FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

COUNTRY CODE
PE

REPORT DATE
25 Feb 2022

ORDERED TEST #
ORD-1306820-01

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

**PATIENT**
**DISEASE** Lung non-small cell lung carcinoma (NOS)
**NAME** Bravo Villanueva, Adolfo
**DATE OF BIRTH** 01 April 1946
**SEX** Male
**MEDICAL RECORD #** Not given

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

**SPECIMEN**
**SPECIMEN SITE** Thorax
**SPECIMEN ID** 22QX-523
**SPECIMEN TYPE** Block
**DATE OF COLLECTION** 03 February 2022
**SPECIMEN RECEIVED** 18 February 2022

## Biomarker Findings

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

## Genomic Findings

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

***EGFR*** exon 19 deletion (E746_A750del)
***MET*** amplification - equivocal†
***CCNE1*** amplification
***MYC*** amplification
***RNF43*** R145*
***RAD21*** amplification
***TP53*** P151T
***ZNF217*** amplification

6 Disease relevant genes with no reportable alterations: ***ALK, BRAF, ERBB2, KRAS, RET, ROS1***

† See About the Test in appendix for details.

## Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Afatinib** (p. 10), **Dacomitinib** (p. 12), **Capmatinib** (p. 11), **Crizotinib** (p. 11), **Tepotinib** (p. 12)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Erlotinib** (p. 13), **Gefitinib** (p. 14), **Osimertinib** (p. 15)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 17)

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



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| GENOMIC FINDINGS | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|
| ***EGFR*** **-** exon 19 deletion (E746_A750del) | Afatinib 1 | none |
| | Dacomitinib 1 | |
| | *Erlotinib* ⊗ | |
| | *Gefitinib* ⊗ | |
| **10 Trials** see p. 18 | *Osimertinib* ⊗ | |
| ***MET*** **-** amplification - equivocal | Capmatinib 2A | Cabozantinib |
| | Crizotinib 2A | |
| | Tepotinib 2A | |
| | *Erlotinib* ⊗ | |
| | *Gefitinib* ⊗ | |
| **10 Trials** see p. 20 | *Osimertinib* ⊗ | |
| ***CCNE1*** **-** amplification | none | none |
| **3 Trials** see p. 17 | | |
| ***MYC*** **-** amplification | none | none |
| **4 Trials** see p. 22 | | |
| ***RNF43*** **-** R145* | none | none |
| **3 Trials** see p. 23 | | |

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

## GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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



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

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



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BIOMARKER

# Microsatellite status

**RESULT**
MS-Stable

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

## FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2021).

## FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

# Tumor Mutational Burden

**RESULT**
4 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

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

## FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[42]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[50]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[44]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[51]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[51-52].

## 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[53-54] and cigarette smoke in lung cancer[32,55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,63].



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GENE
# *EGFR*

**ALTERATION**
exon 19 deletion (E746_A750del)

**TRANSCRIPT ID**
NM_005228

**CODING SEQUENCE EFFECT**
2235_2249delGGAATTAAGAGAAGC

**VARIANT ALLELE FREQUENCY (% VAF)**
33.5%

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[64], gefitinib[65], afatinib[66], dacomitinib[67], and osimertinib[68]; however, the data for patients with other tumor types are limited[69-74]. The Phase 1 CHRYSALIS study of amivantamab monotherapy or in combination with lazertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) has produced encouraging preliminary results for treatment-naive patients and patients who relapsed after treatment with osimertinib with and without chemotherapy, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[75-78] . In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 39% (22/57, 1 CR) and a median PFS of 8.2 months for patients with non-small cell lung cancer previously treated with an EGFR TKI, many of whom displayed TKI resistance alterations[79]. A Phase 1 trial evaluating the EGFR inhibitor AZD3759 reported a reduction in the volume of brain metastases in 40% (8/20) of patients with previously treated non-small cell lung cancer (NSCLC) harboring either the EGFR L858R alteration or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[80-81]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54% (69/127) for all evaluable patients and 44% (8/18, intracranial) for patients with brain metastases[82].

### — Potential Resistance —

Patients with NSCLC harboring EGFR mutation and MET amplification are unlikely to respond to first- and third-generation EGFR inhibitors (NCCN NSCLC Guidelines, v2.2021). A retrospective study reported significantly shorter PFS and OS on gefitinib treatment for patients with EGFR-mutated non-small cell lung cancer (NSCLC) additionally harboring MET amplification than for those with EGFR-mutated tumors without MET amplification[83]. Additionally, numerous clinical studies have reported MET amplification as an emergent alteration associated with acquired resistance of EGFR-mutated NSCLC to first-generation EGFR inhibitors such as erlotinib and gefitinib[84-100] and third-generation EGFR inhibitors such as osimertinib[91,101-109]. For a small number of patients with EGFR-mutated NSCLC, studies have also reported MET amplification in association with resistance to second-generation EGFR inhibitors such as afatinib and dacomitinib[97,110-113]. Patients with NSCLC harboring EGFR mutation and MET amplification may benefit from combination treatment with MET- and EGFR-targeting agents[87,90,104,106,112,114-116].

### — Nontargeted Approaches —

Patients with EGFR-mutated non-squamous metastatic non-small cell lung cancer previously treated with EGFR TKI have benefited from immune checkpoint inhibitors combined with anti-angiogenic and chemotherapy, particularly atezolizumab plus bevacizumab plus carboplatin and paclitaxel (OS HR 0.61 compared with bevacizumab/chemotherapy)[117-119] or sintilimab plus bevacizumab biosimilar plus cisplatin and pemetrexed (PFS HR 0.46 compared with chemotherapy alone)[120].

## FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[48,121-122] and in 4% of lung squamous cell carcinomas[123]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[124-129]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[130-131]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[132-133]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[134] or resected Stage 1 NSCLC[135].

## FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[136]. EGFR exon 19 deletion mutations, such as seen here, have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib[137-139], afatinib[140], osimertinib[141], and dacomitinib[67,142], although limited preclinical data suggest reduced sensitivity to lapatinib[143-144].



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GENE
# *MET*

ALTERATION
amplification - equivocal

## 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. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[145-148], gastroesophageal cancer[149], glioblastoma[150], and carcinoma of unknown primary[151]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[152-153] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[114,154-155]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[156] and NSCLC[157] as a monotherapy, as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[158-160] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[161] and gastric cancer either alone or in combination with docetaxel[162-163]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[164]. Patients with MET-amplified NSCLC[165] or MET-amplified gastric cancer[166] 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[167]. 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[168]. 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[169]. A Phase 1 study for patients with MET-altered NSCLC treated with MET inhibitor bozitinib monotherapy reported an overall ORR of 30.6% (11/36) and DCR of 97.2% (35/36) with MET overexpression, amplification, and exon 14 skipping demonstrating ORRs of 35.7% (5/14), 41.2% (7/17), and 66.7% (10/15), respectively; increased ORRs were observed in patients with both exon 14 skipping and amplification (100%, 4/4) and with both amplification and overexpression (50%, 3/6)[170].

### — Potential Resistance —

Patients with NSCLC harboring EGFR mutation and MET amplification are unlikely to respond to first- and third-generation EGFR inhibitors (NCCN NSCLC Guidelines, v2.2021). A retrospective study reported significantly shorter PFS and OS on gefitinib treatment for patients with EGFR-mutated non-small cell lung cancer (NSCLC) additionally harboring MET amplification than for those with EGFR-mutated tumors without MET amplification[83]. Additionally, numerous clinical studies have reported MET amplification as an emergent alteration associated with acquired resistance of EGFR-mutated NSCLC to first-generation EGFR inhibitors such as erlotinib and gefitinib[84-100] and third-generation EGFR inhibitors such as osimertinib[91,101-109]. For a small number of patients with EGFR-mutated NSCLC, studies have also reported MET amplification in association with resistance to second-generation EGFR inhibitors such as afatinib and dacomitinib[97,110-113]. Patients with NSCLC harboring EGFR mutation and MET amplification may benefit from combination treatment with MET- and EGFR-targeting agents[87,90,104,106,112,114-116].

## FREQUENCY & PROGNOSIS

MET amplification has been reported at incidences of 14-48% in non-small cell lung cancer (NSCLC), is correlated with increased MET protein expression, and occurs more frequently following treatment with EGFR inhibitors[127,165,171-177]. In the Phase 2 VISION study of patients with NSCLC, MET amplification was reported in 4.9% of samples[178]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[127,171,175,179-183], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[184]. MET exon 14 splice alteration, which has predominantly been observed in lung cancer, was found to be an independent poor prognostic factor in a study of 687 patients with NSCLC[185]. However, other studies did not find MET exon 14 splice alteration as a major risk factor for overall survival for NSCLC patients, although recurrence rate was significantly higher in patients with exon 14 splice alteration compared to those with ALK fusion[186-187]. Among NSCLC patients with exon 14 alterations that had not been previously treated with a MET inhibitor, a non-significant trend for reduced survival was noted in the context of concurrent MET amplification (5.2 vs 10.5 months, p = 0.06)[188].

## 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[189-190]. MET has been reported to be amplified in cancer[191], with amplification positively correlating with protein expression in some cancer types[171,192-195] and associating with therapeutic response to MET inhibitors in a variety of cancer types[145-147,149-151,196-197].

GENE
## *CCNE1*

**ALTERATION**
amplification

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no approved therapies that directly target CCNE1 alterations. Because amplification or overexpression of CCNE1 leads to increased genomic instability though the ATR-CHK1-WEE1 pathway[198-199] and cyclin E1 promotes cell cycle progression in a complex with CDK2[200], clinical and preclinical studies have investigated inhibitors of CHK1, ATR, CDK2, and WEE1 as potential therapeutic approaches for tumors with CCNE1 activation. Clinical benefit has been reported for patients with recurrent high-grade serous ovarian carcinoma (HGSOC) with CCNE1 amplification or expression in response to treatment with the CHK1 inhibitor prexasertib[201]. Studies of the WEE1 inhibitor adavosertib observed PRs in patients with CCNE1-amplified HGSOC and ovarian cancer[202-203]. Similarly, in a Phase 2 study of patients with CCNE1-amplified solid tumors, adavosertib elicited an ORR of 26% with PRs reported for patients with ovarian cancer, urothelial carcinoma, or melanoma[204]. Preclinical studies have demonstrated that cell lines with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR[205-206], CDK2[207], or WEE1[199,208]. However, other studies have shown that sensitivity of various cell lines to CDK2 inhibitors, including SNS-032, dinaciclib, and seliciclib, at clinically achievable doses, is largely independent of CCNE1 copy number or expression[209-212]. One study has reported a reduction in tumor CCNE1 levels in 4/6 lung and esophageal cancer cases following treatment with the HDAC inhibitor vorinostat[213].

### FREQUENCY & PROGNOSIS

In the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets, putative high-level CCNE1 amplification has been reported in 2.6%[122] and 5.6%[123] of cases, respectively. CCNE1 amplification was identified in 6% (6/98) of patients with non-small cell lung cancer (NSCLC) and was associated with TP53 mutation[214]. A study of 68 NSCLC samples observed cyclin E1 overexpression to significantly correlate with centrosome abnormalities[215]. Published data investigating the prognostic implications of CCNE1 in NSCLC are limited (PubMed, Jul 2021).

### FINDING SUMMARY

CCNE1 encodes the protein cyclin E1, which plays a role in the regulated transition from the G1 to S phase by binding to and activating cyclin-dependent protein kinase 2 (CDK2). It also has a direct role in initiation of replication and the maintenance of genomic stability[200]. Amplification of chromosomal region 19q12-q13 has been demonstrated in many types of cancer, and CCNE1 is a well-studied gene within this amplicon[216-217]. Increased copy number of CCNE1 is highly associated with overexpression of the cyclin E1 protein[218-219]. Cyclin E1 overexpression can lead to cell transformation as a result of an increase in cyclin E1 activity[200,220].

GENE
## *MYC*

**ALTERATION**
amplification

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1[221-222], CDK2[223], Aurora kinase A[224-231], Aurora kinase B[232-235], glutaminase[236-239], or BET bromodomain-containing proteins[240-243], as well as agents targeting both HDAC and PI3K[244-246]. A Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer but not for patients without MYC overexpression[247]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor[248]. The glutaminase inhibitor CB-839, in combination with either everolimus or cabozantinib, has demonstrated encouraging efficacy in Phase 1 and 2 studies enrolling patients with pretreated advanced renal cell carcinoma[249-250] .

**— Nontargeted Approaches —**

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[251-252]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[253-254].

### FREQUENCY & PROGNOSIS

MYC amplification has been reported in 10-50% of non-small cell lung cancer (NSCLC) samples, including adenocarcinoma and/or squamous cell carcinoma subtypes[255-259]. In the Lung Adenocarcinoma TCGA and Lung Squamous Cell Carcinoma TCGA datasets, putative MYC amplification has been reported in 9% and 4.5% of cases, respectively[122-123]. MYC amplification has been associated with metastasis in NSCLC, as well as with poor prognosis in early stage lung adenocarcinoma specifically[255-258].

### FINDING SUMMARY

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[260]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[261]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[260,262-263].



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GENE
## *RNF43*

**ALTERATION**
R145*

**TRANSCRIPT ID**
NM_017763

**CODING SEQUENCE EFFECT**
433C>T

**VARIANT ALLELE FREQUENCY (% VAF)**
16.6%

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Preclinical studies have reported that RNF43 is a negative regulator of WNT signaling, and RNF43 loss or inactivation leads to WNT activation and confers sensitivity to WNT pathway inhibitors, particularly Porcupine inhibitors, in multiple tumor types[264-268]. In a Phase 1 basket study for the Porcupine inhibitor RXC004, 1 of 2 patients with tumors harboring an RNF43 mutation achieved SD[269]. Of the patients with WNT-ligand-dependent tumors, including those with RNF43 mutations, RSPO fusions, or those with biliary tract or thymus cancer, 71% (5/7) experienced SD[269]. Therefore, patients whose tumors harbor inactivating alterations in RNF43 may benefit from WNT pathway inhibitors, which are under investigation in clinical trials.

### FREQUENCY & PROGNOSIS

Mutations in RNF43 have been reported in 18-27% of endometrial cancers[270-271], 3-5% of pancreatic cancers[272], 21% of ovarian mucinous carcinomas[273], 9% of liver fluke-associated cholangiocarcinomas[274], and up to 18% of colorectal cancers[61,271]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[271], endometrial[271], and gastric cancers[275-276]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[275].

### FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[277] that was discovered because it is overexpressed in colon cancer[278]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[264-268]. An additional tumor-suppressor-like role for RNF43 in colon cancer is hypothesized to occur via its interaction with the ubiquitin-protein ligase NEDL1, which is predicted to enhance the pro-apoptotic effects of p53[279].

GENE
## *RAD21*

**ALTERATION**
amplification

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no therapies to target alterations in this gene.

### FREQUENCY & PROGNOSIS

RAD21 amplifications, point mutations, and truncating mutations have been reported in various cancers[280]. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes[281-282], including sporadic Grade 3 but not Grade 1 cancers[281], as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers[281]. Furthermore, SNPs in or near RAD21 have been linked with risk of breast cancer development[283-284]. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer[285] and in colorectal cancer (CRC), especially in KRAS-mutant CRC[286]. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer[287]. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression[288]. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic[289]. Downregulation of RAD21 expression resulted in sensitization of cultured breast[282,290] and CRC[286] cells to chemotherapy, thereby suggesting that RAD21 overexpression confers resistance to chemotherapy.

### FINDING SUMMARY

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[291-294]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[295], but also leads to an increase in deletions, insertions, and other rearrangements[296]. High RAD21 expression has also been associated with increased genomic instability[281]. Cohesin complex also organizes chromatin domains and regulates gene expression[297-298]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[299]. RAD21 amplification has been correlated with increased expression in breast[281-282,300] and endometrial[285] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.



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GENE
# *TP53*

**ALTERATION**
P151T

**TRANSCRIPT ID**
NM_000546

**CODING SEQUENCE EFFECT**
451C>A

**VARIANT ALLELE FREQUENCY (% VAF)**
36.9%

## 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[301-304], or p53 gene therapy and immunotherapeutics such as SGT-53[305-309] and ALT-801[310]. 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[311]. 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[312]. 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[313]. 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[314]. 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[162]. 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[315]. 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[316]. 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[309]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[317-319]. 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[320]. 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[321-322]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[323-324]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

## FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[122-123,325-330], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2022)[48-49,122-123]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2022)[191,331]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[332]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[333].

## FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[334]. Alterations such as seen here may disrupt TP53 function or expression[335-339].

## 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)[340]. 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[341-343], including sarcomas[344-345]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[346] to 1:20,000[345]. 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[347]. 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[348-353]. 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[348-349]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[354]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[352,355-356]. 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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GENE
## *ZNF217*

**ALTERATION**
amplification

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no available targeted therapies to address genomic alterations in ZNF217. Expression of ZNF217 may predict relapse of estrogen receptor (ER)-positive breast cancer under hormone therapy through its direct interaction with ER-alpha[357-358]. ZNF217 overexpression has also been associated with resistance to paclitaxel[359] and doxorubicin[360] in breast cancer cell lines. ZNF217 has been suggested as a potential biomarker for treatment with the DNA synthesis inhibitor and AKT inhibitor triciribine in breast cancer based on preclinical findings in cultured cells and xenografts expressing high levels of ZNF217; triciribine treatment also restored sensitivity to doxorubicin in these cells[361].

### FREQUENCY & PROGNOSIS

Amplification and/or overexpression of ZNF217 has been reported in breast[362], ovarian[363-364], gastric[365-366], colon[367], prostate[368], esophageal[369], and urothelial carcinomas[370], glioblastoma[371], and ovarian carcinosarcomas[372]. Overexpression in these tumors has generally been linked with aggressive tumor behavior and poor clinical prognosis. High levels of ZNF217 expression result in dysregulation of a broad range of genes that may contribute to tumorigenesis[373-375], and increased expression or activation of ERBB3[362,376], FAK[362], Aurora kinase A[359], AKT[360], and TGF-beta/SMAD signaling[362] has been demonstrated in ZNF217-expressing tumors or cells.

### FINDING SUMMARY

ZNF217 encodes a candidate oncogene that has likely roles in histone modification and transcriptional repression[360,377]. ZNF217 amplification has been correlated with protein overexpression in breast carcinoma tumors and cell lines[378]. The role of ZNF217 in promoting tumorigenesis was established in preclinical studies demonstrating that expression of ZNF217 results in the immortalization of both human mammary epithelial cells and ovarian surface epithelial cells in culture[379-380].

# Afatinib

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

## AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[66-67,381-382] , whereas data for patients with other tumor types are limited[69-74,383] . On the basis of limited clinical data, MET amplification may be associated with reduced efficacy of EGFR inhibitors such as afatinib and dacomitinib. Several studies have reported patients with EGFR-mutated non-small cell lung cancer (NSCLC) who experienced emergence of MET amplification in association with acquired resistance to afatinib or dacomitinib[97,110-113] .

## SUPPORTING DATA

Afatinib has shown significant clinical activity for patients with NSCLC and the EGFR common sensitizing mutations L858R or exon 19 deletions, based on extensive clinical evidence[66,381,384-387] . Two randomized Phase 3 trials reported significantly improved median PFS from afatinib compared with chemotherapy for patients with EGFR common sensitizing mutations (LUX-Lung 3, 13.6 vs. 6.9 months, HR 0.47, p<0.001; LUX-Lung 6, 11.0 vs. 5.6 months, HR 0.28, p<0.0001)[66,381] . However, while afatinib significantly increased OS relative to chemotherapy for patients with EGFR exon 19 alterations in these two trials (LUX-Lung 3, 33.3 vs. 21.1 months, HR=0.54; LUX-Lung 6, 31.4 vs. 18.4 months, HR=0.64), no significant OS differences were observed in treatment for patients with L858R mutation[140]. A similar alteration-specific difference was observed for EGFR-mutated treatment-naive NSCLC in a retrospective analysis, which reported numerically longer median OS from second- versus first-generation EGFR TKIs (48.8 vs. 26.4 months, HR=0.59) for patients with exon 19 deletions, but no substantial difference for patients with L858R (25.4 vs. 20.6 months, HR=0.90)[384]. A Phase 2b study of first-line afatinib compared with gefitinib, also for NSCLC with exon 19 deletions or L858R, reported similar median OS for the two therapies (27.9 vs. 24.5 months, HR=0.86) but significantly longer time-to-treatment-failure (13.7 vs. 11.5 months, HR=0.75) and higher ORR (73% vs. 56%, p=0.0018) with afatinib[385]. Patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50.0% (30/60) from afatinib in a Phase 4 trial[386]. As first-line therapy for NSCLC with EGFR exon 19 deletions or L858R, prospective or randomized Phase 2 trials have reported a median PFS of 10.2 months and OS of 24.8 months for patients unfit for chemotherapy[387] and an ORR of 72.5% (n=40, 1 CR), DCR of 100% (40/40), and median PFS and OS of 15.2 and 30.0 months, respectively, for elderly patients ≥70 years old[388]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27.4% (63/230) for patients with common sensitizing EGFR mutations and an ORR of 24.4% (105/431) for the entire cohort[389]. In a case report, a patient with NSCLC with exon 19 deletion and leptomeningeal metastases experienced an ongoing 16-month PR from afatinib in extracranial, brain, and leptomeningeal lesions[390]. For patients with erlotinib- or gefitinib-resistant NSCLC and EGFR mutations, Phase 2/3 studies of afatinib treatment have generally reported ORRs of only 7 to 9%[391-396] ; however, DCRs of more than 50% have been observed[395]. In a Phase 1b or observational study, patients with EGFR-mutated NSCLC who progressed on afatinib experienced further clinical benefit from subsequent treatment with afatinib and cetuximab[397] or osimertinib[398], respectively. Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[66,140,381,385,387,389,399] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[395,400-410] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[399]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[411].

# Capmatinib

*Assay findings association*

**MET**
amplification - equivocal

### 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[152,157-160,412] , hepatocellular carcinoma[156], renal cell carcinoma[161], and gastric cancer[162], MET amplification may predict sensitivity to selective MET inhibitors.

### SUPPORTING DATA

In the Phase 2 GEOMETRY mono-1 study for patients with advanced NSCLC and MET gene copy number (GCN) ≥10, capmatinib elicited ORRs of 29–40%, median PFS of 4.1–4.2 months, and median OS of 9.6–10.6 months across treatment-naive and previously treated cohorts[413]. A Phase 1 study of capmatinib monotherapy for advanced EGFR- and ALK-wild-type NSCLC reported ORRs of 46.7% (7/15) for patients with MET GCN ≥6, 25% (3/12) for patients with MET GCN 4–6, and 5.9% (1/17) for patients with MET GCN <4; median PFS was 3.7 months overall, and 7.9 months for patients with MET GCN ≥6[414]. Phase 1b/2 trial of capmatinib and nazartinib for patients with EGFR-mutated, EGFR-TKI-resistant NSCLC and unknown MET status reported a 42% (14/33, 2 CRs) ORR, with no correlation observed between responses and T790M status[415]. Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with glioblastoma (n=10)[416], gastric cancer (n=9), or other advanced solid tumors (n=24)[417-418] .

# Crizotinib

*Assay findings association*

**MET**
amplification - equivocal

### 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)[145-147,419-420] , gastric cancer[196], gastroesophageal cancer[149], glioblastoma[150], and carcinoma of unknown primary[151], as well as in patients with MET-mutated cancers, including NSCLC[421-426] , renal cell carcinoma (RCC)[427], and histiocytic sarcoma[421]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[188,421-422,424-426] .

### SUPPORTING DATA

In a small study for patients with NSCLC and MET overexpression with or without gene amplification, crizotinib elicited 11 PRs and 3 SDs in 19 evaluable patients[420]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[428-432] , ROS1 rearrangements[433-437] , an NTRK1 fusion[438], or MET activation[145-147,419-420,422-426,439-445] . The Phase 2 METROS and AcSe trials have reported ORRs of 31.3% to 32.0%, median PFS of 3.2 to 5.0 months, and median OS of 5.4 to 7.7 months for patients with MET amplified advanced non-small cell lung cancer (NSCLC); a higher level of amplification was predictive of better response in the AcSe trial (P=0.04)[433,446] . Additional patients with MET amplified NSCLC have been reported to experience clinical benefit from crizotinib in several case studies[145-147,442,445,447] . A patient with lung adenocarcinoma harboring K860I and L858R EGFR mutations, who acquired both EGFR T790M and MET amplification upon various treatments, experienced clinical benefit from subsequent combination treatment of osimertinib and crizotinib[106]. Two patients with ALK-positive NSCLC and acquired MET amplification experienced benefit from crizotinib monotherapy and crizotinib in combination with lorlatinib[448].

# Dacomitinib

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

### AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[66-67,381-382] , whereas data for patients with other tumor types are limited[69-74,383] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions achieved an ORR of 76%[142] and a median OS of 34.1 months with dacomitinib[67]. On the basis of limited clinical data, MET amplification may be associated with reduced efficacy of EGFR inhibitors such as afatinib and dacomitinib. Several studies have reported patients with EGFR-mutated non-small cell lung cancer (NSCLC) who experienced emergence of MET amplification in association with acquired resistance to afatinib or dacomitinib[97,110-113] .

### SUPPORTING DATA

A randomized Phase 3 trial in patients with NSCLC with activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59)[142,449] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[450]. A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs, 9.6 months, HR=0.717; median OS, 26.6 vs, 23.2 months, HR=0.737)[451]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[452-454] . A Phase 1 trial of combination dacomitinib and a MEK1/2 inhibitor for patients with KRAS-mutated CRC, NSCLC, or pancreatic cancer reported 20/36 SDs and 16 PDs, however toxicity from this combination prevented long-term treatment in this patient population[455]. A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66)[453]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[456].

# Tepotinib

*Assay findings association*

**MET**
amplification - equivocal

### AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with metastatic 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[152,157-160,412] , hepatocellular carcinoma[156], renal cell carcinoma[161], and gastric cancer[162], MET amplification may predict sensitivity to selective MET inhibitors.

### SUPPORTING DATA

For patients with NSCLC and concurrent MET amplification and EGFR mutation, the Phase 2 INSIGHT study showed that tepotinib plus gefitinib improved ORR (66.7% [8//12] vs. 42.9% [3/7]), median PFS (16.6 vs. 4.2 months, HR=0.13), and median OS (37.3 vs. 13.1 months, HR=0.08) compared with chemotherapy[159-160] . The Phase 2 VISION study of tepotinib reported an ORR of 42% (10/24) and an mPFS of 4.2 months for patients with MET-amplified advanced non-small cell lung cancer, with responses observed in the first-, second-, and third-line settings[157]. Tepotinib has primarily been investigated in non-small cell lung cancer (NSCLC) and has demonstrated efficacy as a single agent for patients with MET amplification[157] and MET exon 14-skipping alterations[457-458] . 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[159-160] . A case study reported 1 PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC metastatic to the brain[459].

# *Erlotinib*

Resistance of variant(s) to associated therapy is likely

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

**MET**
amplification - equivocal

## AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[64,460-462] . On the basis of extensive clinical data, MET amplification may predict resistance to first-generation EGFR inhibitors, including erlotinib and gefitinib (NCCN NSCLC Guidelines, v2.2021). A retrospective study of patients with EGFR-mutated lung adenocarcinoma treated with gefitinib reported that increased MET copy number was associated with significantly shorter PFS (7.6 vs. 15.9 months, HR=3.83, p=0.0008) and OS (16.8 vs. 33.0 months, HR=2.25, p=0.03), compared with cases without MET copy number increase[83]. Additionally, studies have reported >30 patients with EGFR-mutated non-small cell lung cancer (NSCLC) who experienced emergence of MET amplification in association with acquired resistance to erlotinib or gefitinib[84-100,116,463] .

## SUPPORTING DATA

For patients with EGFR-mutated NSCLC, the Phase 3 EURTAC trial reported improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37)[64]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[464]. Meta-analysis of studies comparing erlotinib or gefitinib versus chemotherapy in the first-line setting reported no significant improvement in OS for patients with EGFR-mutated NSCLC; however, the lack of improved OS was attributed to the effectiveness of postprogression salvage therapy[465]. In the maintenance setting, the placebo-controlled Phase 3 SATURN trial reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy irrespective of EGFR status; however, the largest effect was seen for patients with EGFR mutations (HR=0.10)[460]. In the neoadjuvant setting, a Phase 2 trial reported a numerically improved ORR and significantly longer PFS with erlotinib compared with chemotherapy for patients with advanced EGFR-mutated NSCLC[461]. In the placebo-controlled Phase 3 RELAY trial, the addition of ramucirumab to erlotinib improved PFS for previously untreated patients with NSCLC harboring EGFR L858R or exon 19 deletion (19.4 vs. 12.4 months, HR=0.59)[466]. In a Phase 2 trial, no clinical benefit was observed from the addition of bevacizumab to erlotinib for patients with NSCLC harboring EGFR exon 19 deletion or L858R mutation[467]. In one study, median PFS (4.1 vs. 11.7 months, HR=9.7) and median OS (14.1 vs. 47.0 months, HR=10.2) were significantly shorter for patients with NSCLC harboring EGFR L747_A750>P (n=6) relative to those with deletions affecting EGFR E746_A750 (n=24) treated with first-line erlotinib[468]. The Phase 3 BR.21 trial demonstrated prolonged OS for genomically unselected patients with NSCLC treated with erlotinib compared with those treated with standard chemotherapy[469].

# *Gefitinib*

Resistance of variant(s) to associated therapy is likely

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

**MET**
amplification - equivocal

## AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[462,470-475] , and responses have been reported for patients with EGFR-rearranged NSCLC[476-477] . On the basis of extensive clinical data, MET amplification may predict resistance to first-generation EGFR inhibitors, including erlotinib and gefitinib (NCCN NSCLC Guidelines, v2.2021). A retrospective study of patients with EGFR-mutated lung adenocarcinoma treated with gefitinib reported that increased MET copy number was associated with significantly shorter PFS (7.6 vs. 15.9 months, HR=3.83, p=0.0008) and OS (16.8 vs. 33.0 months, HR=2.25, p=0.03), compared with cases without MET copy number increase[83]. Additionally, studies have reported >30 patients with EGFR-mutated non-small cell lung cancer (NSCLC) who experienced emergence of MET amplification in association with acquired resistance to erlotinib or gefitinib[84-100,116,463] .

## SUPPORTING DATA

A Phase 3 trial of first-line gefitinib therapy for patients with NSCLC and EGFR exon 19 deletions or L858R mutations reported a longer PFS (9.2 months vs. 6.3 months)[472] but no change in median OS (34.9 months vs. 37.2 months) compared with patients treated with cisplatin plus docetaxel (median OS of 37.2 months)[478]. In patients with EGFR-mutated NSCLC who progressed on 1st or 2nd generation EGFR TKIs, combination of gefitinib with the MET inhibitor capmatinib achieved ORRs of 32-47% and DCRs of 74-75% in cohorts with MET amplification or overexpression[114]. In this same setting, gefitinib in combination with the MET inhibitor tepotinib elicited the largest benefit in patients with MET amplification or high-level MET overexpression[479]; in the cohort with MET amplification, gefitinib with tepotinib significantly improved ORR (75.0% vs. 42.9%, OR = 4.00) and median PFS (19.8 vs. 5.5 months, HR = 0.25) as compared with pemetrexed and platinum chemotherapy[480]. Gefitinib achieved an ORR of 69.8% and an OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations[65]. In the retrospective analysis of a Phase 3 study for East Asian patients, gefitinib was reported to have a longer PFS for patients with EGFR mutation-positive NSCLC compared with carboplatin/paclitaxel doublet chemotherapy[473,481] . Two Phase 3 trials of gefitinib plus pemetrexed and carboplatin compared with gefitinib alone for patients with advanced NSCLC harboring EGFR activating mutations reported significantly higher ORRs (75.3% and 84% vs. 62.5% and 67%), longer median PFSs (16 and 20.9 months vs. 8 and 11.9 months), and longer median OSs (50.9 months and not reached vs. 17 and 38.8 months) with combination treatment; however, combination treatment was associated with increased Grade 3 or higher adverse events[482-483] . Retrospective analysis of East Asian patients with advanced NSCLC receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced a longer median PFS (10.9 months) compared with patients with EGFR mutations in exon 18 (7.9 months), exon 20 (1.2 months), exon 21 (7.7 months), or double mutations (5.7 months); however, no differences in OS were seen between EGFR mutations[484]. In a Phase 1 study for treatment-naive patients with NSCLC, best ORRs of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination after gefitinib monotherapy[485].

# *Osimertinib*

Resistance of variant(s) to associated therapy is likely

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

**MET**
amplification - equivocal

## AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 21 L858R mutations, or T790M mutations. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[68,141,476,486-487] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions or L858R mutations achieved an ORR of 80% and a median PFS of 21.4 and 14.4 months, respectively[141]. On the basis of extensive clinical data, MET amplification may predict resistance to third-generation EGFR inhibitors, including osimertinib (NCCN NSCLC Guidelines, v2.2021). Studies have reported >30 patients with EGFR-mutated non-small cell lung cancer (NSCLC) who experienced emergence of MET amplification in association with acquired resistance to osimertinib[91,101-109,488-491] .

## SUPPORTING DATA

In EGFR-mutated, MET-positive NSCLC, combination of osimertinib with the MET inhibitor savolitinib elicited an ORR of 64.4% (56/87) with a median PFS of 9.0 to 9.1 months for T790M-negative patients with progression on first- or second-generation TKIs, and an ORR of 66.7% (12/18) with a median PFS of 11.0 months for T790M-positive patients with progression on first- or second-generation TKIs[492]. Patients with progression on third-generation TKIs achieved an ORR of 30.4% (21/69) and a median PFS of 5.4 months[492]. The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced NSCLC and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[141,493] . In the Phase 3 ADAURA study, patients with early Stage (IB/II/IIIA) EGFR-mutated NSCLC experienced longer PFSs on osimertinib compared to placebo in the adjuvant setting (not reached vs. 28.1 months; HR=0.21)[494]. A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and a median PFS of 2.8 months[68]. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/19), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). A Phase 2 trial of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with untreated advanced non-small cell lung cancer (NSCLC) harboring EGFR del19 or L858R reported no difference in ORR (82% vs 86%) and median PFS (22.1 vs 20.2 months, HR 0.862 p=0.213)[495]. The Phase 2 BOOSTER study of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with advanced NSCLC with EGFR-sensitizing mutations (exon 19 del or L858R) and L790M at progression on prior EGFR TKI reported no difference in ORR (55% vs 55%), median OS (24.0 vs 24.3 months, HR 1.03 p=0.91), or median PFS (15.4 vs 12.3 months, HR 0.96 p=0.83), although improved PFS was observed for the combination in the subgroup of current or former smokers (16.5 vs 8.4, HR 0.52) while nonsmokers had no benefit (HR 1.47)[496]. The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated NSCLC reported ORRs of 42% (15/36), 44% (8/18), and 44% (10/23), respectively[497].

# Cabozantinib

*Assay findings association*

**MET**
amplification - equivocal

## 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[422,498] , as well as by extensive preclinical data[499-505] .

## SUPPORTING DATA

Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[422]. A Phase 2 randomized discontinuation trial of cabozantinib reported a 10.0% (6/60) ORR and a 58.3% (35/60) DCR, with median PFS of 4.2 months, for patients with genomically unselected, heavily pretreated NSCLC[506]. Patients with EGFR wild-type non-squamous NSCLC who had progressed after previous treatment experienced longer median PFS with cabozantinib alone or combined with erlotinib (4.3 and 4.7 months, HR=0.39 and 0.37, respectively) compared with single agent erlotinib (1.8 months) in a randomized Phase 2 trial[507]. A Phase 1 study of cabozantinib for advanced solid tumors reported an ORR of 20.0% (4/20; 4 PRs, all in EGFR-mutated tumors) and DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[508].

**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**
*CCNE1*

**ALTERATION**
amplification

**RATIONALE**
Strong preclinical and clinical data suggest that CCNE1 amplification may predict sensitivity to WEE1 inhibitors.

## NCT02513563

**PHASE 2**

AZD1775 Plus Carboplatin-Paclitaxel in Squamous Cell Lung Cancer

**TARGETS**
WEE1

**LOCATIONS:** Florida, Ohio

## NCT04768868

**PHASE 1**

The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients With Advanced Solid Tumors

**TARGETS**
WEE1

**LOCATIONS:** Georgia, Texas, Kentucky, Kansas, Beijing (China), Taipei (Taiwan), Taoyuan (Taiwan), Wuhan (China), Taichung (Taiwan)

## NCT03968653

**PHASE 1**

Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors

**TARGETS**
WEE1

**LOCATIONS:** Barcelona (Spain), Leiden (Netherlands), Nijmegen (Netherlands), Groningen (Netherlands)

**GENE**
## *EGFR*

**ALTERATION**
exon 19 deletion (E746_A750del)

**RATIONALE**
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies. On the basis of extensive clinical evidence, MET amplification may predict resistance to first-, second-, and third-generation EGFR TKIs in EGFR-mutated non-small cell lung cancer (NSCLC).

### NCT03778229

**PHASE 2**

Osimertinib Plus Savolitinib in EGFRm+/MET+ NSCLC Following Prior Osimertinib

**TARGETS**
EGFR, MET

**LOCATIONS:** Santiago (Chile), Barretos (Brazil), Porto Alegre (Brazil), São Paulo (Brazil), Sao Paulo (Brazil), Hato Rey (Puerto Rico), Rio de Janeiro (Brazil), Salvador (Brazil), Florida, District of Columbia

### NCT04606771

**PHASE 2**

A Study Comparing Savolitinib Plus Osimertinib vs Savolitinib Plus Placebo in Patients With EGFRm+ and MET Amplified Advanced NSCLC

**TARGETS**
MET, EGFR

**LOCATIONS:** Caba (Argentina), Buenos Aires (Argentina), California, Mumbai (India), Rohini (India), Bangalore (India), Taipei 112 (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan)

### NCT03940703

**PHASE 2**

A Study of Tepotinib Plus Osimertinib in Epidermal Growth Factor Receptor (EGFR ) Tyrosine Kinase Inhibitor (TKI) Relapsed Mesenchymal-epithelial Transition Factor (MET) Amplified Non-small Cell Lung Cancer (NSCLC)

**TARGETS**
MET, EGFR

**LOCATIONS:** Florida, Texas, Tennessee, Kentucky, Maryland, New York, Massachusetts, Illinois, California

### NCT04077463

**PHASE 1**

A Study of Lazertinib as Monotherapy or in Combination With JNJ-61186372 in Japanese Participants With Advanced Non-small Cell Lung Cancer

**TARGETS**
EGFR, MET

**LOCATIONS:** Rio Piedras (Puerto Rico), Florida, Virginia, Pennsylvania, Missouri, New York, Massachusetts, Michigan, California

### NCT02795156

**PHASE 2**

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

**TARGETS**
BRAF, VEGFRs, RET, KIT, EGFR, ERBB4, ERBB2, MET, ROS1

**LOCATIONS:** Florida, Tennessee, Missouri, Wisconsin, Colorado

### NCT02609776

**PHASE 1**

A Dose Escalation Study of JNJ-61186372 in Participants With Advanced Non-Small Cell Lung Cancer

**TARGETS**
MET, EGFR

**LOCATIONS:** Florida, Texas, Virginia, Maryland, Pennsylvania, Missouri, New York, Massachusetts, Michigan, Illinois

## NCT02716116

**PHASE 1/2**

A Trial of AP32788 in Non-Small Cell Lung Cancer

**TARGETS**
EGFR, ERBB2

**LOCATIONS:** Florida, Georgia, North Carolina, Virginia, Arizona, California

## NCT03755102

**PHASE NULL**

A Study of Dacomitinib in Patients With Metastatic EGFR Mutant Lung Cancer Previously Treated With Osimertinib

**TARGETS**
ERBB4, EGFR, ERBB2

**LOCATIONS:** New Jersey, New York

## NCT03944772

**PHASE 2**

Phase 2 Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy (ORCHARD)

**TARGETS**
EGFR, PD-L1, RET, MET, ALK

**LOCATIONS:** Texas, Maryland, New York, Connecticut, Massachusetts, Illinois, California

## NCT03392246

**PHASE 2**

A Phase 2 Study of Osimertinib in Combination With Selumetinib in EGFR Inhibitor naïve Advanced EGFR Mutant Lung Cancer

**TARGETS**
MEK, EGFR

**LOCATIONS:** North Carolina, Massachusetts

**GENE**
*MET*

**ALTERATION**
amplification - equivocal

**RATIONALE**
Activating MET alterations may confer sensitivity to MET inhibitors. On the basis of extensive clinical evidence, MET amplification may predict resistance to first-, second-, and third-generation EGFR TKIs in EGFR-mutated non-small cell lung cancer (NSCLC).

## NCT03778229

**PHASE 2**

Osimertinib Plus Savolitinib in EGFRm+/MET+ NSCLC Following Prior Osimertinib

**TARGETS**
EGFR, MET

**LOCATIONS:** Santiago (Chile), Barretos (Brazil), Porto Alegre (Brazil), São Paulo (Brazil), Sao Paulo (Brazil), Hato Rey (Puerto Rico), Rio de Janeiro (Brazil), Salvador (Brazil), Florida, District of Columbia

## NCT04606771

**PHASE 2**

A Study Comparing Savolitinib Plus Osimertinib vs Savolitinib Plus Placebo in Patients With EGFRm+ and MET Amplified Advanced NSCLC

**TARGETS**
MET, EGFR

**LOCATIONS:** Caba (Argentina), Buenos Aires (Argentina), California, Mumbai (India), Rohini (India), Bangalore (India), Taipei 112 (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan)

## NCT03940703

**PHASE 2**

A Study of Tepotinib Plus Osimertinib in Epidermal Growth Factor Receptor (EGFR ) Tyrosine Kinase Inhibitor (TKI) Relapsed Mesenchymal-epithelial Transition Factor (MET) Amplified Non-small Cell Lung Cancer (NSCLC)

**TARGETS**
MET, EGFR

**LOCATIONS:** Florida, Texas, Tennessee, Kentucky, Maryland, New York, Massachusetts, Illinois, California

## NCT03539536

**PHASE 2**

Study of Telisotuzumab Vedotin (ABBV-399) in Subjects With Previously Treated c-Met+ Non-Small Cell Lung Cancer

**TARGETS**
MET

**LOCATIONS:** Florida, Alabama, Mississippi, Texas, Craiova (Romania), Tennessee

## NCT03175224

**PHASE 1/2**

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

**TARGETS**
MET

**LOCATIONS:** Rio Piedras (Puerto Rico), Florida, Louisiana, South Carolina

## NCT04077099

**PHASE 1/2**

REGN5093 in Patients With MET-Altered Advanced Non-Small Cell Lung Cancer

**TARGETS**
MET

**LOCATIONS:** Bordeaux Cedex 9 (France), Montpellier (France), Florida, Texas, Alabama, Kentucky, District of Columbia, Pennsylvania, Missouri

## NCT02795156

**PHASE 2**

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

**TARGETS**
BRAF, VEGFRs, RET, KIT, EGFR, ERBB4, ERBB2, MET, ROS1

**LOCATIONS:** Florida, Tennessee, Missouri, Wisconsin, Colorado

## NCT03170960

**PHASE 1/2**

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

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

**LOCATIONS:** Florida, Louisiana, South Carolina, Texas, Georgia, Virginia

## NCT02609776

**PHASE 1**

A Dose Escalation Study of JNJ-61186372 in Participants With Advanced Non-Small Cell Lung Cancer

**TARGETS**
MET, EGFR

**LOCATIONS:** Florida, Texas, Virginia, Maryland, Pennsylvania, Missouri, New York, Massachusetts, Michigan, Illinois

## NCT03297606

**PHASE 2**

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

**GENE**
*MYC*

**ALTERATION**
amplification

**RATIONALE**
MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

## NCT04553133

**PHASE 1/2**

PF-07104091 as a Single Agent and in Combination Therapy

**TARGETS**
CDK6, Aromatase, CDK4, CDK2

**LOCATIONS:** Texas, Massachusetts, Michigan

## NCT04555837

**PHASE 1/2**

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

**TARGETS**
Aurora kinase A, PD-1

**LOCATIONS:** Texas

## NCT01434316

**PHASE 1**

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

**TARGETS**
PARP, CDK1, CDK9, CDK5, CDK2

**LOCATIONS:** Massachusetts

## NCT03220347

**PHASE 1**

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

**TARGETS**
BRD2, BRD3, BRD4, BRDT

**LOCATIONS:** Madrid (Spain), Kashiwa (Japan), Koto-ku (Japan), Chikusa-ku (Japan)

**GENE**
*RNF43*

**ALTERATION**
R145*

**RATIONALE**
Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway.

## NCT02521844

**PHASE 1**

A Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours

**TARGETS**
PORCN

**LOCATIONS:** Texas, North Carolina, Colorado, Singapore (Singapore)

## NCT01351103

**PHASE 1**

A Study of LGK974 in Patients With Malignancies Dependent on Wnt Ligands

**TARGETS**
PORCN, PD-1

**LOCATIONS:** Texas, Maryland, New York, California, Madrid (Spain), Valencia (Spain), Hospitalet de LLobregat (Spain), Barcelona (Spain), Rotterdam (Netherlands), Utrecht (Netherlands)

## NCT03447470

**PHASE 1**

Study to Evaluate the Safety and Tolerability of RXC004 in Advanced Malignancies

**TARGETS**
PORCN

**LOCATIONS:** Manchester (United Kingdom), Oxford (United Kingdom), Sutton (United Kingdom), London (United Kingdom), Newcastle (United Kingdom)

**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.

***ASXL1***
L1213F

***ATR***
amplification

***CARD11***
S794T

***EGFR***
T259M

***EPHB1***
amplification

***ERG***
amplification

***FANCA***
L1038V

***MED12***
F1221fs*74

***MLL2***
G2493E

***PDGFRB***
A1099V

***PIK3CB***
amplification

***PRKCI***
amplification

***SGK1***
E84K and amplification

***TEK***
L549V

***TERC***
amplification

***TIPARP***
amplification

***TNFAIP3***
amplification

***U2AF1***
amplification



Electronically signed by Erik Williams, M.D. | 25 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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

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

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

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

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

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

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



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

## ABOUT FOUNDATIONONE CDX

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

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

## INTENDED USE

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

## TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

## THE REPORT

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

### Diagnostic Significance

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

### Qualified Alteration Calls (Equivocal and Subclonal)

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

### Ranking of 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



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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 6.0.0

The median exon coverage for this sample is 910x



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

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