PATIENT	PHYSICIAN	SPECIMEN
DISEASE Lung adenocarcinoma	ORDERING PHYSICIAN	SPECIMEN SITE
NAME	MEDICAL FACILITY	SPECIMEN ID
DATE OF BIRTH	ADDITIONAL RECIPIENT	SPECIMEN TYPE
SEX	MEDICAL FACILITY ID	DATE OF COLLECTION
MEDICAL RECORD #	PATHOLOGIST	SPECIMEN RECEIVED

CDx Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR exon 19 deletion (T751_I759>S)	Gilotrif® (Afatinib) Iressa® (Gefitinib) Tarceva® (Erlotinib)

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §

Tumor Mutation Burden 5.04 Muts/Mb §

CDKN2A loss §

CDKN2B loss §

EGFR amplification §

ERBB3 P1212S

MET T263M

MTAP loss §

NFKBIA amplification §

NKX2-1 amplification §

TP53 R282G

§ *Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.*

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the 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. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

TABLE 1

INDICATIONS	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E or V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Rubraca® (Rucaparib)

ABOUT THE TEST FoundationOne CDx™ is the first FDA-approved broad companion diagnostic for solid tumors.

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Foundation Medicine, Inc. | 1.888.988.3639

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FDA APPROVED CLAIMS - PAGE 1 of 1

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PATIENT

DISEASE Lung adenocarcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Microsatellite Status - MS-Stable
Tumor Mutation Burden - TMB-Low (5 Muts/Mb)

Genomic Findings

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

EGFR amplification, exon 19 deletion (T751_I759>S)
ERBB3 P1212S
MET T263M - subclonal †
CDKN2A/B loss
MTAP loss
NFKBIA amplification
NKX2-1 amplification
TP53 R282G

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

----

† See About the Test in appendix for details.

5 Therapies with Clinical Benefit in patient's tumor type   25 Clinical Trials

8 Therapies with Clinical Benefit in other tumor type

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutation Burden - TMB-Low (5 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)
EGFR - amplification, exon 19 deletion (T751_I759>S)	Afatinib	Cetuximab
	Erlotinib	Lapatinib
	Gefitinib	Panitumumab
	Osimertinib	
10 Trials *see p. 15*		
ERBB3 - P1212S	Afatinib	Ado-trastuzumab emtansine
		Lapatinib
		Pertuzumab
		Trastuzumab
		Trastuzumab-dkst
5 Trials *see p. 18*		
MET - T263M	Crizotinib	Cabozantinib
10 Trials *see p. 19*		

The content provided as a professional service by Foundation Medicine, Inc., has not been reviewed or approved by the FDA.

GENOMIC FINDINGS AND BIOMARKERS 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 Alterations section.

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. 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.

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PROFESSIONAL SERVICES - PAGE 2 of 20

BIOMARKER
Microsatellite status

CATEGORY
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[4-5]. 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)[6]. Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%)[5]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without[4].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported at various frequencies in non-small cell lung cancer (NSCLC) as well as in small cell lung cancer[7-12]. One study observed MSI-H in 0.8% (4/480) of lung adenocarcinoma cases; the MSI-H tumors occurred in patients with smoking history, and 3/4 MSI-H cases had nonsynchronous carcinomas in other organs, although none of the patients were diagnosed with Lynch syndrome[7].

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[13]. 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[13-15]. The tumor seen here is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[16-18]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[13,15,17-18].

BIOMARKER
Tumor Mutation Burden

CATEGORY
TMB-Low (5 Muts/Mb)

POTENTIAL TREATMENT STRATEGIES

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4[19], anti-PD-L1[20-22], and anti-PD-1 therapies[5,23-24]; FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) in patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[24]. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbor elevated mutational burden reported higher overall response rates to pembrolizumab[5,23-24]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses following treatment with pembrolizumab[25] or nivolumab[26], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab[27], and two pediatric patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[28]. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[19,29] and anti-PD-1/anti-PD-L1 treatments[21]. For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load [12.4 mutations (muts) per megabase (Mb)] compared to nonresponders (6.4 muts/Mb)[20], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival[22].

FREQUENCY & PROGNOSIS

Low TMB is observed more commonly in non-small cell lung carcinomas (NSCLC) harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are observed in approximately half of intermediate-high TMB cases[30]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[31-33], several other large studies did find a strong association with increased TMB[34-37]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median overall survival (OS) for tumors with a higher number of mutations in a limited gene set compared with lower mutation number (48.4 vs. 61.0 months)[32].

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[38-39] and cigarette smoke in lung cancer[24,40], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[41-45], and microsatellite instability (MSI)[41,44-45]. The tumor seen here harbors a low TMB. Compared to patients with tumors harboring higher TMB levels, patients with tumors harboring low TMB levels have experienced lower rates of clinical benefit from treatment with immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma[19], anti-PD-L1 therapy in urothelial carcinoma[20], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer[5,24].

GENE
EGFR

ALTERATION
amplification, exon 19 deletion (T751_I759>S)

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations or amplification may predict sensitivity to EGFR inhibitors including erlotinib, gefitinib, afatinib, osimertinib, cetuximab, panitumumab, and lapatinib[46-50]. Other EGFR-targeted therapies are also in clinical trials. A Phase 2 trial of the pan-ERBB inhibitor dacomitinib in patients with lung adenocarcinoma reported 98% (44/45) disease control [partial response (PR) or stable disease], including a 76% PR rate, in patients with EGFR exon 19 deletions or the L858R mutation; lower disease control and PR rates were reported in patients with other EGFR mutations, wild-type EGFR, or unknown EGFR status[51]. Third-generation EGFR inhibitors, such as osimertinib or rociletinib, selectively target mutated EGFR including the EGFR resistance variant T790M. Osimertinib is FDA approved to treat patients with EGFR T790M-positive advanced NSCLC and disease progression on EGFR inhibitor therapy[49]. Necitumumab is an anti-EGFR antibody that is FDA approved for the treatment of metastatic squamous NSCLC in combination with gemcitabine and cisplatin. Addition of necitumumab increased overall and progression-free survival in patients with squamous NSCLC relative to chemotherapy alone; however, it exhibited a poor tolerability profile in non-squamous NSCLC, and EGFR expression has not been demonstrated to be predictive of clinical benefit in NSCLC[52-53]. HSP90 inhibitors have been clinically evaluated for patients with EGFR-mutated NSCLC[54-58] and have shown activity against NSCLC with certain EGFR mutations[59]. The reovirus Reolysin, which targets cells that harbor activated RAS signaling due to alterations in RAS genes or upstream activators such as EGFR[60-62], is also in clinical trials in some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for head and neck cancer[63-71].

FREQUENCY & PROGNOSIS

Amplification of EGFR has been reported in 6-42% of non-small cell lung carcinoma (NSCLC) samples[72-75]. EGFR mutations have been reported in 12-36% of lung adenocarcinoma samples, with amplification found in 7% of cases[34,73,76], and EGFR protein expression/overexpression has been reported in up to 70% of NSCLC tumors[77]. EGFR mutations were shown to predict survival advantage for patients with Stage 1-3 resected lung adenocarcinoma or NSCLC[78-79].

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[80]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[72,81-82]. The mutation seen here is a deletion in exon 19, encoding a portion of the kinase domain of EGFR; such mutations have been shown to activate EGFR kinase activity and to confer sensitivity to inhibitors such as erlotinib and gefitinib[83-85].

GENE
ERBB3

ALTERATION
P1212S

POTENTIAL TREATMENT STRATEGIES

ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling[86-88]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, such as pertuzumab, trastuzumab, ado-trastuzumab, lapatinib, and afatinib. In a study of afatinib monotherapy for patients with metastatic urothelial carcinoma, patients with ERBB3 mutation or ERBB2 amplification had significantly improved overall survival compared to patients without alterations (6.6 months vs. 1.4 months)[89]. A patient with HER2-negative breast cancer harboring an activating ERBB3 mutation had a partial response to the combination of trastuzumab and lapatinib[90]. In preclinical studies, cells with ERBB3 activating mutations were reported to be sensitive to anti-ERBB2 inhibition[86]. Antibodies targeting ERBB3 are also being studied in clinical trials. However, as the mutation reported here has not been characterized, it is not known if these therapeutic approaches would be relevant.

FREQUENCY & PROGNOSIS

ERBB3 mutations have been reported in up to 1% of lung adenocarcinomas[73,86]. ERBB3 protein expression has been reported in 18% (9/51) of lung adenocarcinomas[91]. High-level expression of ERBB3 mRNA has been associated with distant site metastases and poor overall survival in non-small cell lung cancer (NSCLC) patients[92].

FINDING SUMMARY

ERBB3, which is also known as HER3, encodes a member of the epidermal growth factor receptor (EGFR) family[93]. This ERBB3 mutation has not been characterized and its effect on ERBB3 function is unknown; however, mutation at this position has been reported previously in the context of cancer, which may indicate biological significance.

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

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GENOMIC FINDINGS

GENE
MET

ALTERATION
T263M

POTENTIAL TREATMENT STRATEGIES

Strong evidence suggests that MET activation may predict sensitivity to targeted therapies[94] such as crizotinib, FDA approved for the treatment of ALK-positive NSCLC[95], and cabozantinib, FDA approved for the treatment of metastatic medullary thyroid cancer[96]. Sensitivity to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[97-98][99-101], gastric cancer[102], gastroesophageal cancer[103], glioblastoma[104], and carcinoma of unknown primary[105], as well as in patients with MET-mutated cancers, including NSCLC[106-110], renal cell carcinoma (RCC)[111] and histiocytic sarcoma[106], and in patients with NSCLC[112] and pulmonary sarcomatoid carcinoma[113] whose tumors harbored both MET mutation and amplification. Sensitivity to cabozantinib is suggested by clinical benefit derived by a patient with MET-amplified and MET-mutated

NSCLC in one case report[107], as well as by extensive preclinical data[114-120]. Strong clinical data also suggest sensitivity of MET-altered tumors to various other MET inhibitors, with examples including AMG 337 in gastric, esophageal, or gastroesophageal junction cancer[121-122], volitinib in RCC[123], tepotinib in colorectal cancer[124], capmatinib in NSCLC[106], MGCD265 in NSCLC[125], PF-04217903 in RCC[126], and foretinib in RCC[127]. Furthermore, the MET-targeting antibodies onartuzumab and MetMAb have elicited responses for patients with MET-amplified NSCLC[128] or gastric cancer[129]. In addition, high MET expression has been suggested to predict patient response to therapy regimens involving rilotumumab, a monoclonal antibody that targets the MET ligand HGF[130]. However, in cases of uncharacterized alterations, such as seen here, it is unclear whether these therapeutic approaches would be relevant.

FREQUENCY & PROGNOSIS

In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in ~3% of samples[106]. In the TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung

squamous cell carcinomas[73,131]. MET amplification has been reported in up to 11% of non-small-cell lung cancer (NSCLC) cases and has been found to increase following treatment with EGFR inhibitors[74,132-134]. The prognostic implications of MET amplification, gain, and/or protein overexpression in NSCLC have yielded conflicting results, with some studies reporting no association and others finding a correlation with decreased survival and poor prognosis[74,132,135-138].

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[94,139]. Alterations such as reported here have not been characterized and are of unclear functional significance; however, similar alterations have been reported in the context of cancer, which may indicate biological relevance. Multiple MET activating alterations have exhibited clinical sensitivity to a variety of MET inhibitors in multiple cancer types[106-111,126-127].

GENE
CDKN2A/B

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Preclinical data suggest that tumors with loss of p16INK4a and p15INK4b function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[140-143]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[144-145], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[146-147][148-152]; it is not known whether CDK4/6 inhibitors would be

beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[153-154], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A/B loss or mutation has been reported in 19% and 4% of lung adenocarcinomas, respectively[73]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-43% of NSCLC samples[155-159]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[156,160-162].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[163-164]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[155,165]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[166-167]. This alteration is predicted to inactivate p16INK4a[168-171], p15INK4b[172], and p14ARF[173-174].

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Foundation Medicine, Inc. | 1.888.988.3639

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PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

GENOMIC FINDINGS

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Inactivation of MTAP is being explored for specific metabolic vulnerabilities. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, providing competition to purine poisons lacking in MTAP-deficient cells[175-183]. However, such combination approaches are not being clinically tested, and a Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy in 65 patients with MTAP-deficient cancers reported no responses and stable disease in 24% of patients[184]. Other

approaches have been described in preclinical studies[185-187], but these have not been clinically tested.

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[188-189]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[190], gastrointestinal stromal tumors[191], mantle cell lymphoma (MCL)[192], melanoma[193-194], gastric cancer[195], myxofibrosarcoma[196], nasopharyngeal carcinoma[197], ovarian carcinoma[188] and non-small cell lung cancer[198]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[199] or in astrocytoma[200]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[201], and MTAP retention is thought to be important for prostate cancer growth due to

continuous supply of SAM[202]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[203-204], esophageal cancer[205-206], osteosarcoma[207], and CRC[208].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[209-210]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[190,211-212], thereby reducing intracellular arginine methylation[185-187] and altering cell signaling[212-213]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE
NFKBIA

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no therapies that directly target NFKBIA amplification or expression.

FREQUENCY & PROGNOSIS

In the TCGA datasets, amplification of NFKBIA has been reported with the highest incidence in

lung adenocarcinoma (11.7%)[73], esophageal carcinoma (3.8%), uterine carcinosarcoma (3.6%), lung squamous cell carcinoma (3.4%), and ovarian serous cystadenocarcinoma (2.6%) (cBioPortal, 2017). Amplification or increased expression of NFKBIA in EGFR-mutant lung cancer has been reported to predict improved response to EGFR tyrosine kinase inhibitors[214-215]. Certain NFKBIA polymorphisms, which may affect IkBa expression levels, have been studied as risk factors for some cancer types, although the data are mixed and conflicting[216-218].

FINDING SUMMARY

NFKBIA encodes IkBa, an inhibitor of the NF-kappaB (NFkB)/REL complex. It has been reported to act as a tumor suppressor in Hodgkin's lymphoma[219-223] and in glioblastoma[216,224-225]. NFKBIA has been reported to be amplified in cancer[226] and may be biologically relevant in this context[227-228]. In contrast, truncating mutations that result in loss of the majority of the IkBa protein are predicted to be inactivating.

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Foundation Medicine, Inc. | 1.888.988.3639

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PROFESSIONAL SERVICES · PAGE 6 of 20

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PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

GENOMIC FINDINGS

GENE
NKX2-1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies or trials that target tumors with TTF-1 amplification or overexpression. Lung cancer cell lines that express both TTF-1 and NKX2-8, which is located in the same amplicon as NKX2-1, have demonstrated resistance to cisplatin therapy[229], although conflicting data has also been reported[230].

FREQUENCY & PROGNOSIS

Putative amplification of NKX2-1 has been reported with the highest incidence in lung cancer, and has been observed in 14% of adenocarcinomas[73] and 5% of squamous cell carcinomas (SCC)[131] as well as other tumor types including prostate adenocarcinomas (6%)[231], and poorly differentiated and anaplastic thyroid cancers (4%)[232]. NKX2-1 mutation has been observed in 9% of acinar cell carcinomas of the pancreas[233], 5% of uterine carcinosarcomas[234], and is infrequent in other tumor types (cBioPortal, COSMIC, 2017). TTF-1 is expressed in a majority of lung adenocarcinomas and small cell carcinomas, as well as in a subset of thyroid and CNS tumors[235-237]. Cytoplasmic TTF-1 expression has been reported as an adverse prognostic factor in breast carcinoma[238-239]. However, whether amplification and/or expression status of NKX2-1 have prognostic implications for patients with lung cancer is controversial[229-230,240-243]. TTF-1 has been observed to have tumor-promoting as well as anti-oncogenic roles[244-245].

FINDING SUMMARY

NKX2-1 (NK2 homeobox 1) encodes the thyroid transcription factor TTF-1[246]. Amplification of NKX2-1 results in overexpression of TTF-1 and upregulated transcription of downstream target genes[247].

GENE
TP53

ALTERATION
R282G

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 AZD1775[248-251], therapies that reactivate mutant p53 such as APR-246[252-255], or p53 gene therapy and immunotherapeutics such as SGT-53[256-260] and ALT-801[261]. In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53-wild-type[262]. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer[263]. Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel[264]. In a Phase 1b trial in 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% disease control rate[252]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage[260]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[265]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53[266]. Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer. TP53 mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[73,131,158,267-271]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[272]. 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[23].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[273]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[274-276]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[277-282]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[283] to 1:20,000[282], and in the appropriate clinical context, germline testing of TP53 is recommended.

FOUNDATIONONE CDx™

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Afatinib

Assay findings association

EGFR
ERBB3
P1212S

APPROVED INDICATIONS

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.

GENE ASSOCIATION

Activation or amplification of EGFR 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)[284], and 2/5 patients with EGFR amplification in other solid tumors experienced stable disease[285]. ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling, ERBB2/HER2 in particular[86-88,286]; therefore, ERBB3 amplification or activating mutations may indicate sensitivity to therapies such as afatinib. Partial response (PR) or stable disease (SD) was elicited in 5/7 patients with urothelial carcinoma harboring ERBB3 mutations (V104M, R103G, or G284R) and/or HER2 copy number gain treated with afatinib[89].

SUPPORTING DATA

Phase 3 clinical trials have demonstrated that treatment with afatinib, compared with chemotherapy, leads to significantly increased progression-free survival (PFS) for patients with EGFR-mutant NSCLC[48,287] and increased overall survival (OS) for patients with EGFR exon 19 alterations specifically[288]. A Phase 3 trial comparing afatinib with erlotinib as second-line therapies for advanced lung squamous cell carcinoma reported significantly higher OS (7.9 months vs. 6.8 months) and disease control rate (DCR) (51% vs. 40%) for patients treated with afatinib[289]. A Phase 2b trial comparing afatinib with gefitinib in patients with EGFR-mutant NSCLC reported similar OS (27.9 months vs. 24.5 months), but significantly higher time-to-treatment failure (13.7 months vs. 11.5 months), and overall response rate (73% vs. 56%)[290]. Phase 2/3 studies of afatinib treatment for patients with erlotinib- or gefitinib-resistant NSCLC have generally reported partial responses (PRs) of only 7-9%[291-296] and DCRs of more than 50%[295]; in particular, disease control was achieved for 2/2 patients with EGFR-amplified NSCLC[295] and 9/14 patients with T790M-positive NSCLC[296]. The T790M mutation has been implicated in reduced response to afatinib[294,297-299], with a secondary T790M mutation reported in 48% (20/42) of patients with afatinib-resistant lung adenocarcinoma[297]. The combination of afatinib with cetuximab resulted in a higher response rate (29%) for patients with erlotinib- or gefitinib-resistant disease[300], including T790M-positive cases[300-301], although adverse reactions may be a concern with this combination[302]. Upon progression on afatinib, further benefit has been reported from combination treatment with afatinib and paclitaxel[303] and with afatinib and cetuximab[304].

Crizotinib

Assay findings association

MET
T263M

APPROVED INDICATIONS

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are positive for ALK rearrangements or ROS1 rearrangements.

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)[97-98,99-101], gastric cancer[102], gastroesophageal cancer[103], glioblastoma[104], and carcinoma of unknown primary[105], as well as in patients with MET-mutated cancers, including NSCLC[106-110], renal cell carcinoma (RCC)[111] and histiocytic sarcoma[106]. However, it is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data indicate activity of crizotinib in MET-activated NSCLC, including lung adenocarcinoma and lung squamous cell carcinoma. In two ongoing studies of crizotinib (AcSé, NCT02034981 and PROFILE 1001, NCT00585195), 4 partial responses (PRs) and 4 stable diseases (SDs) were reported in 14 evaluable patients[97], and 4 PRs were reported in 12 evaluable patients[305] with MET-amplified NSCLC. Additional patients with MET-amplified NSCLC have been reported to experience clinical benefit from crizotinib in several case studies[99-101,306-308]. 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; this combination regimen was well tolerated[309]. A case report of a patient with chemotherapy-refractory, pulmonary sacomatoid carcinoma with a MET exon 14 splice site alteration and amplification experienced a partial response to crizotinib treatment[113]. In an ongoing expansion cohort of the PROFILE 1001 study, patients with NSCLC harboring MET exon 14 alterations experienced an overall response rate of 44% to crizotinib, including 8 confirmed PRs and 9 SDs out of 18 patients; treatment duration ranged from 0.5 to 12.2+ months, with 76% (16/21) of patients still on study[310]. Several case studies have also reported response to crizotinib in NSCLC with MET exon 14 alterations, with or without concomitant MET amplification[107-110,112,306,311-313]. In patients with NSCLC and MET overexpression with or without gene amplification, crizotinib elicited 11 PRs and 3 SDs in 19 evaluable patients[98]. However, as the mutation reported here has not been characterized, it is not known if this therapeutic approach would be relevant.

Erlotinib

Assay findings association

EGFR
amplification, exon 19 deletion
(T751_I759>S)

APPROVED INDICATIONS

Erlotinib is a small molecule inhibitor of EGFR. It is FDA approved both as first-line and maintenance therapy, as well as second- or greater line of treatment after chemotherapy failure, 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.

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 [hazard ratio (HR)=0.44][314]. 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 overall survival (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[315-317].

SUPPORTING DATA

The initial approval of erlotinib in NSCLC was based on the BR.21 Phase 3 randomized trial demonstrating prolonged overall survival for unselected patients with NSCLC treated with erlotinib compared with standard chemotherapy[318]. Furthermore, several randomized Phase 3 trials have shown a significant improvement in response and progression-free survival for erlotinib compared with combination chemotherapy in patients with known EGFR mutations. This includes the EURTAC trial of erlotinib versus platinum-based chemotherapy as first-line treatments[46] and the SATURN trial of erlotinib as maintenance therapy following first-line platinum-based chemotherapy[319]. On the other hand, the efficacy of erlotinib for patients lacking the common EGFR activating alterations (exon 19 deletion or L858R mutation) may be regimen-dependent. For patients with NSCLC and wild-type EGFR, chemotherapy was found to be more effective than erlotinib as first-, second-, or third-line treatment[320-322]. However, as maintenance therapy, erlotinib reduced risk for progression compared with placebo by 19% (hazard ratio = 0.81)[322]. The single-arm, Phase IV TRUST trial for genomically unselected patients with advanced NSCLC who failed on, or were unsuitable for, chemotherapy or who were ineligible for erlotinib clinical trials reported a disease control rate of 69%[323].

Gefitinib

Assay findings association

EGFR
amplification, exon 19 deletion
(T751_I759>S)

APPROVED INDICATIONS

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.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as gefitinib. In a prospective study of advanced NSCLC treated with gefitinib (n=102), EGFR copy gain was significantly associated with improved survival [hazard ratio (HR)=0.44][314]. 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 overall survival (HR=0.72 to 0.77), although the survival benefit was not observed for East Asian populations (HR=0.79 to 1.11)[315-317].

SUPPORTING DATA

Gefitinib achieved an objective response rate of 69.8% and an overall survival of 19.2 months as first-line treatment of Caucasian patients with NSCLC and EGFR sensitizing mutations, which were mostly EGFR exon 19 deletions and EGFR L858R[47]. In the retrospective analysis of a Phase 3 study in Asia, gefitinib increased progression-free survival in a subgroup of patients with EGFR mutation-positive NSCLC as compared with carboplatin/paclitaxel doublet chemotherapy (hazard ratio for progression 0.48)[324-325].

Osimertinib

Assay findings association

EGFR
amplification, exon 19 deletion
(T751_I759>S)

APPROVED INDICATIONS

Osimertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI) that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved to treat patients with metastatic EGFR T790M-positive non-small cell lung cancer (NSCLC) and disease progression on or after EGFR TKI therapy.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations and/or the EGFR T790M mutation may predict sensitivity to osimertinib[49,326]. T790M-positive patients showed higher response rates than T790M-negative cases in a Phase 1 study for patients with acquired EGFR TKI resistance (61% vs. 21%)[49]. Although tumors with EGFR amplification may not be sensitive to osimertinib, which selectively targets mutated EGFR, preclinical data indicate sensitivity of various activating EGFR alterations to osimertinib[326].

SUPPORTING DATA

Osimertinib has been studied primarily for the treatment of EGFR-mutated NSCLC. In a Phase 3 study for patients with EGFR T790M-positive advanced NSCLC who progressed on EGFR tyrosine kinase inhibitor (TKI) therapy, osimertinib compared with combination platinum therapy led to longer median progression-free survival (PFS; 10.1 months vs. 4.4 months), including for patients with metastases to the central nervous system (CNS; 8.5 months vs. 4.2 months). An objective response rate (ORR) of 71% was achieved with osimertinib compared to 31% with combination platinum therapy[327]. Earlier phase studies confirmed the efficacy of osimertinib in this setting[49,328-329]. In contrast, T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and median PFS of 2.8 months[49]. As first-line therapy for advanced NSCLC with activating, sensitizing EGFR mutations, osimertinib compared with erlotinib or gefitinib significantly increased median PFS (18.9 vs. 10.2 months, hazard ratio of 0.46), including for patients with CNS metastases, and showed a superior toxicity profile[330]. First-line efficacy of osimertinib is supported by Phase 1 data (ORR of 77% and median PFS of 20.5 months across doses)[331]. A Phase 1b study combined osimertinib with the immunotherapy durvalumab, MEK inhibitor selumetinib, or MET inhibitor savolitinib and observed partial responses (PRs) for each of the combinations (9/14 PRs with durvalumab, 9/23 PRs with selumetinib, 6/11 PRs with savolitinib)[332]. Case studies report that 2 patients with T790M-mutated NSCLC achieved durable PRs to osimertinib rechallenge after the adverse events induced by initial osimertinib treatment had been resolved[333-334].

Electronically signed by Shakti Ramkissoon, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director
Foundation Medicine, Inc. | 1.888.988.3639

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

PROFESSIONAL SERVICES · PAGE 10 of 20

Ado-trastuzumab emtansine

Assay findings association

ERBB3
P1212S

APPROVED INDICATIONS

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, inhibiting HER2 signaling[335-336]; it also releases the cytotoxic therapy DM1 into cells, leading to cell death[336-337]. T-DM1 is FDA approved for the treatment of HER2-positive (HER2+), metastatic breast cancer.

GENE ASSOCIATION

ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling, ERBB2/HER2 in particular[86-88,286]; therefore, ERBB3 amplification or activating mutations may indicate sensitivity to therapies such as T-DM1. However, it is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A patient with non-small cell lung cancer, disease progression on two prior lines of chemotherapy, and an activating ERBB2 alteration (exon 20 insertion) experienced a rapid and durable response to T-DM1[338-339]. The vast majority of data on the therapeutic use of T-DM1 has been collected in the context of breast cancer, although clinical trials investigating T-DM1 are underway in several tumor types, primarily in HER2+ cancers. A Phase 3 trial in 602 patients with HER2+ breast cancer reported that those who received T-DM1 showed an improved progression-free survival (PFS) and a lower rate of adverse events than patients who received the physician's choice of therapy[340]. A second Phase 3 trial in 991 patients with HER2+ breast cancer reported that T-DM1 brought about significantly longer overall survival (OS) and PFS, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab plus a taxane[341-342]. Two separate Phase 2 trials reported robust activity for single-agent T-DM1 as a treatment for HER2+ metastatic breast cancer in patients previously treated with standard HER2-directed therapies or HER2-directed therapies plus chemotherapy, with objective response rates of 34.5% and 25.9%, respectively, and PFS of 6.9 months and 4.9 months, respectively[343-344].

Cabozantinib

Assay findings association

MET
T263M

APPROVED INDICATIONS

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved to treat advanced renal cell carcinoma (RCC), after prior anti-angiogenic therapy, and progressive, metastatic medullary thyroid cancer (MTC).

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[107,345], as well as by extensive preclinical data[114-120]. However, it is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Early clinical data report promising activity of cabozantinib in non-small cell lung carcinoma (NSCLC) harboring RET fusions or MET alterations. A Phase 2 study of cabozantinib in RET-rearranged lung adenocarcinoma reported an objective response rate (ORR) of 28%, with 7 partial responses (PRs) in 25 evaluable patients, median progression-free survival (PFS) of 6 months and overall survival of 10 months[346-347]. In a retrospective analysis of patients with RET-rearranged NSCLC treated with various RET inhibitors, of the 14 patients treated with cabozantinib, 1 complete response (CR), 3 PRs, and 4 stable diseases (SDs) were reported, for an ORR of 31% and a disease control rate of 62%[348]. Additional studies of single-agent cabozantinib have reported 2 PRs and 1 SD in a series of 5 patients with RET-rearranged lung adenocarcinoma[349], a CR in a patient with lung adenocarcinoma harboring MET amplification and a mutation associated with MET exon 14 skipping[107], and intracranial activity of cabozantinib in a patient with MET-mutated NSCLC without co-occurring MET amplification who had previously progressed on crizotinib[345]. In genomically unselected patients with metastatic NSCLC, a Phase 2 randomized discontinuation trial of cabozantinib in a heavily pretreated cohort reported PRs in 10% (6/60) of patients, tumor regression in 65% (31/48) of patients, a median PFS of 4.2 months, and a safety profile similar to that of other tyrosine kinase inhibitors[350]. In patients with EGFR wild-type non-squamous NSCLC who have progressed after previous treatment, patients treated with cabozantinib alone or in combination with erlotinib experienced a longer median PFS (4.3 months and 4.7 months, respectively) compared to single agent erlotinib (1.8 months)[351].

Cetuximab

Assay findings association

EGFR
amplification, exon 19 deletion
(T751_I759>S)

APPROVED INDICATIONS

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 metastatic colorectal cancer (CRC).

GENE ASSOCIATION

EGFR activating mutations or amplification may confer sensitivity to EGFR inhibitory antibodies such as cetuximab. For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved overall survival (hazard ratio = 0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[352]. In HNSCC, however, EGFR copy number did not associate with the efficacy of cetuximab plus chemotherapy[353].

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[50]. There was no clear association between cetuximab response and EGFR mutations in the FLEX trial[50]. In a Phase 2 study of 31 patients with Stage 3 NSCLC, addition of cetuximab to radiotherapy and chemotherapy produced an overall response rate of 67%; EGFR gene copy number was not predictive of efficacy outcome[354]. A Phase 3 study of 938 patients with progressive NSCLC after platinum-based therapy concluded that, in unselected patients, the addition of cetuximab to chemotherapy was not recommended in this second-line setting[355]. 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%)[300]. 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[356].

Lapatinib

Assay findings association

EGFR
ERBB3
P1212S

APPROVED INDICATIONS

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.

GENE ASSOCIATION

Activation or amplification of EGFR may predict sensitivity to lapatinib. However, a Phase 2 study of lapatinib in non-small cell lung cancer (NSCLC) did not observe any responses for five patients with EGFR amplification[357]. ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling, ERBB2/HER2 in particular[86-88,286]; therefore, ERBB3 amplification or activating mutations may indicate sensitivity to therapies such as lapatinib[86]. A patient with HER2-negative breast cancer harboring an activating ERBB3 mutation had a partial response to the combination of trastuzumab and lapatinib[90].

SUPPORTING DATA

Investigations into the efficacy of lapatinib have primarily been in the context of breast cancer. In preclinical assays, lapatinib reduced cell proliferation in vitro and reduced the number and size of tumors in mouse xenograft models of EGFR- and ERBB2-amplified NSCLC cells[358]. A Phase 1 study of single-agent lapatinib included 9 unselected patients with lung cancer and reported 1 case of prolonged stable disease[359]. In a Phase 2 trial in patients with advanced or metastatic NSCLC, lapatinib monotherapy did not result in significant tumor reduction, but further investigation of lapatinib in combination with other therapies may be warranted[357].

FOUNDATIONONE CDx™

Panitumumab

Assay findings association

EGFR
amplification, exon 19 deletion
(T751_I759>S)

APPROVED INDICATIONS

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of KRAS wild-type metastatic colorectal cancer (CRC).

GENE ASSOCIATION

EGFR activating mutations or amplification may confer sensitivity to EGFR inhibitory antibodies such as panitumumab. For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved overall survival (hazard ratio = 0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[352].

SUPPORTING DATA

In a Phase 2 trial of advanced non-small cell lung cancer (NSCLC), the addition of panitumumab to paclitaxel/carboplatin did not result in improved clinical benefit[360], and subsequent studies investigating the addition of panitumumab to pemetrexed/cisplatin reported no benefit for patients with wild-type KRAS lung adenocarcinoma[361]. The combination of afatinib and panitumumab has been explored for 2 patients with EGFR T790M NSCLC, with 1 partial response reported[302].

Pertuzumab

Assay findings association

ERBB3
P1212S

APPROVED INDICATIONS

Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is FDA approved in combination with trastuzumab and docetaxel to treat patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. It is also approved in combination with trastuzumab and chemotherapy as neoadjuvant treatment for HER2+, locally advanced, inflammatory, or early stage breast cancer and as adjuvant treatment for patients with HER2+ early breast cancer at high risk of recurrence.

GENE ASSOCIATION

ERBB3 amplification or activating mutations may predict sensitivity to pertuzumab. However, it is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Pertuzumab received FDA approval based on a Phase 3 randomized study that demonstrated significant improvement in progression-free survival (PFS), with a trend toward improvement in overall survival (OS), for the combination of pertuzumab, trastuzumab, and docetaxel, as compared to treatment with trastuzumab and docetaxel alone, for patients with HER2-positive breast cancer[362-363]. In a Phase 1 study of pertuzumab in advanced cancer, 2/19 patients reported partial responses and 6/19 patients reported stable disease after two cycles, including one patient with lung cancer[364]. In another Phase 1 study in Japanese patients with solid tumors, no responses were observed and stable disease was reported in 1 of 7 patients with NSCLC[365]. In a Phase 2 study of pertuzumab in NSCLC, no responses were observed and the progression-free survival was 6.1 weeks[366]. Phase 1 and 2 trials of pertuzumab in combination with erlotinib in NSCLC have reported a response rate of 20% (3/15, 2 of the responders had mutant EGFR)[367]; a reduction in circulating tumor cells was noted and correlated with reduction in tumor size[368]. In a Phase 2 study of pertuzumab plus erlotinib in relapsed patients with NSCLC, PET-CT imaging showed that the primary endpoint of response rate (RR) was met in 19.5% of all patients (n = 41) and in 8.7% of patients with wild-type EGFR NSCLC (n = 23); however, 68.3% (28/41) of patients showed treatment-related grade 3 (or higher) adverse events[369].

THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE

Trastuzumab

Assay findings association

ERBB3
P1212S

APPROVED INDICATIONS

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with other therapies for HER2-positive (HER2+) metastatic and early breast carcinoma and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma.

GENE ASSOCIATION

ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling, ERBB2/HER2 in particular[86-88,286]; therefore, ERBB3 amplification or activating mutations may indicate sensitivity to therapies such as trastuzumab[86]. A patient with HER2-negative breast cancer harboring an activating ERBB3 mutation had a partial response to the combination of trastuzumab and lapatinib[90]. However, it is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 clinical trial of docetaxel with trastuzumab in non-small cell lung cancer (NSCLC) reported partial responses in 8% of patients; response did not correlate with HER2 status as assessed by immunohistochemistry[370]. Another Phase 2 study of 169 patients with NSCLC reported an objective response rate of 23% (7/30 patients) in the patients treated with a combination therapy of docetaxel and trastuzumab, and 32% (11/34) in patients treated with paclitaxel and trastuzumab[371]. HER2 expression did not impact the results of this study[371]. In a Phase 2a umbrella basket study, trastuzumab plus pertuzumab elicited objective responses for 2/7 patients with NSCLC and ERBB2 amplification or overexpression[372]. A patient with lung adenocarcinoma that was HER-positive by FISH and harbored an ERBB2 G776L mutation experienced a partial response on trastuzumab and paclitaxel[373]. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported in 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy[374].

Trastuzumab-dkst

Assay findings association

ERBB3
P1212S

APPROVED INDICATIONS

Trastuzumab-dkst is FDA approved as a biosimilar therapy to trastuzumab. Trastuzumab-dkst is a monoclonal antibody that targets the protein ERBB2/HER2, and is FDA approved as monotherapy and in combination with chemotherapy for HER2-positive (HER2+) metastatic and early breast carcinoma and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal junction adenocarcinoma.

GENE ASSOCIATION

ERBB3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling, HER2 in particular[86-88,286]; therefore, ERBB3 amplification or activating mutations may indicate sensitivity to anti-HER2 therapies such as trastuzumab-dkst[86]. A patient with HER2-negative breast cancer

harboring an activating ERBB3 mutation had a partial response to the combination of trastuzumab and lapatinib[90]. However, it is not known if this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

The Phase 3 Heritage study demonstrated comparable 24-week objective response rates (69.6% vs. 64.0%) and progression-free survival for patients with treatment-naïve HER2+ metastatic breast cancer treated with either trastuzumab-dkst or trastuzumab in combination with taxane[375]. In both patients with HER2+ breast cancer and in healthy adults, trastuzumab-dkst demonstrated comparable pharmacokinetic, safety, and immunomodulation profiles to trastuzumab[375-376 377].

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

FOUNDATIONONE CDx™

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

CLINICAL TRIALS

IMPORTANT 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, exon 19 deletion (T751_I759>S)

RATIONALE
EGFR amplification or activating mutations may predict sensitivity to EGFR-targeted therapies. Several strategies to circumvent resistance are under investigation, including irreversible EGFR tyrosine kinase inhibitors and the use of HSP90 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "EGFR", "cetuximab", "panitumumab", "erlotinib", "gefitinib", "lapatinib", "afatinib", "osimertinib", "BIBW 2992", "CO-1686", "AZD9291", "PF-00299804", "HSP90", "reolysin", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

NCT02193282	PHASE 3

Randomized Double Blind Placebo Controlled Study of Erlotinib or Placebo in Patients With Completely Resected Epidermal Growth Factor Receptor (EGFR) Mutant Non-Small Cell Lung Cancer (NSCLC)

TARGETS
EGFR

LOCATIONS: Kentucky, Tennessee, New Jersey, Alaska, Delaware, North Dakota, Montana, Ohio, Rhode Island, Maine, New Hampshire, Arizona, Wyoming, Hawaii, Georgia, South Carolina, West Virginia, Connecticut, Vermont, California, Michigan, Alabama, Nebraska, Texas, Arkansas, Nevada, Idaho, Washington, Iowa, Mississippi, Missouri, Wisconsin, Colorado, Louisiana, Virginia, South Dakota, New York, Oklahoma, Utah, Massachusetts, Florida, Maryland, Oregon, Indiana, Kansas, District of Columbia, Illinois, Minnesota, North Carolina, Pennsylvania, New Mexico

NCT02511106	PHASE 3

A Phase III, Double-blind, Randomized, Placebo-controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 Versus Placebo, in Patients With Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA).

TARGETS
EGFR

LOCATIONS: Maryland, Guangzhou (China), Rio Grande do Sul (Brazil), Beer-Sheva (Israel), Hoofddorp (Netherlands), Vinnytsia (Ukraine), Nanjing (China), Taichung (Taiwan), Hamburg (Germany), Poznan (Poland), Kurralta Park (Australia), Iasi (Romania), Beijing (China), Saint-Petersburg (Russian Federation), Ankara (Turkey), Virginia, Milano (Italy), Seoul (Korea, Republic of), Muang (Thailand), Dnipropetrovsk (Ukraine), Fortaleza (Brazil), Zaporizhzhya (Ukraine), Limoges (France), Brussels (Belgium), Gent (Belgium), St. Petersburg (Russian Federation), Halle (Germany), Budapest (Hungary), New Jersey, Bron (France), Lugo (Spain), Changchun (China), Saint Petersburg (Russian Federation), Lyon (France), Curitiba (Brazil), Hawaii, Hangzhou (China), Zaragoza (Spain), Camperdown (Australia), Bergamo (Italy), Yonago-shi (Japan), Großhansdorf (Germany), Chiayi (Taiwan), Roma (Italy), Tainan (Taiwan), Łódź (Poland), Paris (France), Illinois, Otwock (Poland), Colorado, Immenhausen (Germany), Bedford Park (Australia), São José do Rio Preto (Brazil), Aachen (Germany), Arnhem (Netherlands), Washington, Kashiwa-shi (Japan), Taipei (Taiwan), Parma (Italy), Racibórz (Poland), San Sebastian (Spain), Shinjuku-ku (Japan), Liou Ying Township (Taiwan), Ho Chi Minh (Vietnam), Sagamihara-shi (Japan), Bunkyo-ku (Japan), Málaga (Spain), Sunto-gun (Japan), Kanazawa (Japan), Kogarah (Australia), Timisoara (Romania), Sankt-Peterburg (Russian Federation), Ube-shi (Japan), Suwon-si (Korea, Republic of), Suwon (Korea, Republic of), Yangzhou (China), Yangzhou (China), Livorno (Italy), Changhua (Taiwan), Xi'an (China), Székesfehérvár (Hungary), Sakai-shi (Japan), Osakasayama-shi (Japan), Khonkaen (Thailand), Izmir (Turkey), Meldola (Italy), Urumqi (China), Sendai-shi (Japan), Matsuyama-shi (Japan), Yokohama-shi (Japan), Sasebo-shi (Japan), Bruxelles (Belgium), Phitsanulok (Thailand), Lucca (Italy), Gauting (Germany), Homburg (Germany), Ryazan (Russian Federation), Gerlingen (Germany), Suzhou (China), Linköping (Sweden), Lübeck (Germany), Arkhangelsk (Russian Federation), Chom Thon (Thailand), Tennessee, Hanoi (Vietnam), São Paulo (Brazil), Hirakata-shi (Japan), Hiroshima-shi (Japan), Focsani (Romania), Bangkok (Thailand), Tianjin (China), Coswig (Germany), Salvador (Brazil), Ottignies (Belgium), Urumchi (China), Brussels (Anderlecht) (Belgium), Torokbalint (Hungary), Bologna (Italy), Pyatigorsk (Russian Federation), Rhode Island, Majadahonda (Spain), Uzhgorod (Ukraine), Valencia (Spain), Porto Alegre (Brazil), Florida, Hong Kong (Hong Kong), Georgia, Cheongju-si (Korea, Republic of), Tel Hashomer (Israel), Las Palmas de Gran Canaria (Spain), A Coruña (Spain), Köln (Germany), Eindhoven (Netherlands), Kassel (Germany), Shanghai (China), Santa Catarina (Brazil), Madrid (Spain), Florianópolis (Brazil), Cachoeira De Itapemirim (Brazil), Lille cedex (France), Bursa (Turkey), Bari (Italy), Nagoya-shi (Japan), Palermo (Italy), Heidelberg (Australia), Lviv (Ukraine), Songkla (Thailand), Padova (Italy), Haifa (Israel), Kunming (China), Istanbul (Turkey), Zwolle (Netherlands), Barcelona (Spain), Kortrijk (Belgium), Barretos (Brazil), Zhengzhou (China), Moscow (Russian Federation), Trier (Germany), Bucuresti (Romania), Itajai (Brazil), Craiova (Romania), Berlin (Germany), Dalian (China), Oslo (Norway), Baudour (Belgium), Novara (Italy), Tel Aviv (Israel), Connecticut, Kfar Saba (Israel), Cremona (Italy), Petah Tikva (Israel), Nanning (China), Kitakyushu-shi (Japan), Elche (Spain), Woolloongabba (Australia), Kazan (Russian Federation), Darlinghurst (Australia), Xiamen (China), Sumy (Ukraine), Kobe-shi (Japan), Bucharest (Romania), Frankston (Australia)

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Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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NCT02411448 — PHASE 3

A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination With Ramucirumab or Placebo in Previously Untreated Patients With EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

TARGETS
EGFR, VEGFR2

LOCATIONS: Pordenone (Italy), Jinju (Korea, Republic of), Pok Fu Lam (Hong Kong), Texas, Chemnitz (Germany), Kaohsiung City (Taiwan), Poitiers (France), Hyogo (Japan), Dongjak-gu (Korea, Republic of), Taichung (Taiwan), Osaka (Japan), Cluj-Napoca (Romania), Pennsylvania, Kobe (Japan), Fukuoka (Japan), Grenoble (France), Gerlingen (Germany), Pamplona (Spain), Málaga (Spain), Okayama (Japan), Suwon (Korea, Republic of), Bucuresti (Romania), Torino (Italy), Milano (Italy), Montpellier (France), Taipei (Taiwan), Taoyuan (Taiwan), Hong Kong (Hong Kong), Akashi (Japan), Lille (France), New York, Berlin (Germany), Merseyside (United Kingdom), Wolverhampton (United Kingdom), Nagoya (Japan), Massachusetts, Nottingham (United Kingdom), Miyagi (Japan), Barcelona (Spain), Ravenna (Italy), Himeji (Japan), Hirakata (Japan), Paris (France), Ube (Japan), Hawaii, North Carolina, Edmonton (Canada), California, Ulm (Germany), Matsuyama (Japan), Kyoto (Japan), Hwasun (Korea, Republic of), Yau Ma Tei (Hong Kong), Bron (France), Kurume (Japan), London (United Kingdom), Nagasaki (Japan), Wakayama (Japan), Kansas, London (Canada), Lai Chi Kok (Hong Kong), Tokyo (Japan), Seowon-gu (Korea, Republic of), Kashiwa (Japan), Saitama (Japan), Preston (United Kingdom), Kishiwada (Japan), Florida, Großhansdorf (Germany), Sevilla (Spain), Otopeni (Romania), Valencia (Spain), Habikino (Japan), Bunkyo-Ku (Japan), Yokohama (Japan), Chelsea (United Kingdom), Palma de Mallorca (Spain), Tainan (Taiwan), Bologna (Italy), Osakasayama (Japan), Kanazawa (Japan), Niigata (Japan), Seoul (Korea, Republic of), Asahikawa (Japan), Athens (Greece), Seongnam-Si (Korea, Republic of), Shizuoka (Japan), Patras (Greece), Padova (Italy), Oregon, Sakai (Japan), Köln (Germany), Chiba (Japan), Ulsan-si (Korea, Republic of), Madrid (Spain), Heidelberg (Germany)

NCT02438722 — PHASE 2 / PHASE 3

A Randomized Phase II/III Trial of Afatinib Plus Cetuximab Versus Afatinib Alone in Treatment-Naive Patients With Advanced, EGFR Mutation Positive Non-small Cell Lung Cancer (NSCLC)

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Vermont, Kentucky, New York, Mississippi, Idaho, Iowa, New Jersey, Massachusetts, Florida, Indiana, Wisconsin, Oregon, North Dakota, Montana, Ohio, Tennessee, Maine, South Dakota, New Hampshire, Oklahoma, West Virginia, Hawaii, Pennsylvania, Colorado, South Carolina, Wyoming, California, Michigan, Kansas, Nebraska, Illinois, Missouri, Minnesota, North Carolina, Georgia, Connecticut, Texas, Washington, New Mexico, Arkansas

NCT01822496 — PHASE 2

A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer (NSCLC)

TARGETS
MET, EGFR, ALK, TOP2, ROS1, AXL, TRKC, TRKA

LOCATIONS: Connecticut, Idaho, Iowa, New Jersey, Massachusetts, Indiana, Oregon, Missouri, New Hampshire, Maine, Illinois, Colorado, Maryland, Oklahoma, Arizona, Wisconsin, South Carolina, Nebraska, Florida, Minnesota, Texas, Pennsylvania, California, West Virginia, Michigan, Ohio, Delaware, Georgia, North Carolina, New York

NCT01857271 — PHASE 2

EValuation of Erlotinib as a Neoadjuvant Therapy in Stage III NSCLC Patients With EGFR Mutations (EVENT Trial)

TARGETS
EGFR

LOCATIONS: New York

NCT02108964 — PHASE 1 / PHASE 2

A Phase I/II, Multicenter, Open-label Study of EGFRmut-TKI EGF816, Administered Orally in Adult Patients With EGFRmut Solid Malignancies

TARGETS
EGFR

LOCATIONS: Madrid (Spain), Taipei (Taiwan), Nagoya (Japan), Fukuoka (Japan), Massachusetts, Singapore (Singapore), Seoul (Korea, Republic of), New York, Berlin (Germany), Koeln (Germany), Milano (Italy), Amsterdam (Netherlands), Barcelona (Spain), Toronto (Canada)

NCT02716116 — PHASE 1 / PHASE 2

A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor AP32788 in Non-Small Cell Lung Cancer

TARGETS
EGFR, ERBB2

LOCATIONS: New York, California, Tennessee, Massachusetts, Colorado, Virginia

Electronically signed by Shakti Ramkissoon, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director
Foundation Medicine, Inc. | 1.888.988.3639

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

FOUNDATIONONE **CDx**™

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

CLINICAL TRIALS

NCT02574078

PHASE 1 / PHASE 2

A Master Protocol of Phase 1/2 Studies of Nivolumab in Advanced NSCLC Using Nivolumab as Maintenance After Induction Chemotherapy or as First-line Treatment Alone or in Combination With Standard of Care Therapies (CheckMate 370: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 370)

TARGETS
EGFR, PD-1

LOCATIONS: Mississippi, Nebraska, North Carolina, Ohio, Colorado, California, Tennessee, Oklahoma, Pennsylvania, New Mexico, Indiana, Alabama, Virginia, Kansas, Illinois, North Dakota, Minnesota, Oregon, New York, Michigan, Missouri, Louisiana, South Carolina, Maine, Texas, Nevada, Kentucky, Georgia, New Jersey, Washington, West Virginia, Montana, Arizona, Connecticut, South Dakota, Maryland, Florida

NCT02349633

PHASE 1 / PHASE 2

Phase 1/2 Open-Label Study Of PF-06747775 (Epidermal Growth Factor Receptor T790m Inhibitor) In Patients With Advanced Epidermal Growth Factor Receptor Mutant (Del 19 Or L858R ± T790M) Non-Small Cell Lung Cancer

TARGETS
EGFR

LOCATIONS: Seoul (Korea, Republic of), Washington, California, Connecticut, Pennsylvania

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Foundation Medicine, Inc. | 1.888.988.3639

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FOUNDATIONONE CDx™

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

CLINICAL TRIALS

GENE
ERBB3

ALTERATION
P1212S

RATIONALE

ERBB3 amplification or activating mutations may be associated with response to therapies targeting ERBB3. Additionally, the oncogenic effects of ERBB3 mutations have been shown to depend on ERBB2/HER2, and tumors with ERBB3 oncogenic mutations may therefore be sensitive to therapies that target ERBB2/HER2. However, because this mutation has not been functionally characterized, it is not known whether these approaches are beneficial here. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "ERBB3", "MM-121", "U3-1287", "AV-203", "afatinib", "pertuzumab", "lapatinib", "trastuzumab", "ado-trastuzumab emtansine", "lung", "NSCLC", "solid tumor", and/or "advanced cancer".

NCT01920061	PHASE 1

A Phase 1b Open-label Three-arm Multi-center Study To Assess The Safety And Tolerability Of Pf-05212384 (pi3k/Mtor Inhibitor) In Combination With Other Anti-tumor Agents

TARGETS
EGFR, mTORC1, ERBB2, PI3K-gamma, mTORC2, PI3K-alpha, ERBB4

LOCATIONS: London (United Kingdom), Massachusetts, South Carolina, California, Milan (Italy), Vancouver (Canada), Madrid (Spain), Pennsylvania, Toronto (Canada), Barcelona (Spain), Michigan, Roma (Italy)

NCT01306045	PHASE 2

Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies

TARGETS
AKTs, EGFR, RET, ERBB2, MEK, FLT3, VEGFRs, CSF1R, PDGFRs, KIT

LOCATIONS: Maryland

NCT02506517	PHASE 2

Molecular Basket Trial In Multiple Malignancies With Common Target Pathway Aberrancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Toronto (Canada)

NCT02451553	PHASE 1

Phase I/IB Multi-center Study of Irreversible EGFR/HER2 Tyrosine Kinase Inhibitor Afatinib (BIBW 2992) in Combination With Capecitabine for Advanced Solid Tumors and Pancretico-Biliary Cancers

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Indiana, Washington

NCT02912949	PHASE 1 / PHASE 2

A Phase I/II Study of MCLA-128, a Full Length IgG1 Bispecific Antibody Targeting HER2 and HER3, in Patients With Solid Tumors

TARGETS
ERBB2, ERBB3

LOCATIONS: Milan (Italy), Madrid (Spain), Paris (France), Amsterdam (Netherlands), Barcelona (Spain)

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GENE
MET

ALTERATION
T263M

RATIONALE

Activation of MET may lead to increased MET expression and activation and may therefore confer sensitivity to MET inhibitors. However, it is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "c-MET", "crizotinib", "cabozantinib", "INC280", "MGCD265", "NSCLC", and/or "solid tumor".

NCT01639508 — PHASE 2

A Phase II Study of 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, ROS1, RET, VEGFRs

LOCATIONS: New York, New Jersey

NCT02414139 — PHASE 2

A Phase II, Multicenter Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type (wt), Advanced Non-small Cell Lung Cancer (NSCLC)

TARGETS
MET

LOCATIONS: Arkansas, California, Connecticut, Florida, Georgia, Illinois, Iowa, Massachusetts, Michigan, Minnesota, Nebraska, New Hampshire, New York, Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Virginia, multiple ex-US locations

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NCT02954991 — PHASE 2

A Parallel Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination With Nivolumab in Advanced or Metastatic Non-Small Cell Lung Cancer

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

LOCATIONS: Virginia, Tennessee, Wisconsin, Pennsylvania, Alabama, Ohio, Michigan, California

---

NCT02693535 — PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
ABL, CDK4, PARP, EGFR, DDR2, VEGFRs, PDGFRs, ROS1, CSF1R, ERBB2, PD-1, ERBB3, MEK, RAF1, KIT, SMO, AXL, TRKC, mTOR, TRKA, MET, ALK, BRAF, RET, SRC, FLT3, CDK6

LOCATIONS: North Dakota, Pennsylvania, Washington, Illinois, Georgia, Arizona, Utah, North Carolina, Oklahoma, South Dakota, Michigan, Oregon, Nebraska

---

NCT02584634 — PHASE 2

A Phase 1b/2, Open Label, Dose Finding Study To Evaluate Safety, Efficacy, Pharmacokinetics And Pharmacodynamics Of Avelumab (msb0010718c) In Combination With Either Crizotinib Or Pf 06463922 In Patients With Advanced Or Metastatic Non Small Cell Lung Cancer Javelin Lung 101

TARGETS
MET, ALK, PD-L1, ROS1, AXL, TRKC, TRKA

LOCATIONS: Badalona (Spain), Camperdown (Australia), Barcelona (Spain), Georgia, Tennessee, Goyang-Si (Korea, Republic of), Goyang-si (Korea, Republic of), Melbourne (Australia), Massachusetts, Parkville (Australia), Fukuoka (Japan), Seoul (Korea, Republic of), Chermside (Australia)

FOUNDATIONONE CDx™

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

CLINICAL TRIALS

NCT00585195

PHASE 1

Phase 1 Safety, Pharmacokinetic And Pharmacodynamic Study Of Pf-02341066, A C-met/Hgfr Selective Tyrosine Kinase Inhibitor, Administered Orally To Patients With Advanced Cancer

TARGETS
MET, ALK, ROS1, AXL, TRKC, TRKA

LOCATIONS: New York, Michigan, California, Colorado, Pennsylvania, Akashi (Japan), Massachusetts, Melbourne (Australia), North Carolina, Ohio, Seoul (Korea, Republic of), Vermont, Sapporo (Japan), Osakasayama (Japan)

NCT00697632

PHASE 1

Open-Label Dose-Escalation Trial to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Daily Oral MGCD265 Administered Without Interruption to Subjects With Advanced Malignancies

TARGETS
MET, AXL

LOCATIONS: Texas, North Carolina, Pennsylvania, New York, Gyeonggi-do (Korea, Republic of), Edmonton (Canada), Montreal (Canada), Utah, Illinois, Massachusetts, Missouri, Vancouver (Canada), Seoul (Korea, Republic of), Washington, California

NCT02219711

PHASE 1

A Phase 1/1b Study of MGCD516 in Patients With Advanced Solid Tumor Malignancies

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

LOCATIONS: Texas, Nebraska, Tennessee, Wisconsin, Florida, Pennsylvania, Seoul (Korea, Republic of), Alabama, Virginia, South Carolina, Illinois, Utah, California, Missouri, New York, Washington, Massachusetts, Michigan, New Mexico

NCT02099058

PHASE 1

A Multicenter, Phase 1/1b, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors

TARGETS
MET, EGFR, VEGFA, PD-1

LOCATIONS: Villejuif, Cedex (France), Colorado, Illinois, Massachusetts, Tennessee, Michigan, Missouri, Marseille (France), California, North Carolina, Virginia, Texas

NCT02132598

PHASE 2

A Single-Arm Phase II Clinical Trial of Cabozantinib (XL184) in Patients With Previously Treated Non-Small Cell Lung Cancer (NSCLC) With Brain Metastases With and Without C Met Amplification

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Pennsylvania

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Electronically signed by Shakti Ramkissoon, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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FOUNDATIONONE CDx™

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

APPENDIX   Variants of Unknown Significance

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.

ATR A2165T	**EPHB1** I332V	**IDH1** I102T	**IRF2** E232G
IRF4 amplification	**NOTCH3** V508L	**ROS1** S1463N	**SDHA** amplification
TEK loss			

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APPENDIX - PAGE 1 of 13

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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the 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. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

INDICATION	GENOMIC FINDINGS	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E or V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib), in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Rubraca® (Rucaparib)

TABLE 1

The median exon coverage for this sample is 869x

FOUNDATIONONE CDx™

PATIENT

TUMOR TYPE
Lung adenocarcinoma

QRF#

APPENDIX   About FoundationOne CDX™

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 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 microsatellite instability (MS) and tumor mutational burden (TMB) will be reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
4. A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
5. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
6. Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.

7. Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
8. 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. Refer to the Summary of Safety of Effectiveness Data (SSED) for additional details on methodology. 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.
9. TMB by F1CDx is defined based on counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit. The clinical validity of TMB defined by this panel has not been established.
10. 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.
11. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.

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Foundation Medicine, Inc. | 1.888.988.3639

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FoundationOne CDx™ is designed to include all 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 28 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	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	WHSC1L1	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 A NCRNA
**THE PROMOTER REGION OF TERT INTERROGATED

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite Status (MS)
Tumor Mutation Burden (TMB)

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PATIENT

TUMOR TYPE
Lung adenocarcinoma

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APPENDIX | Information Provided as a Professional Service

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.

PROFESSIONAL SERVICES FINDINGS

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. 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.

RANKING OF ALTERATIONS AND DRUGS

Biomarker Findings
Appear at the top of the report, but are not ranked higher than Genomic Findings.

Genomic Findings
Therapies with Clinical Benefit In Patient's Tumor Type → Therapies with Clinical Benefit in Other Tumor Type → Clinical Trial Options → No Known Options (if multiple findings exist within any of these categories, the results are listed alphabetically by gene name).

Therapies
Sensitizing therapies → Resistant therapies (if multiple therapies exist within any of these categories, they are listed in no particular order).

Clinical Trials
Pediatric trial qualification → Geographical Proximity → Later trial phase.

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

Foundation Medicine makes no promises or guarantees that a particular drug will be effective in the treatment of disease of 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 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 with the 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.

Genomic Findings with Evidence of Clinical Significance
Genomic findings listed at Level 2 are associated with clinical significance. Clinical significance may be indicated by evidence of therapeutic sensitivity or resistance and/or diagnostic, prognostic or other clinically relevant implications. Included in this category will be findings associated with clinical validity as supported by professional guidelines and/or peer-reviewed publications.

Genomic Findings with Potential Clinical Significance
Genomic findings listed at Level 3 are cancer-related mutations and biomarkers with potential clinical significance. These include findings in genes known to be associated with cancer and are supported by evidence from publicly available databases, and/or peer-reviewed publications.

A Fluid Approach to Reporting Levels
As additional information becomes available, as recognized by the clinical community (professional guidelines and/or peer-reviewed publications), findings may move between Levels 2 and 3 in accordance with the above descriptions.

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

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Foundation Medicine, Inc. | 1.888.988.3639

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TUMOR TYPE
Lung adenocarcinoma

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Electronically signed by Shakti Ramkissoon, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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APPENDIX   References Associated with Professional Services Content

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PATIENT

TUMOR TYPE
Lung adenocarcinoma

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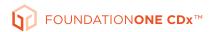
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TUMOR TYPE
Lung adenocarcinoma

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TUMOR TYPE
Lung adenocarcinoma

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APPENDIX | References Associated with Professional Services Content

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Electronically signed by Shakti Ramkissoon, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Directo
Foundation Medicine, Inc. | 1.888.988.3639

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

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PATIENT

TUMOR TYPE
Lung adenocarcinoma

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Electronically signed by Shakti Ramkissoon, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director
Foundation Medicine, Inc. | 1.888.988.3639

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

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