC (HR = 2.95)[173], epithelial ovarian cancer (HR = 4.53)[190], or glioma (HR = 3.21)[202].

## FINDING SUMMARY

EPHB4 encodes a member of the EPH family of receptor tyrosine kinases[211]. Ephrin signaling has been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration[212], and signaling between EPHB4 and its ligand EphrinB2 is particularly important for angiogenesis[213-214]. EPHB receptors, including EPHB4, have been shown to undergo dysregulation (amplification, mutation, under- or overexpression) in a number of different cancer types[215]. EPHB4 amplification has been reported in several solid tumor types[170-171,176,216-217] and was associated with advanced disease stage in head and neck squamous cell carcinoma (HNSCC)[170]. Activating missense mutations in or near the tyrosine kinase domain, including G723S, A742V, and P881S, have also been identified in lung cancer[166].



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GENE
# *TP53*

**ALTERATION**
E285K

**TRANSCRIPT ID**
NM_000546

**CODING SEQUENCE EFFECT**
853G>A

**VARIANT ALLELE FREQUENCY (% VAF)**
78.2%

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[218-221], or p53 gene therapy and immunotherapeutics such as SGT-53[222-226] and ALT-801[227]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[228]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[229]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[230]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[231]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[66]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[232]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[233]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[226]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[234-236]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[237]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[238-239]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[240-241]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

## FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs[242-243]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[114]. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively[244-249]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[250]. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM[114]. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN[251].

## FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[252]. Alterations such as seen here may disrupt TP53 function or expression[253-257].

## POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2021)[258]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[259-261], including sarcomas[262-263]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[264] to 1:20,000[263]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[265]. In the appropriate clinical context, germline testing of TP53 is recommended.

## POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[266-271]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[266-267]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[272]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[270,273-274]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.



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## Cabozantinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

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

### GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[275-276] , as well as by extensive preclinical data[277-283] .

### SUPPORTING DATA

In a Phase 2 study, cabozantinib treatment achieved objective responses in 7 of 31 patients with glioblastoma (GBM) without prior antiangiogenic therapy and tumor shrinkage in 3 of 9 patients with prior antiangiogenic therapy, including bevacizumab[284]. In a preclinical study, cabozantinib treatment reduced GBM tumor growth in 3 xenograft mouse lines, and increased survival in two of these lines, while showed no effect on the overall survival in the third line; however, combination treatment with cabozantinib resulted in sensitization of these xenografts to TMZ treatment[285]. A Phase 1 ascending dose study of cabozantinib in patients with advanced solid tumors has reported early indications of drug response and prolonged stable disease, with no dose-limiting toxicities or serious adverse events[286]. Another Phase 1 study of cabozantinib in high-grade gliomas included 1 patient with anaplastic astrocytoma who had stable disease for >900 days[287]. A Phase 1 study examining the combination of cabozantinib and temozolomide for patients with high-grade gliomas reported that the combination was safe; however, dose reductions were common and 62% of patients experienced treatment-related grade 3/4 adverse events[288]. The combination of cabozantinib and crizotinib has been found to result in an increase in overall survival in a glioblastoma xenograft model[279]. Cabozantinib treatment has also been reported to result in decreased endothelial cell proliferation, increased apoptosis, and an inhibition of tumor growth in mouse models of breast, glioma, and lung tumors[277].

## Capmatinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[55,61-64,289] , hepatocellular carcinoma[60], renal cell carcinoma[65], and gastric cancer[66], MET amplification may predict sensitivity to selective MET inhibitors.

### SUPPORTING DATA

A Phase 1b/2 study of capmatinib with or without buparlisib did not result in CR or PR for patients with recurrent PTEN-deficient glioblastoma, and 30% (3/10) of patients treated with capmatinib monotherapy experienced SD[47].

## Crizotinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

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

### GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[48-50,290-291] , gastric cancer[88], gastroesophageal cancer[52], glioblastoma[53], and carcinoma of unknown primary[54], as well as in patients with MET-mutated cancers, including NSCLC[275,292-296] , renal cell carcinoma (RCC)[297], and histiocytic sarcoma[292]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[275,292,294-296,298] .

### SUPPORTING DATA

Case reports describe 2 patients with glioblastoma who benefited from crizotinib: 1 patient with MET amplification experienced a rapid radiographic regression[53] and another patient with overexpression of MET and ALK showed prolonged SD[299]; another patient with MET amplification did not respond to crizotinib[299]. A Phase 1 study of crizotinib combined with temozolomide and radiotherapy reported a median PFS of 16.8 months and a median OS of 31.4 months for patients with glioblastoma[300]. A Phase 1 study of crizotinib in pediatric patients with solid tumors or lymphoma reported intratumoral hemorrhage in 2 patients with primary central nervous system (CNS) tumors, and patients with CNS lesions were subsequently excluded from the study[301].

## Tepotinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[55,61-64,289] , hepatocellular carcinoma[60], renal cell carcinoma[65], and gastric cancer[66], MET amplification may predict sensitivity to selective MET inhibitors.

### SUPPORTING DATA

Clinical data on the efficacy of tepotinib for the treatment of CNS tumors are limited (PubMed, Mar 2022). Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[61] and MET exon 14-skipping alterations[302-303] . Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[63-64] . In advanced hepatocellular carcinoma, Phase 2 studies of tepotinib reported improved ORR and PFS for both treatment-naive and previously treated patients with MET protein overexpression[60,304-306] . In a Phase 1 study of advanced solid tumors, tepotinib monotherapy yielded an ORR of 1.3% and a DCR of 24%, with 2 confirmed PRs observed for patients with esophageal or lung cancer and 2 unconfirmed PRs for patients with colorectal or nasopharyngeal cancer[307]. In another Phase 1 study of solid tumors, tepotinib yielded a DCR of 17% (2/12), with 2 SD of ≥12 weeks observed in a patient with gastric cancer and another with urachal cancer[308].

**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.



Electronically signed by Erik Williams, M.D. | 11 April 2022
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**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**
*MET*

**RATIONALE**
Activating MET alterations may confer sensitivity to MET inhibitors.

**ALTERATION**
amplification

## NCT03175224

**PHASE 1/2**

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

**TARGETS**
MET

**LOCATIONS:** Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), Saransk (Russian Federation), North Adelaide (Australia), Bedford Park (Australia)

## NCT04647838

**PHASE 2**

Tepotinib in Solid Tumors Harboring MET Alterations

**TARGETS**
MET

**LOCATIONS:** Cheonan (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

## NCT04116541

**PHASE 2**

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

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

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

## NCT04887194

**PHASE 1**

PK Study to Assess Drug-drug Interaction and QTc Between Sitravatinib and a Cocktail of Substrates

**TARGETS**
AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB, PD-1

**LOCATIONS:** Texas, Virginia

## NCT04693468

**PHASE 1**

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

**TARGETS**
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

**LOCATIONS:** Texas



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**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.

***APC***
N372D

***BRD4***
V193I

***CIC***
A62V

***CUL4A***
G35R

***EZH2***
amplification

***FGFR3***
L164V

***GNAS***
P137S

***MAPK1***
rearrangement

***PDGFRB***
rearrangement

***SETD2***
N801T

***SF3B1***
T448N

***TSC1***
A567V

***TSC2***
A1141T

***ZNF217***
R903W



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# APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

## DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *ALK* | *BCL2* | *BCR* | *BRAF* | *BRCA1* | *BRCA2* | *CD74* | *EGFR* | *ETV1* |
| *ETV4* | *ETV5* | *ETV6* | *EWSR1* | *EZR* | *FGFR1* | *FGFR2* | *FGFR3* | *KIT* |
| *KMT2A (MLL)* | *MSH2* | *MYB* | *MYC* | *NOTCH2* | *NTRK1* | *NTRK2* | *NUTM1* | *PDGFRA* |
| *RAF1* | *RARA* | *RET* | *ROS1* | *RSPO2* | *SDC4* | *SLC34A2* | *TERC** | *TERT*** |
| *TMPRSS2* | | | | | | | | |

*TERC is an NCRNA

**Promoter region of TERT is interrogated

## ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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



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

## ABOUT FOUNDATIONONE CDX

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

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

## INTENDED USE

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

## TEST PRINCIPLES

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

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

## THE REPORT

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

### Diagnostic Significance

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

### Qualified Alteration Calls (Equivocal and Subclonal)

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

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

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

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

## REPORT HIGHLIGHTS

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

## VARIANT ALLELE FREQUENCY

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

*Precision of VAF for base substitutions and indels*

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

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

## VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

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

### LEVEL OF EVIDENCE NOT PROVIDED

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

### NO GUARANTEE OF CLINICAL BENEFIT

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

### NO GUARANTEE OF REIMBURSEMENT

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

### TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

### SELECT ABBREVIATIONS

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

MR Suite Version 6.1.0

The median exon coverage for this sample is 749x



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Electronically signed by Erik Williams, M.D. | 11 April 2022
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Electronically signed by Erik Williams, M.D. | 11 April 2022
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