FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
PE

REPORT DATE
01 Feb 2021
ORDERED TEST #
ORD-1002521-02

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

PATIENT

DISEASE Lung adenocarcinoma

DATE OF BIRTH 20 November 1953
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID BP20-00860-1-A
SPECIMEN TYPE Block
DATE OF COLLECTION 21 December 2020
SPECIMEN RECEIVED 23 January 2021

Biomarker Findings

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

Genomic Findings

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

EGFR amplification
MET amplification - equivocal†
HGF amplification - equivocal†
RICTOR amplification
FGF10 amplification - equivocal†
PARP1 amplification
TP53 splice site 376-1G>A

† See About the Test in appendix for details.

9 Therapies with Clinical Benefit
0 Therapies with Lack of Response
28 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**
***MET* -** amplification - equivocal	Capmatinib 2A	Cabozantinib
10 Trials *see p. 18*	Crizotinib 2A	
***EGFR* -** amplification	Afatinib	Cetuximab
	Dacomitinib	Panitumumab
	Erlotinib	
10 Trials *see p. 14*	Gefitinib	
***HGF* -** amplification - equivocal	none	none
10 Trials *see p. 16*		
***RICTOR* -** amplification	none	none
9 Trials *see p. 20*		

☐ *NCCN category*

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

FGF10 - amplification - equivocal ..... p. 7
PARP1 - amplification ..... p. 7
TP53 - splice site 376-1G>A ..... p. 8

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

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]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Oct 2020).

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
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

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[26-30]. 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);[22-23,26-28,31-38]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[39], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[40], 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[41]. 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[42]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[43-44], several other large studies did find a strong association with increased TMB[45-48]. 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[49]. 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)[43]. 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[50]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[50-51].

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[52-53] and cigarette smoke in lung cancer[31,54], treatment with temozolomide-based chemotherapy in glioma[55-56], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[57-61], and microsatellite instability (MSI)[57,60-61]. 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[22-23,26-28,31-38,62].

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GENE
EGFR

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

EGFR amplification or expression may be associated with benefit from anti-EGFR antibodies, such as cetuximab[63-66], panitumumab[64], or necitumumab[67], or EGFR TKIs that target wild-type EGFR[68-72]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[73-74] that has also shown benefit in patients with CRC and melanoma[75-76]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[77-80]. Preclinical studies have reported that EGFR-mutant cells[77-79], including cells with exon 20 insertions[81], are sensitive to HSP90 inhibitors. Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[82-83]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases[84]. The reovirus Reolysin targets cells with activated RAS signaling[85-87] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[88-96]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[97]. Clinical and preclinical studies of lung cancer have shown that MET amplification is a common mechanism of resistance to EGFR inhibitors in first-line and later treatment settings[98-104]. Multiple studies have demonstrated that patients with a concurrent EGFR mutation and MET amplification, as recurrently observed at progression in patients with EGFR-mutated NSCLC on EGFR TKI, have benefited from a combination of MET- and EGFR-targeted therapies[98,103-106].

FREQUENCY & PROGNOSIS

Amplification of EGFR has been variously reported in 4-42% of non-small cell lung carcinoma (NSCLC) samples[107-111]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[109-114]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[115-116]. In lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival in all patients and of poor overall survival in patients with EGFR mutations[117-118]. Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival[119]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[120] or resected Stage 1 NSCLC[121].

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[122]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[110,123-124].

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GENE
MET

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

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. 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)[125]. Crizotinib has benefited patients with MET-amplified NSCLC of varied histologies[126-129], gastroesophageal cancer[130], glioblastoma[131], and carcinoma of unknown primary[132]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[133-134] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[135-136]. Tepotinib has demonstrated efficacy for patients with MET-amplified HCC[137] as a monotherapy, and in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[138-140] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[141] and gastric cancer either alone or in combination with docetaxel[142-143]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[144]. Patients with MET-amplified NSCLC[145] and gastric cancer[146] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapy regimens including rilotumumab, a monoclonal HGF-targeting antibody, as well as emibetuzumab, a monoclonal MET-targeting antibody, combined with ramucirumab[147]. Telisotuzumab vedotin, a MET antibody-drug conjugate, was reported to be active in MET-positive NSCLC with an ORR of 18.8% (3/16) and a DCR of 56.3%[148]. Clinical and preclinical studies of lung cancer have shown that MET amplification is a common mechanism of resistance to EGFR inhibitors in first-line and later treatment settings[98-104]. Multiple studies have demonstrated that patients with a concurrent EGFR mutation and MET amplification, as recurrently observed at progression in patients with EGFR-mutated NSCLC on EGFR TKI, have benefited from a combination of MET- and EGFR-targeted therapies[98,103-106].

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[109,145,149-155]. In the Phase 2 VISION study of patients with NSCLC, MET amplification was reported in 4.9% of samples[156]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[109,149,153,157-161], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[162]. 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[163]. 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[164-165]. 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)[166].

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[167-168]. MET has been reported to be amplified in cancer[169], with amplification positively correlating with protein expression in some cancer types[149,170-173] and associating with therapeutic response to MET inhibitors in a variety of cancer types[126-128,130-132,174-175].

GENE
HGF

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
On the basis of several preclinical studies in different cancer types, high HGF gene expression may associate with sensitivity to MET-targeted therapies, such as the approved multikinase inhibitors crizotinib and cabozantinib[176-180]. However, this hypothesis has not been extensively tested in clinical studies. Whereas patients with glioblastoma and high tumor HGF gene expression experienced longer survival and a higher objective response rate (5/14 vs. 0/16) on the MET-targeting antibody onartuzumab combined with the anti-VEGF antibody bevacizumab than with placebo plus bevacizumab[181], tumor HGF gene expression did not predict significant benefit from onartuzumab added to the EGFR-inhibitor erlotinib for patients with non-small cell lung cancer[182]. Anti-HGF antibodies, such as ficlatuzumab, are also under clinical investigation[183-184]. Preclinical studies have shown that increased HGF protein levels can induce resistance of EGFR-mutant lung tumors to EGFR inhibitors and of BRAF-mutant melanoma cells to RAF inhibitors; this resistance could be overcome by combination therapy with MET inhibitors[185-190].

FREQUENCY & PROGNOSIS
HGF mutation or amplification has been reported in 9% and 2% of lung adenocarcinomas, respectively[107], and in 3% and 1% of lung squamous cell carcinomas, respectively[108]. HGF protein expression has been identified in 57% of lung adenocarcinoma samples in one study, and associated with poor survival[191]. In patients with non-small cell lung cancer (NSCLC), including lung adenocarcinoma, low HGF protein levels and high HGF serum concentrations have been associated with longer and shorter overall survival, respectively[192-193].

FINDING SUMMARY
HGF encodes hepatocyte growth factor, also known as scatter factor, an activating ligand of the receptor tyrosine kinase MET. Certain splice isoforms of HGF may also act as MET antagonists[194-195]. HGF plays an important role in normal development, acting as a growth factor in a number of different tissues[194-195]. HGF and its receptor, MET, have been implicated in growth, invasion, and metastasis of many solid tumors[195]. HGF has been reported to be amplified in cancer[169], and may be biologically relevant in this context[196-197].

GENE
RICTOR

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
RICTOR amplification may indicate sensitivity to mTORC1/2 inhibitors[198] or dual PI3K/mTOR inhibitors[199]. A patient with RICTOR-amplified lung adenocarcinoma experienced SD for >18 months upon treatment with the dual mTORC1/2 inhibitor CC-223[198], and a patient with RICTOR-amplified metastatic thymic carcinoma achieved a PR upon treatment with a pan-PI3K/mTORC1/2 inhibitor PQR309[199]. However, 4/4 patients with small cell lung cancer and RICTOR amplification did not achieve an objective response or SD (PFS of 1.25 months) from treatment with vistusertib[200], and additional trials of vistusertib were terminated due to lack of efficacy[142]. RICTOR alterations, including amplification, have been implicated in resistance to the EGFR tyrosine kinase inhibitor erlotinib in patients with non-small cell lung carcinoma[201].

FREQUENCY & PROGNOSIS
In a genomic study of 1,070 lung cancer cases, focal amplification of RICTOR was detected in 14.6% of small cell lung cancers (7/48), 8.7% of large cell neuroendocrine carcinomas (2/23), 8.4% of adenocarcinomas (61/724), and 7.4% of squamous cell carcinomas (8/108)[198]. Published data investigating the prognostic implications of RICTOR alterations in lung cancer are limited (PubMed, Dec 2020). RICTOR amplification in lung cancer often co-occurs with mutations in KRAS, EGFR, or the PI3K–AKT–mTOR pathway, but has also been characterized as a driver alteration in lung cancer[198].

FINDING SUMMARY
RICTOR encodes an mTOR-binding protein that forms part of the rapamycin-insensitive mTORC2 complex, a regulator of cell metabolism and the cytoskeleton[202-204]. RICTOR amplification has been reported in cancer[205] and has been associated with clinical response to mTORC1/2 inhibition[206-207] .

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GENE
FGF10

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
A preclinical study reported that FGF10-driven migration and invasion of pancreatic cancer cell lines could be blocked by inhibitory antibodies targeting FGFR2[208], and a second study found that expression of dominant-negative FGFR1 or FGFR2 led to a decrease in tumor size in a prostate cancer xenograft model driven by FGF10, although the decrease was not statistically significant[209]. Clinical trials are ongoing for multiple inhibitors that target FGFR2 and other kinases, including the approved agents pazopanib, ponatinib, and lenvatinib, as well as pan-FGFR inhibitors such as AZD4547, infigratinib, CH5183284, and TAS-120; however, these agents have not been comprehensively tested in the context of FGF10 amplification or overexpression.

FREQUENCY & PROGNOSIS
Infrequent but recurrent amplification of FGF10 has been reported in multiple solid tumor types, including gallbladder cancer[210], gastric cancer[211], and esophageal squamous cell carcinoma (SCC)[212]; one small-scale study reported FGF10 amplification in 7/7 oral SCC cases[213]. Preclinical studies have shown that increased FGF10 expression and FGF10-FGFR1/2 signaling promotes cancer cell proliferation, invasion, migration, and tumorigenesis in a variety of tumor models[208-209,214-215].

FINDING SUMMARY
FGF10 encodes fibroblast growth factor 10, a ligand that primarily binds to FGFR2, but also FGFR1[216], with a broad range of functions in development and wound healing. FGF10 has been implicated in regulating the epithelial-mesenchymal transition in cancer cells[217] and during normal development[218]. Germline mutations in FGF10 have been implicated in aplasia of the lacrimal and salivary glands, an autosomal dominant developmental disorder[219]. Amplification of FGF10 has been reported in cancer[169] and may be biologically relevant in this context[196-197].

GENE
PARP1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
Multiple PARP inhibitors with activity against PARP1, including the approved therapies olaparib, niraparib, and rucaparib, are in clinical trials in solid and hematologic cancers, and have shown efficacy against cancers harboring inactivating mutations in DNA repair genes such as BRCA1/2[220-228]. A Phase 1/2 trial of olaparib and temozolomide in SCLC, which is characterized by strong expression of PARP1[229], showed a superior response rate compared to historical data for temozolomide alone[230]. However, further work is required to ascertain the strength of association between PARP1 amplification and expression, as well as between PARP1 amplification or expression and efficacy of PARP inhibitors. On the basis of preclinical studies, PARP1 mutations are not predicted to confer sensitivity to PARP inhibitors[231-233].

FREQUENCY & PROGNOSIS
PARP1 mutations have been reported in 1% of solid tumors, including in 8% of nonmelanoma skin cancers and 3% each of endometrial cancer, anal cancer, melanoma, and small bowel cancer samples[234]. PARP1 amplification is less frequent, reported in 0.3% of cases, with highest incidence of 3% in anal cancer and 2% in endometrial cancer[234]. In one study, high expression of PARP1 was associated with shorter overall survival of patients with classical GBM, but not in other GBM subtypes[235]. In the context of lung cancer, neuroendocrine tumors have been shown to express PARP1 at higher levels than adenocarcinomas and squamous cell carcinomas, with highest expression seen in small cell lung cancer (SCLC)[236].

FINDING SUMMARY
PARP1 encodes the dominant member of the poly(ADP-ribose) polymerase (PARP) family that plays roles in DNA damage repair (DDR) and cell cycle progression[237-238]. Several missense mutations in PARP1 have been reported in cancer, including the activating mutation L713F[231] and the hypomorphic variants F304L, V762A, and E988K[231,239-240]. PARP1 amplification has been reported as a rare but recurrent event in glioblastoma multiforme (GBM), where it was found to be associated with increased expression of PARP1 as well as with higher tumor grade[235]. Limited and conflicting data have been reported on the potential roles of PARP1 germline mutations in cancer predisposition[231,239-240].

GENE
TP53

ALTERATION
splice site 376-1G>A

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
376-1G>A

VARIANT ALLELE FREQUENCY (% VAF)
47.9%

POTENTIAL TREATMENT STRATEGIES

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[241-244], or p53 gene therapy and immunotherapeutics such as SGT-53[245-249] and ALT-801[250]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[251]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[252]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[253]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[254]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[142]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[255]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[249]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[256]. 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[257-258]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[259-260]. 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)[107-108,261-266], including 38-54% of lung adenocarcinomas and 47-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Sep 2020)[47-48,107-108]. 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[267]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[268]. 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[269-274]. 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[269-270]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[275]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[273,276-277]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[278]. Alterations such as seen here may disrupt TP53 function or expression[279-283].

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 with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Sep 2020)[284]. 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[285-287], including sarcomas[288-289]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[290] to 1:20,000[289]. 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[291]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Afatinib

Assay findings association

EGFR
amplification

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 or amplification may indicate sensitivity to afatinib. In Phase 2 studies of afatinib, patients with EGFR-amplified NSCLC achieved an objective response rate of 20% (5/25) and a disease-control rate of 64% (16/25)[71], and 2/5 patients with EGFR amplification in other solid tumors experienced stable disease[72].

SUPPORTING DATA

Afatinib enabled 1 PR and 1 SD for 2 patients with EGFR-amplified NSCLC in a Phase 2 study[292]. 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[293-299] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[292,300-308] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma 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[298]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[309].

Capmatinib

Assay findings association

MET
amplification - equivocal

AREAS OF THERAPEUTIC USE

Capmatinib is a Type Ib MET inhibitor that is FDA approved to treat patients with metastatic non-small cell lung cancer harboring MET exon 14 skipping-associated alterations.

GENE ASSOCIATION

On the basis of clinical data in NSCLC[133,138-140,310] , HCC[137], RCC[141], and gastric cancer[142], MET amplification may predict sensitivity to Type 1b 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[311].

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[312]. 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[313]. 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)[314], gastric cancer (n=9), or other advanced solid tumors (n=24)[315-316] .

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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)[126-128,317-318] , gastric cancer[174], gastroesophageal cancer[130], glioblastoma[131], and carcinoma of unknown primary[132], as well as in patients with MET-mutated cancers, including NSCLC[319-324] , renal cell carcinoma (RCC)[325], and histiocytic sarcoma[319]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[166,319-320,322-324] .

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[318]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[326-330] , ROS1 rearrangements[331-335] , an NTRK1 fusion[336], or MET activation[126-128,317-318,320-324,337-343] . 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)[331,344] . Additional patients with MET amplified NSCLC have been reported to experience clinical benefit from crizotinib in several case studies[126-128,340,343,345] . 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[346].

Dacomitinib

Assay findings association

EGFR
amplification

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

On the basis of clinical[347-349] and preclinical[350-351] data, EGFR amplification or activating mutation may indicate sensitivity to dacomitinib.

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)[347,352] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[353]. 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)[354]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[355-357] . 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[358]. 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)[356]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[359].

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Erlotinib

Assay findings association

EGFR
amplification

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. In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival (HR=0.44)[70]. Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved OS (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[68-69,360] .

SUPPORTING DATA

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[361].

Gefitinib

Assay findings association

EGFR
amplification

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

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy[362-368] . In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival (HR=0.44)[70]. Several meta-analyses spanning 14 to 20 studies of patients with advanced NSCLC receiving single-agent erlotinib or gefitinib (n=1725 to 1854) reported the association of increased EGFR copy number with improved OS (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[68-69,360] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[369-370] .

SUPPORTING DATA

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[105]. 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[371]; 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[372]. 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[373]. 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[365,374] . 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[375-376] . 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[377]. 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[378].

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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 to treat patients with advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) after prior treatment with sorafenib, or progressive, metastatic medullary thyroid cancer (MTC). 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[320,379] , as well as by extensive preclinical data[380-386] .

SUPPORTING DATA

Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[320]. 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[387]. 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[388]. 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[389].

Cetuximab

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[64].

SUPPORTING DATA

In previously untreated patients with non-small cell lung cancer (NSCLC), the FLEX study demonstrated that in NSCLC tumors with high expression of EGFR, treatment with cetuximab plus chemotherapy resulted in longer overall survival compared to chemotherapy alone; there was no clear association between cetuximab response and EGFR mutations in this trial[63]. In a Phase 2 study of 31 patients with Stage 3 NSCLC, the addition of cetuximab to radiotherapy and chemotherapy produced an overall response rate of 67%; EGFR gene copy number was not predictive of efficacy outcome[390]. A Phase 3 study of 938 patients with progressive non-small cell lung cancer after platinum-based therapy concluded that, in unselected patients, the addition of cetuximab to chemotherapy was not recommended in this second-line setting[391]. Cetuximab is also being studied as part of a therapeutic regimen for patients with EGFR mutations who develop secondary resistance to erlotinib or gefitinib. A Phase 1b study combining afatinib and the anti-EGFR antibody cetuximab in patients with advanced EGFR-mutant lung cancer with acquired resistance to erlotinib/gefitinib observed an overall objective response rate of 29%, and comparable response rates in both T790M-positive and T790M-negative tumors (32% vs. 25%)[392]. A Phase 1 study of combination erlotinib and cetuximab treatment in patients with NSCLC, including those with squamous tumors, inhibitor-resistant EGFR mutations, and wild-type EGFR, as well as those who had progressed on prior erlotinib treatment, reported partial responses in two of 20 patients and stable disease lasting at least 6 months in three of 20 patients[393]; however, in this study a patient identified with an exon 19 deletion and T790M progressed rapidly on cetuximab and erlotinib[394].

Panitumumab

Assay findings association

EGFR
amplification

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[64].

SUPPORTING DATA

In a Phase 2 trial in patients with advanced non-small cell lung cancer (NSCLC), the addition of panitumumab to paclitaxel/carboplatin did not result in improved clinical benefit[395], and subsequent studies investigating the addition of panitumumab to pemetrexed/cisplatin reported no benefit for patients with wild-type KRAS lung adenocarcinoma[396]. The combination of afatinib and panitumumab has been explored for 2 patients with EGFR T790M NSCLC, with 1 partial response reported[397].

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.

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

GENE
EGFR

ALTERATION
amplification

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Several strategies to overcome resistance are under investigation, including next-generation EGFR TKIs and EGFR inhibitor combinations.

NCT03137771

PHASE 2

Maintenance Chemotherapy With or Without Stereotactic Body Radiation Therapy in Treating Patients With Stage IV Non-small Cell Lung Cancer

TARGETS
EGFR, PD-1

LOCATIONS: Florida, Georgia, South Carolina, Louisiana

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Oklahoma, Pennsylvania, Indiana

NCT02795156

PHASE 2

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

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

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

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

NCT03829436

PHASE 1

TPST-1120 as Monotherapy and in Combination With (Nivolumab, Docetaxel or Cetuximab) in Subjects With Advanced Cancers

TARGETS
PD-1, PPARalpha, EGFR

LOCATIONS: Florida, North Carolina, Tennessee, Oklahoma, Maryland, Pennsylvania, New York, Massachusetts, Michigan

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

LOCATIONS: Florida, Virginia, Maryland, Pennsylvania, Missouri, New York, Massachusetts, Michigan, Illinois, Toronto (Canada)

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRPα, in Subjects With Advanced Solid and Hematologic Cancers

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Texas, Alabama, North Carolina, Tennessee, Oklahoma, Pennsylvania, Toronto (Canada), Arizona

NCT02099058

PHASE 1

A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors

TARGETS
MET, EGFR, PD-1

LOCATIONS: Texas, Tennessee, Virginia, New Jersey, Massachusetts, Michigan, Illinois, Colorado, California

NCT01553942

PHASE 2

Afatinib With CT and RT for EGFR-Mutant NSCLC

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Massachusetts

NCT02947386

PHASE 1/2

Nimotuzumab and Nivolumab in Treating Patients With Advanced Non-small Cell Lung Cancer

TARGETS
EGFR, PD-1

LOCATIONS: New York

GENE
HGF

ALTERATION
amplification - equivocal

RATIONALE
HGF amplification or activating mutations may predict sensitivity to therapeutic agents targeting its receptor, MET, or to agents directly targeting HGF.

NCT03906071

PHASE 3

Phase 3 Study of Sitravatinib Plus Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC

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

LOCATIONS: Florida, Louisiana

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

NCT04310007

PHASE 2

Testing the Addition of the Pill Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer

TARGETS
MET, RET, ROS1, VEGFRs, PD-1

LOCATIONS: Florida, Louisiana, Georgia, South Carolina, Texas, North Carolina

NCT02795156

PHASE 2

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

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

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

NCT02414139

PHASE 2

Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Florida, Georgia, Texas, South Carolina, North Carolina, Arkansas, Tennessee, Virginia, District of Columbia

NCT04173338

PHASE 1

Cabozantinib With Pemetrexed in Advanced Non-small Cell Lung Cancer, Urothelial Cancer and Malignant Mesothelioma

TARGETS
MET, RET, ROS1, VEGFRs

LOCATIONS: Georgia

NCT02099058

PHASE 1

A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors

TARGETS
MET, EGFR, PD-1

LOCATIONS: Texas, Tennessee, Virginia, New Jersey, Massachusetts, Michigan, Illinois, Colorado, California

NCT04139317

PHASE 2

Safety and Efficacy of Capmatinib (INC280) Plus Pembrolizumab vs Pembrolizumab Alone in NSCLC With PD-L1≥ 50%

TARGETS
MET, PD-1

LOCATIONS: Tennessee, Madrid (Spain), Valencia (Spain), Barcelona (Spain), Badalona (Spain), Toulouse Cedex 9 (France), LILLE Cédex (France), Bruxelles (Belgium), Yvoir (Belgium), Liege (Belgium)

NCT01639508

PHASE 2

Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity

TARGETS
MET, RET, ROS1, VEGFRs

LOCATIONS: New Jersey, New York

GENE
MET

RATIONALE
Activation of MET may lead to increased MET expression and activation and may therefore confer sensitivity to MET inhibitors.

ALTERATION
amplification - equivocal

NCT03906071

PHASE 3

Phase 3 Study of Sitravatinib Plus Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC

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

LOCATIONS: Florida, Louisiana

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

NCT04310007

PHASE 2

Testing the Addition of the Pill Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer

TARGETS
MET, RET, ROS1, VEGFRs, PD-1

LOCATIONS: Florida, Louisiana, Georgia, South Carolina, Texas, North Carolina

NCT02795156

PHASE 2

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

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

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

NCT02414139

PHASE 2

Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Florida, Georgia, Texas, South Carolina, North Carolina, Arkansas, Tennessee, Virginia, District of Columbia

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

LOCATIONS: Florida, Virginia, Maryland, Pennsylvania, Missouri, New York, Massachusetts, Michigan, Illinois, Toronto (Canada)

NCT03539536

PHASE 2

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

TARGETS
MET

LOCATIONS: Alabama, Texas, Tennessee, Kentucky, Arkansas, Virginia, Missouri, Pennsylvania

NCT04173338

PHASE 1

Cabozantinib With Pemetrexed in Advanced Non-small Cell Lung Cancer, Urothelial Cancer and Malignant Mesothelioma

TARGETS
MET, RET, ROS1, VEGFRs

LOCATIONS: Georgia

NCT02099058

PHASE 1

A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors

TARGETS
MET, EGFR, PD-1

LOCATIONS: Texas, Tennessee, Virginia, New Jersey, Massachusetts, Michigan, Illinois, Colorado, California

GENE
RICTOR

ALTERATION
amplification

RATIONALE
RICTOR amplification may predict sensitivity to dual mTORC1/mTORC2 inhibitors, as well as dual PI3K/mTOR inhibitors.

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, New Jersey, New York

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT04250545

PHASE 1

Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer

TARGETS
mTORC1, mTORC2, GLS

LOCATIONS: New York, California

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT03154294

PHASE 1

Evaluation of the Safety and Tolerability of TAK-228 With TAK-117 and Paclitaxel in Advanced Solid Tumors

TARGETS
PI3K-alpha, mTORC1, mTORC2

LOCATIONS: South Dakota

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Exeter (United Kingdom), Belfast (United Kingdom), Cardiff (United Kingdom), Bristol (United Kingdom), Wirral (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

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.

ALK
M338I

ARFRP1
A114V

C11ORF30 (EMSY)
E917A

ERRFI1
amplification

FLT1
S356C

H3F3A
amplification

MAP3K1
S939C

MLL2
P2717S

SDHA
amplification

TNFRSF14
amplification

Electronically signed by Donna Ferguson, M.D. | 01 February 2021
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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 Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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. 2020. All rights reserved. To view the most recent and complete version of the guideline, 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. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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

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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.

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 with no conflicts), 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 *BAP1, BRCA1, BRCA2, BRIP1, 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.

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 2.2.0

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The median exon coverage for this sample is 742x

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