FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
05 May 2021
ORDERED TEST #
ORD-1075808-01

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

PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)

DATE OF BIRTH 11 June 1957
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Pleura
SPECIMEN ID 21-2591 A
SPECIMEN TYPE Block
DATE OF COLLECTION 06 April 2021
SPECIMEN RECEIVED 23 April 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

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

MET amplification, exon 14 splice site (3028+2_3028+23del22)
MDM2 amplification
MTAP loss
MYC amplification - equivocal†
CDKN2A/B CDKN2A loss, CDKN2B loss
PARP3 W101*

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

† See About the Test in appendix for details.

4 Therapies with Clinical Benefit
0 Therapies with Lack of Response
20 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**
***MET* -** amplification, exon 14 splice site (3028+2_3028+23del22)	Capmatinib 2A Crizotinib 2A Tepotinib 2A	Cabozantinib
10 Trials *see p. 12*		
***MDM2* -** amplification	none	none
4 Trials *see p. 11*		
***MTAP* -** loss	none	none
1 Trial *see p. 14*		
***MYC* -** amplification - equivocal	none	none
5 Trials *see p. 15*		

☐ *NCCN category*

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Oct 2020).

FINDING SUMMARY

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

BIOMARKER

Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-30]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[22-23,26-28,31-38]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[39], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[40], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[41]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[42]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[43-44], several other large studies did find a strong association with increased TMB[45-48]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[49]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[43]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[50]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[50-51].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[52-53] and cigarette smoke in lung cancer[31,54], treatment with temozolomide-based chemotherapy in glioma[55-56], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[57-61], and microsatellite instability (MSI)[57,60-61]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,31-38,62].

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GENE
MET

ALTERATION
amplification, exon 14 splice site (3028+2_3028+23del22)

TRANSCRIPT ID
NM_000245

CODING SEQUENCE EFFECT
3028+2_3028+23del22

VARIANT ALLELE FREQUENCY (% VAF)
50.9%

POTENTIAL TREATMENT STRATEGIES

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. Crizotinib has benefited patients with MET-amplified NSCLC of varied histologies[63-66], gastroesophageal cancer[67], glioblastoma[68], and carcinoma of unknown primary[69]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[70-71] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[72-73]. Tepotinib has demonstrated efficacy for patients with MET-amplified HCC[74] as a monotherapy, and in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[75-77] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[78] and gastric cancer either alone or in combination with docetaxel[79-80]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[81]. Patients with MET-amplified NSCLC[82] and gastric cancer[83] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapy regimens including rilotumumab, a monoclonal HGF-targeting antibody, as well as emibetuzumab, a monoclonal MET-targeting antibody, combined with ramucirumab[84]. Telisotuzumab vedotin, a MET antibody-drug conjugate, was reported to be active in MET-positive NSCLC with an ORR of 18.8% (3/16) and a DCR of 56.3%[85]. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, savolitinib, and foretinib have provided benefit for patients with MET-mutated papillary renal cell carcinoma (RCC)[86-89], histiocytic sarcoma[90], and non-small cell lung cancer (NSCLC) of varied histologies[91-95]. Patients with MET exon 14 mutated NSCLC who were treated with 1 of several MET inhibitors exhibited superior outcomes (median OS 24.6 vs. 8.1 months; HR=0.11, p=0.04) compared with patients who were not treated with a MET inhibitor[96]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations[97], and yielded a PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC[98]. In another study, 11 patients with hereditary papillary RCC and germline MET mutations (4 of which were H1094R) experienced 5 PRs and 5 SDs after treatment with foretinib[86]. Savolitinib yielded ORRs of 49% (30/61) in patients with MET exon 14 mutated NSCLC[99] and numerically higher ORR for patients with MET-driven papillary RCC compared to sunitinib (27% [9/33] vs. 7.4% [2/27])[89]. A Phase 1 study for patients with MET-altered NSCLC treated with MET inhibitor bozitinib monotherapy reported an overall ORR of 30.6% (11/36) and DCR of 97.2% (35/36) with MET overexpression, amplification, and exon 14 skipping demonstrating ORRs of 35.7% (5/14), 41.2% (7/17), and 66.7% (10/15), respectively; increased ORRs were observed in patients with both exon 14 skipping and amplification (100%, 4/4) and with both amplification and overexpression (50%, 3/6)[100]. A Phase 2 study evaluating the MET inhibitor savolitinib for patients with MET exon 14 splice site mutation-positive pulmonary sarcomatoid carcinoma and other types of NSCLCs reported 16/31 (52%) of patients achieved a PR[101].

FREQUENCY & PROGNOSIS

In the Phase 2 VISION study of patients with non-small cell lung cancer, MET exon 14 skipping alterations were reported in 3.6% of patients[102]. In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[90]. In TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[103-104]. MET amplification has been reported at incidences of 14-48% in non-small cell lung cancer (NSCLC), is correlated with increased MET protein expression, and occurs more frequently following treatment with EGFR inhibitors[82,105-112]. In the Phase 2 VISION study of patients with NSCLC, MET amplification was reported in 4.9% of samples[102]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[105,109-110,113-117], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[118]. MET exon 14 splice alteration, which has predominantly been observed in lung cancer, was found to be an independent poor prognostic factor in a study of 687 patients with NSCLC[119]. However, other studies did not find MET exon 14 splice alteration as a major risk factor for overall survival for NSCLC patients, although recurrence rate was significantly higher in patients with exon 14 splice alteration compared to those with ALK fusion[120-121]. Among NSCLC patients with exon 14 alterations that had not been previously treated with a MET inhibitor, a non-significant trend for reduced survival was noted in the context of concurrent MET amplification (5.2 vs 10.5 months, p = 0.06)[96].

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[122-123]. MET has been reported to be amplified in cancer[124], with amplification positively correlating with protein expression in some cancer types[105,125-128] and associating with therapeutic response to MET inhibitors in a variety of cancer types[63-65,67-69,129-130]. Certain MET alterations have been associated with the removal of exon 14[92,131-135] and/or loss of a binding site for the ubiquitin ligase CBL, an enzyme that targets MET for degradation[131,136-138]. Loss of either MET exon 14 or a CBL binding site increases MET stability, leading to prolonged signaling upon HGF stimulation and increased oncogenic potential[131,135,137-141]; these mutations are expected to be activating. Responses to various MET inhibitors have been reported for multiple patients with alterations in their tumors predicted to lack MET exon 14[90,92,142-146].

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GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[147]. Preclinical studies have suggested that amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[148-149]. Preliminary Phase 1 studies of the MDM2-p53 antagonist APG-115 reported a PR in a patient with liposarcoma harboring a MDM2 amplification and wild-type for TP53 and SD in 21.4%–38.5% (5/13 and 6/28) of patients in genomically unselected solid tumors[150-151] . Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[152-153] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[154]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wild-type peripheral T-cell lymphoma in a Phase 2 study[155]; responses have also been observed in TP53 wild-type AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[156-157] .

FREQUENCY & PROGNOSIS
In the TCGA datasets, amplification of MDM2 has been reported in 8% of lung adenocarcinoma cases[103] and 2% of lung squamous cell carcinoma cases[104]. Separate studies have reported MDM2 amplification at similar incidences of 6-7% in non-small cell lung cancer (NSCLC), mainly in patients with adenocarcinoma, but a higher incidence of 21% (24/116) has also been observed, with amplification found in various NSCLC subtypes[158-160]. The role of MDM2 expression/amplification as a prognostic marker is complex, with some studies showing a negative and others a positive effect on survival in patients with NSCLC[158,160-162].

FINDING SUMMARY
MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[163-165]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[166-167]. Overexpression or amplification of MDM2 is frequent in cancer[168]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[169] and 2/3 patients with MDM2 or MDM4 amplification[170] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[35]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[35].

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES
Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[171]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[172]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[171,173-174], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[175]; dual PRMT1 and PRMT5 inhibition may be more effective[176-178]. 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, thereby providing competition to purine poisons lacking in MTAP-deficient cells[179-189]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients[190].

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[191-192]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[193], gastrointestinal stromal tumors[194], mantle cell lymphoma (MCL)[195], melanoma[196-197], gastric cancer[198], myxofibrosarcoma[199], nasopharyngeal carcinoma[200], ovarian carcinoma[191] and non-small cell lung cancer[201]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[202] or in astrocytoma[203]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[204], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[205]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[206-207], esophageal cancer[208-209], osteosarcoma[210], and CRC[211].

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[212-213]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[193,214-215], thereby reducing intracellular arginine methylation[171,173,216] and altering cell signaling[215,217]. 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.

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GENE
MYC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1[218-219], CDK2[220], Aurora kinase A[221-228], Aurora kinase B[229-232], glutaminase[233-236], or BET bromodomain-containing proteins[237-240], as well as agents targeting both HDAC and PI3K[241-243]. A Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer but not for patients without MYC overexpression[244]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor[245]. The glutaminase inhibitor CB-839, in combination with either everolimus or cabozantinib, has demonstrated encouraging efficacy in Phase 1 and 2 studies enrolling patients with pretreated advanced renal cell carcinoma[246-247] . MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[248-249]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[250-251].

FREQUENCY & PROGNOSIS
MYC amplification has been reported in 10-50% of non-small cell lung cancer (NSCLC) samples, including adenocarcinoma and/or squamous cell carcinoma subtypes[252-256]. In the Lung Adenocarcinoma TCGA and Lung Squamous Cell Carcinoma TCGA datasets, putative MYC amplification has been reported in 9% and 4.5% of cases, respectively[103-104]. MYC amplification has been associated with metastasis in NSCLC, as well as with poor prognosis in early stage lung adenocarcinoma specifically[252-255].

FINDING SUMMARY
MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[257]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[258]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[257,259-260].

GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES
Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[261-264]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[265-266], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[267-273]; 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[149,274], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[268,270-271,275-277].

FREQUENCY & PROGNOSIS
CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[103]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[104]. 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 21-72% of NSCLC samples[104,278-283]. In patients with lung SCC, loss of CDKN2B associated with poor survival in one study[284]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[280,285-287].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[288-289]. 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[279,290]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[291-292]. One or more alterations observed here are predicted to result in p16INK4a loss of function[293-314]. One or more alterations seen here are predicted to result in p14ARF loss of function[297,314-317]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[318].

POTENTIAL GERMLINE IMPLICATIONS
Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[319]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[320-321]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[322-324]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[325-327]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENE
PARP3

ALTERATION
W101*

TRANSCRIPT ID
NM_005485

CODING SEQUENCE EFFECT
302G>A

VARIANT ALLELE FREQUENCY (% VAF)
11.6%

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies or clinical trials to address genomic alterations in PARP3. However, multiple PARP3 inhibitors are in preclinical development, with a particular focus on combinatorial approaches with other agents[328-330].

FREQUENCY & PROGNOSIS
PARP3 mutations have been reported in 3% of endometrial, 2% of large intestine, 2% of skin, and <1% of other tumor types (COSMIC 2021)[331]. Published studies have not investigated the effects of genomic alterations in PARP3 on the clinical or prognostic features of solid or hematologic malignancies.

FINDING SUMMARY
PARP3 encodes a member of the poly(ADP-ribose) polymerase (PARP) family that plays roles in DNA damage repair and cell cycle progression. Multiple functions of PARP3 have been reported in cellular response to DNA damage, including sensing nicked nucleosomes[332], stabilization of the mitotic spindle[333], promotion of both nonhomologous end-joining and homologous recombination via regulation of G-quadruplex DNA[334], and inhibition of G1/S cell cycle progression[335]. PARP3 alterations have not been characterized, but they have been reported in cancer, which may indicate biological relevance.

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

Capmatinib

Assay findings association

MET
amplification, exon 14 splice site (3028+2_3028+23del22)

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[70,97,99,336-338], MET mutations associated with exon 14 skipping may predict sensitivity to selective MET inhibitors. On the basis of clinical data in NSCLC[70,75-77,339], hepatocellular carcinoma (HCC)[74], renal cell carcinoma (RCC)[78], and gastric cancer[79], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Capmatinib monotherapy has demonstrated clinical activity for patients with advanced NSCLC harboring MET exon 14 skipping alterations and lacking EGFR mutations or ALK rearrangements[340-341]. The Phase 2 GEOMETRY mono-1 study reported a higher ORR (67.9% vs. 40.6%) and DCR (96.4% vs. 78.3%), and longer PFS (12.4 vs. 5.4 months) and median duration of response (12.6 vs. 9.7 months) for treatment-naive patients with exon 14 mutations when compared with those who were previously treated; no correlation was observed between patient responses and the presence of co-occurring MET amplification[336]. Additionally, this study recorded a 53.8% (7/13) intracranial response rate and 92.3% (12/13) intracranial DCR[340]. A retrospective analysis of the GEOMETRY mono-1 study compared with a cohort of real-world (RW) patients with NSCLC harboring MET exon 14 skipping alterations who received first-line chemotherapy and/or immunotherapy reported a longer PFS (mPFS 12.0 vs mrwPFS 6.2 months) for patients that received capmatinib compared to chemotherapy and/or immunotherapy used in the real-world[342]. In the Phase 2 GEOMETRY mono-1 study for patients with advanced NSCLC and MET gene copy number (GCN) ≥10, capmatinib elicited ORRs of 29–40%, median PFS of 4.1–4.2 months, and median OS of 9.6–10.6 months across treatment-naive and previously treated cohorts[343]. A Phase 1 study of capmatinib monotherapy for advanced EGFR- and ALK-wild-type NSCLC reported ORRs of 46.7% (7/15) for patients with MET GCN ≥6, 25% (3/12) for patients with MET GCN 4–6, and 5.9% (1/17) for patients with MET GCN <4; median PFS was 3.7 months overall, and 7.9 months for patients with MET GCN ≥6[341]. Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with glioblastoma (n=10)[344], gastric cancer (n=9), or other advanced solid tumors (n=24)[345-346].

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Crizotinib

Assay findings association

MET
amplification, exon 14 splice site (3028+2_3028+23del22)

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[63-65,347-348] , gastric cancer[129], gastroesophageal cancer[67], glioblastoma[68], and carcinoma of unknown primary[69], as well as in patients with MET-mutated cancers, including NSCLC[90,92-95,349] , renal cell carcinoma (RCC)[88], and histiocytic sarcoma[90]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[90,92-96] .

SUPPORTING DATA

The expansion cohort of the PROFILE 1001 study reported a 32.3% (21/65, 3 CRs) ORR, 7.3 month median PFS, and 20.5 month median OS for patients with advanced MET exon 14-altered NSCLC[350]. Other Phase 2 studies have reported ORRs of 20.0% to 35.7%, median PFS of 2.4 to 2.6 months, and median OS of 3.8 to 8.1 months for patients with MET-mutated NSCLC[351-352] . A retrospective study reported median PFS of 7.4 months in patients with MET exon 14-altered NSCLC treated with crizotinib[353]. In a small study for patients with NSCLC and MET overexpression with or without gene amplification, crizotinib elicited 11 PRs and 3 SDs in 19 evaluable patients[348]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[354-358] , ROS1 rearrangements[352,359-362] , an NTRK1 fusion[363], or MET activation[63-65,92-95,134,347-349,364-369] . The Phase 2 METROS and AcSe trials have reported ORRs of 31.3% to 32.0%, median PFS of 3.2 to 5.0 months, and median OS of 5.4 to 7.7 months for patients with MET amplified advanced non-small cell lung cancer (NSCLC); a higher level of amplification was predictive of better response in the AcSe trial (P=0.04)[351-352] . Additional patients with MET amplified NSCLC have been reported to experience clinical benefit from crizotinib in several case studies[63-65,367,369-370] . 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[371]. Two patients with ALK-positive NSCLC and acquired MET amplification experienced benefit from crizotinib monotherapy and crizotinib in combination with lorlatinib[372].

Tepotinib

Assay findings association

MET
amplification, exon 14 splice site (3028+2_3028+23del22)

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[70,97,99,336-338] , MET mutations associated with exon 14 skipping may predict sensitivity to selective MET inhibitors. On the basis of clinical data in NSCLC[70,75-77,339] , hepatocellular carcinoma (HCC)[74], renal cell carcinoma (RCC)[78], and gastric cancer[79], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

In the Phase 2 VISION study, tepotinib yielded an ORR of 45%, median duration of response (DOR) of 11 months, and median PFS of 8.9 months for patients with NSCLC and MET exon 14 skipping alterations, with similar ORRs observed for treatment-naïve and previously treated patients[97,338] . Among patients with brain metastases, tepotinib yielded an ORR of 57% (8/14)[373], median DOR of 9.5 months, and median PFS of 10.9 months[97]. Tepotinib has primarily been investigated in NSCLC, demonstrating efficacy as a single agent for patients with MET exon 14-skipping alterations[97,338] and in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or overexpression in Phase 2 studies[76-77] . A case study reported 1 PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC metastatic to the brain[98].

Cabozantinib

Assay findings association

MET
amplification, exon 14 splice site (3028+2_3028+23del22)

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved to treat patients with advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) after prior treatment with sorafenib, or progressive, metastatic medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[92,374] , as well as by extensive preclinical data[375-381] .

SUPPORTING DATA

Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[92]. A Phase 2 randomized discontinuation trial of cabozantinib reported a 10.0% (6/60) ORR and a 58.3% (35/60) DCR, with median PFS of 4.2 months, for patients with genomically unselected, heavily pretreated NSCLC[382]. Patients with EGFR wild-type non-squamous NSCLC who had progressed after previous treatment experienced longer median PFS with cabozantinib alone or combined with erlotinib (4.3 and 4.7 months, HR=0.39 and 0.37, respectively) compared with single agent erlotinib (1.8 months) in a randomized Phase 2 trial[383]. A Phase 1 study of cabozantinib for advanced solid tumors reported an ORR of 20.0% (4/20; 4 PRs, all in EGFR-mutated tumors) and DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[384].

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

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

GENE
MDM2

ALTERATION
amplification

RATIONALE
Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or amplification of MDM2 may increase sensitivity to these agents, but more data are required.

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Florida, Texas, Tennessee, Arkansas, Virginia, District of Columbia, Pennsylvania, Missouri

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Florida, Alabama, Texas, Tennessee, Pennsylvania, Ohio, Delaware

NCT03449381

PHASE 1

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TARGETS
MDM2

LOCATIONS: Florida, Tennessee, New York, Connecticut, Ottawa (Canada), Tokyo, Chuo-ku (Japan)

NCT03725436

PHASE 1

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

TARGETS
MDM2, MDM4

LOCATIONS: Texas

GENE
MET

ALTERATION
amplification, exon 14 splice site (3028+2_3028+23del22)

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

NCT03906071

PHASE 3

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

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

LOCATIONS: Florida

NCT03175224

PHASE 1/2

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

TARGETS
MET

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

NCT02693535

PHASE 2

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

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

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

NCT04310007

PHASE 2

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

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

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

NCT03170960

PHASE 1/2

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

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

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

NCT03539536

PHASE 2

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

TARGETS
MET

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

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NCT02795156

PHASE 2

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

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

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

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

NCT02864992

PHASE 2

Tepotinib Phase II Study in Lung Adenocarcinoma Harbouring MET Exon 14 (METex14) Skipping Alterations

TARGETS
MET

LOCATIONS: Texas, Missouri, New York, Madrid (Spain), Bayonne (France), Barcelona (Spain), Toulouse (France), Paris Cedex 10 (France)

NCT04139317

PHASE 2

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

TARGETS
MET, PD-1

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

GENE
MTAP

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors.

ALTERATION
loss

NCT03435250

PHASE 1

Study of AG-270 in Participants With Advanced Solid Tumors or Lymphoma With MTAP Loss

TARGETS
MAT2A

LOCATIONS: Tennessee, New York, Connecticut, Massachusetts, Barcelona (Spain), Villejuif Cedex (France)

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GENE
MYC

ALTERATION
amplification - equivocal

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

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Florida, Texas, Virginia, New York, Arizona

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Texas, New York, Ohio, Massachusetts, California, Madrid (Spain), Nantes (France), Barcelona (Spain), Villejuif (France), Paris (France)

NCT03654547

PHASE 1

Safety of TT-00420 Monotherapy in Patients With Advanced Solid Tumors and Triple Negative Breast Cancer

TARGETS
Aurora kinase A, Aurora kinase B

LOCATIONS: Texas

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK2, CDK5, CDK9

LOCATIONS: Massachusetts

NCT03220347

PHASE 1

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

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Madrid (Spain), Bordeaux (France), Barcelona (Spain), Villejuif (France), Rozzano (MI) (Italy), Meldola (Italy), Napoli, Campania (Italy), Kashiwa (Japan)

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.

ATM
D1935Y

BCOR
D851Y

CSF3R
G366R

FANCA
D953E

GATA6
rearrangement

IRS2
F983V

KDR
V1356A

MERTK
S159T

PDGFRA
F1059I

TSC1
K587R

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Alterations and Therapies

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit.

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Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

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SELECT ABBREVIATIONS

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

MR Suite Version 4.0.0

The median exon coverage for this sample is 904x

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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Warth A, et al. Virchows Arch. (2016) pmid: 26637197
7. Ninomiya H, et al. Br. J. Cancer (2006) pmid: 16641899
8. Vanderwalde A, et al. Cancer Med (2018) pmid: 29436178
9. Zang YS, et al. Cancer Med (2019) pmid: 31270941
10. Dudley JC, et al. Clin. Cancer Res. (2016) pmid: 26880610
11. Takamochi K, et al. Lung Cancer (2017) pmid: 28676214
12. Pylkkänen L, et al. Environ. Mol. Mutagen. (1997) pmid: 9329646
13. Gonzalez R, et al. Ann. Oncol. (2000) pmid: 11061602
14. Chen XQ, et al. Nat. Med. (1996) pmid: 8782463
15. Merlo A, et al. Cancer Res. (1994) pmid: 8174113
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
18. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
19. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
20. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
21. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
22. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
23. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
24. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
25. Cristescu R, et al. Science (2018) pmid: 30309915
26. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
27. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
28. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
29. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
30. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
31. Rizvi NA, et al. Science (2015) pmid: 25765070
32. Colli LM, et al. Cancer Res. (2016) pmid: 27197178
33. Wang VE, et al. J Immunother Cancer (2017) pmid: 28923100
34. Carbone DP, et al. N. Engl. J. Med. (2017) pmid: 28636851
35. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
36. Forde PM, et al. N. Engl. J. Med. (2018) pmid: 29658848
37. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
38. Chae YK, et al. Clin Lung Cancer (2019) pmid: 30425022
39. Paz-Ares et al., 2019; ESMO Abstract LBA80
40. Hellmann MD, et al. N. Engl. J. Med. (2019) pmid: 31562796
41. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
42. Spigel et al., 2016; ASCO Abstract 9017
43. Xiao D, et al. Oncotarget (2016) pmid: 27009843
44. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
45. Govindan R, et al. Cell (2012) pmid: 22980976
46. Ding L, et al. Nature (2008) pmid: 18948947
47. Imielinski M, et al. Cell (2012) pmid: 22980975
48. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
49. Stein et al., 2019; DOI: 10.1200/PO.18.00376
50. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
51. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
52. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
53. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
54. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
55. Johnson BE, et al. Science (2014) pmid: 24336570
56. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
57. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
58. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
59. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
60. Nature (2012) pmid: 22810696
61. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
62. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
63. Ou SH, et al. J Thorac Oncol (2011) pmid: 21623265
64. Schwab R, et al. Lung Cancer (2014) pmid: 24192513
65. Le X, et al. Clin Lung Cancer (2015) pmid: 25922291
66. Schrock AB, et al. J Thorac Oncol (2017) pmid: 28315738
67. Lennerz JK, et al. J. Clin. Oncol. (2011) pmid: 22042947
68. Chi AS, et al. J. Clin. Oncol. (2012) pmid: 22162573
69. Palma NA, et al. Case Rep Oncol (2014) pmid: 25232318
70. Schuler et al., 2016; ASCO Abstract 9067
71. Wu et al., 2018; WCLC Abstract P1.01-97
72. Gainor JF, et al. J Thorac Oncol (2020) pmid: 31864558
73. Gautschi O, et al. J Thorac Oncol (2020) pmid: 31864554
74. Faivre et al. 2021; ASCO GI Abstract 329
75. Yang et al., 2019; AACR Abstract CT193
76. Park et al., 2019; ESMO Abstract 477O
77. Wu et al., 2019; IASLC Abstract MA09.09
78. Gan HK, et al. Clin. Cancer Res. (2019) pmid: 30952639
79. Lee J, et al. Cancer Discov (2019) pmid: 31315834
80. Kim ST, et al. Transl Oncol (2019) pmid: 30695737
81. Kwak et al., 2015; ASCO GI Abstract 01
82. Spigel DR, et al. J. Clin. Oncol. (2013) pmid: 24101053
83. Catenacci DV, et al. Cancer Discov (2011) pmid: 22389872
84. Harding JJ, et al. Clin. Cancer Res. (2019) pmid: 31142504
85. Strickler JH, et al. J. Clin. Oncol. (2018) pmid: 30285518
86. Choueiri TK, et al. J. Clin. Oncol. (2013) pmid: 23213094
87. Diamond JR, et al. J. Clin. Oncol. (2013) pmid: 23610116
88. Stein MN, et al. Eur. Urol. (2015) pmid: 25457019
89. Choueiri TK, et al. JAMA Oncol (2020) pmid: 32469384
90. Frampton GM, et al. Cancer Discov (2015) pmid: 25971938
91. Engstrom LD, et al. Clin. Cancer Res. (2017) pmid: 28765324
92. Paik PK, et al. Cancer Discov (2015) pmid: 25971939
93. Jenkins RW, et al. Clin Lung Cancer (2015) pmid: 25769807
94. Waqar SN, et al. J Thorac Oncol (2015) pmid: 25898962
95. Mendenhall MA, et al. J Thorac Oncol (2015) pmid: 25898965
96. Awad et al., 2017; ASCO Abstract 8511
97. Paik PK, et al. N. Engl. J. Med. (2020) pmid: 32469185
98. Blanc-Durand F, et al. Oncologist (2020) pmid: 32716573
99. Lu et al., 2020; ASCO Abstract 9519
100. Yang et al., 2020; AACR Abstract CT127
101. Lu et al., 2019; AACR Abstract CT031
102. Le et al., 2020; AACR Abstract 3385
103. Nature (2014) pmid: 25079552
104. Nature (2012) pmid: 22960745
105. Dziadziuszko R, et al. J Thorac Oncol (2012) pmid: 22237262
106. Murray S, et al. J. Exp. Clin. Cancer Res. (2012) pmid: 22992338
107. Xia N, et al. Exp. Lung Res. (2013) pmid: 23919423
108. Nakamura Y, et al. Cancer Sci. (2007) pmid: 17459054
109. Park S, et al. Histol. Histopathol. (2012) pmid: 22207554
110. Cappuzzo F, et al. J. Clin. Oncol. (2009) pmid: 19255323
111. Zucali PA, et al. Ann. Oncol. (2008) pmid: 18467317
112. An SJ, et al. PLoS ONE (2012) pmid: 22768234
113. Yang JJ, et al. Lung Cancer (2013) pmid: 23079155
114. Chen YT, et al. J Thorac Oncol (2011) pmid: 22052229
115. Kanteti R, et al. J. Environ. Pathol. Toxicol. Oncol. (2009) pmid: 19817696
116. To C, et al. Exp. Cell Res. (2002) pmid: 11795945
117. Tsuta K, et al. J Thorac Oncol (2012) pmid: 22198430
118. Tanaka A, et al. Lung Cancer (2012) pmid: 21733594
119. Tong JH, et al. Clin. Cancer Res. (2016) pmid: 26847053
120. Lee GD, et al. J Thorac Oncol (2017) pmid: 28502721
121. Gow CH, et al. Lung Cancer (2017) pmid: 28024701
122. J. Clin. Oncol. (2011) pmid: 22042966
123. Jung KH, et al. Arch. Pharm. Res. (2012) pmid: 22553051
124. Gao J, et al. Sci Signal (2013) pmid: 23550210
125. Ang CS, et al. Anticancer Res. (2013) pmid: 23898085
126. Abou-Bakr AA, et al. Gulf J Oncolog (2013) pmid: 23996864
127. Ho JC, et al. Semin Respir Crit Care Med (2013) pmid: 24258573
128. Madoz-Gúrpide J, et al. J Transl Med (2015) pmid: 26319934
129. Ali SM, et al. Oncologist (2015) pmid: 25882375
130. Kwak EL, et al. Cancer Discov (2015) pmid: 26432108
131. Kong-Beltran M, et al. Cancer Res. (2006) pmid: 16397241
132. Onozato R, et al. J Thorac Oncol (2009) pmid: 19096300
133. Okuda K, et al. Cancer Sci. (2008) pmid: 19037978
134. Awad MM, et al. J. Clin. Oncol. (2016) pmid: 26729443
135. Gray MJ, et al. Am. J. Hum. Genet. (2015) pmid: 26637977
136. Peschard P, et al. J. Biol. Chem. (2004) pmid: 15123609
137. Lee JM, et al. Oncogene (2014) pmid: 23208509
138. Lee JH, et al. Exp. Mol. Med. (2006) pmid: 17079873
139. Togashi Y, et al. Lung Cancer (2015) pmid: 26547802
140. Peschard P, et al. Mol. Cell (2001) pmid: 11741535
141. Abella JV, et al. Mol. Cell. Biol. (2005) pmid: 16227611
142. Drilon et al., 2018; WCLC Abstract OA12.02
143. Felip et al., 2018; WCLC Abstract OA12.01
144. Wolf et al., 2018; ESMO Abstract LBA52
145. Moro-Sibilot et al., 2018; WCLC Abstract OA12.03
146. Berry ZS, et al. JAMA (1993) pmid: 8315738
147. Cheok CF, et al. Nat Rev Clin Oncol (2011) pmid: 20975744
148. Ohnstad HO, et al. Cancer (2013) pmid: 23165797
149. Gamble LD, et al. Oncogene (2012) pmid: 21725357
150. Zhang et al., 2019; ASCO Abstract 3124
151. Rasco et al., 2019; ASCO Abstract 3126
152. Martinelli et al., 2016; EHA21 Abstract S504
153. Daver et al., 2018; ASH Abstract 767
154. Mascarenhas et al., 2019; ASH Abstract 134
155. Shustov et al., 2018; ASH Abstract 1623
156. Sallman et al., 2018; ASH Abstract 4066
157. Meric-Bernstam et al., 2017; ASCO Abstract 2505

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158. Higashiyama M, et al. Br. J. Cancer (1997) pmid: 9155050
159. Marchetti A, et al. Diagn. Mol. Pathol. (1995) pmid: 7551299
160. Dworakowska D, et al. Lung Cancer (2004) pmid: 15165086
161. Onel K, et al. Mol. Cancer Res. (2004) pmid: 14757840
162. Ren YW, et al. Asian Pac. J. Cancer Prev. (2013) pmid: 24175836
163. Sdek P, et al. Mol. Cell (2005) pmid: 16337594
164. Brady M, et al. Mol. Cell. Biol. (2005) pmid: 15632057
165. Li M, et al. Mol. Cell (2004) pmid: 15053880
166. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
167. Cordon-Cardo C, et al. Cancer Res. (1994) pmid: 8306343
168. Beroukhim R, et al. Nature (2010) pmid: 20164920
169. Kato S, et al. Clin. Cancer Res. (2017) pmid: 28351930
170. Singavi et al., 2017; ESMO Abstract 1140PD
171. Marjon K, et al. Cell Rep (2016) pmid: 27068473
172. Heist et al., 2019; AACR-NCI-EORTC Abstract B116
173. Mavrakis KJ, et al. Science (2016) pmid: 26912361
174. Endoscopy (1989) pmid: 2691236
175. Guccione E, et al. Nat. Rev. Mol. Cell Biol. (2019) pmid: 31350521
176. Fedoriw A, et al. Cancer Cell (2019) pmid: 31257072
177. Srour N, et al. Cancer Cell (2019) pmid: 31287990
178. Gao G, et al. Nucleic Acids Res. (2019) pmid: 30916320
179. Hansen LJ, et al. Cancer Res. (2019) pmid: 31040154
180. Tang B, et al. Cancer Res. (2018) pmid: 29844120
181. Munshi PN, et al. Oncologist (2014) pmid: 24928612
182. de Oliveira SF, et al. PLoS ONE (2016) pmid: 26751376
183. Lubin M, et al. PLoS ONE (2009) pmid: 19478948
184. Tang B, et al. Cancer Biol. Ther. (2012) pmid: 22825330
185. Collins CC, et al. Mol. Cancer Ther. (2012) pmid: 22252602
186. Bertino JR, et al. Cancer Biol. Ther. (2011) pmid: 21301207
187. Coulthard SA, et al. Mol. Cancer Ther. (2011) pmid: 21282358
188. Miyazaki S, et al. Int. J. Oncol. (2007) pmid: 17912432
189. Efferth T, et al. Blood Cells Mol. Dis. () pmid: 11987241
190. Kindler HL, et al. Invest New Drugs (2009) pmid: 18618081
191. Wei R, et al. Sci Rep (2016) pmid: 27929028
192. Zhao M, et al. BMC Genomics (2016) pmid: 27556634
193. Kirovski G, et al. Am. J. Pathol. (2011) pmid: 21356366
194. Huang HY, et al. Clin. Cancer Res. (2009) pmid: 19887491
195. Marcé S, et al. Clin. Cancer Res. (2006) pmid: 16778103
196. Meyer S, et al. Exp. Dermatol. (2010) pmid: 20500769
197. Wild PJ, et al. Arch Dermatol (2006) pmid: 16618867
198. Kim J, et al. Genes Chromosomes Cancer (2011) pmid: 21412930
199. Li CF, et al. Oncotarget (2014) pmid: 25426549
200. He HL, et al. Medicine (Baltimore) (2015) pmid: 26656376
201. Su CY, et al. Eur J Surg Oncol (2014) pmid: 24969958
202. Mirebeau D, et al. Haematologica (2006) pmid: 16818274
203. Becker AP, et al. Pathobiology (2015) pmid: 26088413
204. Snezhkina AV, et al. Oxid Med Cell Longev (2016) pmid: 27433286
205. Bistulfi G, et al. Oncotarget (2016) pmid: 26910893
206. Antonopoulou K, et al. J. Invest. Dermatol. (2015) pmid: 25407435
207. Maccioni L, et al. BMC Cancer (2013) pmid: 23816148
208. Hyland PL, et al. Int J Epidemiol (2016) pmid: 26635288
209. Lin X, et al. Cancer Sci. (2017) pmid: 27960044
210. Zhi L, et al. J Cancer (2016) pmid: 27994653
211. Gu F, et al. Br. J. Cancer (2013) pmid: 23361049
212. Limm K, et al. PLoS ONE (2016) pmid: 27479139
213. Tang B, et al. G3 (Bethesda) (2014) pmid: 25387827
214. Limm K, et al. Eur. J. Cancer (2013) pmid: 23265702
215. Stevens AP, et al. J. Cell. Biochem. (2009) pmid: 19097084
216. Kryukov GV, et al. Science (2016) pmid: 26912360
217. Limm K, et al. Eur. J. Cancer (2014) pmid: 25087184
218. Horiuchi D, et al. J. Exp. Med. (2012) pmid: 22430491
219. Goga A, et al. Nat. Med. (2007) pmid: 17589519
220. Molenaar JJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19525400
221. Dammert MA, et al. Nat Commun (2019) pmid: 31375684
222. Mollaoglu G, et al. Cancer Cell (2017) pmid: 28089889
223. Cardnell RJ, et al. Oncotarget (2017) pmid: 29088717
224. Wang L, et al. Mol Oncol (2017) pmid: 28417568
225. Takahashi Y, et al. Ann. Oncol. (2015) pmid: 25632068
226. Li Y, et al. Thyroid (2018) pmid: 30226440
227. Mahadevan D, et al. PLoS ONE (2014) pmid: 24893165
228. Park SI, et al. Target Oncol (2019) pmid: 31429028
229. Helfrich BA, et al. Mol. Cancer Ther. (2016) pmid: 27496133
230. Hook KE, et al. Mol. Cancer Ther. (2012) pmid: 22222631
231. Yang D, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20643922
232. He J, et al. Anticancer Drugs (2019) pmid: 30540594
233. Shroff EH, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25964345
234. Effenberger M, et al. Oncotarget (2017) pmid: 29156762
235. Qu X, et al. Biochem. Biophys. Res. Commun. (2018) pmid: 30103944
236. Xiang Y, et al. J. Clin. Invest. (2015) pmid: 25915584
237. Delmore JE, et al. Cell (2011) pmid: 21889194
238. Bandopadhayay P, et al. Clin. Cancer Res. (2014) pmid: 24297863
239. Lovén J, et al. Cell (2013) pmid: 23582323
240. Otto C, et al. Neoplasia (2019) pmid: 31734632
241. Dong LH, et al. J Hematol Oncol (2013) pmid: 23866964
242. Pei Y, et al. Cancer Cell (2016) pmid: 26977882
243. Fu XH, et al. Acta Pharmacol. Sin. (2019) pmid: 30224636
244. Owonikoko TK, et al. J Thorac Oncol (2020) pmid: 31655296
245. Ganesan P, et al. Mol. Cancer Ther. (2014) pmid: 25253784
246. Tannir et al., 2018; ASCO GU Abstract 603
247. Motzer et al., 2019; ESMO Abstract LBA54
248. Pereira CB, et al. PLoS ONE (2013) pmid: 23555992
249. Yasojima H, et al. Eur. J. Cancer (2011) pmid: 21741827
250. Arango D, et al. Cancer Res. (2001) pmid: 11406570
251. Bottone MG, et al. Exp. Cell Res. (2003) pmid: 14516787
252. Lockwood WW, et al. Oncogene (2008) pmid: 18391978
253. Kubokura H, et al. Ann Thorac Cardiovasc Surg (2001) pmid: 11578259
254. Iwakawa R, et al. Clin. Cancer Res. (2011) pmid: 21148746
255. Boelens MC, et al. Lung Cancer (2009) pmid: 19324446
256. Yokota J, et al. Oncogene (1988) pmid: 2838790
257. Dang CV, et al. Semin. Cancer Biol. (2006) pmid: 16904903
258. Nesbit CE, et al. Oncogene (1999) pmid: 10378696
259. Blancato J, et al. Br. J. Cancer (2004) pmid: 15083194
260. Fromont G, et al. Hum. Pathol. (2013) pmid: 23574779
261. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
262. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
263. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
264. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
265. Elvin JA, et al. Oncologist (2017) pmid: 28283584
266. Gao J, et al. Curr Oncol (2015) pmid: 26715889
267. Gopalan et al., 2014; ASCO Abstract 8077
268. Peguero et al., 2016; ASCO Abstract 2528
269. Konecny et al., 2016; ASCO Abstract 5557
270. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
271. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
272. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
273. Johnson DB, et al. Oncologist (2014) pmid: 24797823
274. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
275. Shapiro et al., 2013; ASCO Abstract 2500
276. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
277. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
278. Doxtader EE, et al. Hum. Pathol. (2012) pmid: 21840041
279. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
280. Kratzke RA, et al. Cancer Res. (1996) pmid: 8758904
281. Lee JU, et al. Tuberc Respir Dis (Seoul) (2012) pmid: 23101020
282. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
283. Mounawar M, et al. Cancer Res. (2007) pmid: 17575133
284. Zhao Y, et al. Clin Lung Cancer (2011) pmid: 21889114
285. Kawabuchi B, et al. Int. J. Cancer (1999) pmid: 9988232
286. Xing XB, et al. PLoS ONE (2013) pmid: 23805242
287. Lou-Qian Z, et al. PLoS ONE (2013) pmid: 23372805
288. Quelle DE, et al. Cell (1995) pmid: 8521522
289. Mutat. Res. (2005) pmid: 15878778
290. Oncogene (1999) pmid: 10498883
291. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
292. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
293. Ruas M, et al. Oncogene (1999) pmid: 10498896
294. Jones R, et al. Cancer Res. (2007) pmid: 17909018
295. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
296. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
297. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
298. Gombart AF, et al. Leukemia (1997) pmid: 9324288
299. Yang R, et al. Cancer Res. (1995) pmid: 7780957
300. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
301. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
302. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
303. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
304. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
305. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
306. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
307. Koh J, et al. Nature (1995) pmid: 7777061
308. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
309. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
310. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
311. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262

Electronically signed by Matthew Hiemenz, M.D. | 05 May 2021
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312. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
313. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
314. Rutter JL, et al. Oncogene (2003) pmid: 12853981
315. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
316. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
317. Zhang Y, et al. Cell (1998) pmid: 9529249
318. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
319. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
320. Adv Exp Med Biol (2010) pmid: 20687502
321. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
322. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
323. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
324. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
325. Kaufman DK, et al. Neurology (1993) pmid: 8414022
326. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
327. Chan AK, et al. Clin Neuropathol () pmid: 28699883
328. Lindgren AE, et al. J. Med. Chem. (2013) pmid: 24188023
329. Lindgren AE, et al. ACS Chem. Biol. (2013) pmid: 23742272
330. Oplustil O'Connor L, et al. Cancer Res. (2016) pmid: 27550455
331. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
332. Grundy GJ, et al. Nat Commun (2016) pmid: 27530147
333. Boehler C, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 21270334
334. Day TA, et al. Nat Commun (2017) pmid: 28447610
335. Augustin A, et al. J. Cell. Sci. (2003) pmid: 12640039
336. Wolf et al., 2019; ASCO Abstract 9004
337. Riedel et al., 2019; ASCO abstract 9030
338. Mazieres et al., 2020; ESMO Abstract 1283P
339. Wu et al., 2018; WLCL Abstract P1.01-97
340. Wolf J, et al. N Engl J Med (2020) pmid: 32877583
341. Schuler M, et al. Ann. Oncol. (2020) pmid: 32240796
342. Wolf et al., 2020; ESMO Abstract 1346P
343. Wolf et al., 2020; ASCO Abstract 9509
344. van den Bent M, et al. J. Neurooncol. (2020) pmid: 31776899
345. Bang YJ, et al. Cancer Sci. (2020) pmid: 31778267
346. Esaki T, et al. Cancer Sci. (2019) pmid: 30724423
347. Vassal et al., 2015; ASCO Abstract 2595
348. Li et al., 2015; ASCO Abstract 8090
349. Benderra MA, et al. J Thorac Oncol (2016) pmid: 26845121
350. Drilon A, et al. Nat. Med. (2020) pmid: 31932802
351. Landi L, et al. Clin. Cancer Res. (2019) pmid: 31416808
352. Moro-Sibilot D, et al. Ann. Oncol. (2019) pmid: 31584608
353. Awad MM, et al. Lung Cancer (2019) pmid: 31200835
354. Shaw et al., 2016; ASCO Abstract 9066
355. Lu et al., 2016; ASCO Abstract 9058
356. Yoshida T, et al. J. Clin. Oncol. (2016) pmid: 27354483
357. Solomon BJ, et al. N. Engl. J. Med. (2014) pmid: 25470694
358. Shaw AT, et al. N. Engl. J. Med. (2013) pmid: 23724913
359. Goto et al., 2016; ASCO Abstract 9022
360. Shaw AT, et al. N. Engl. J. Med. (2014) pmid: 25264305
361. Mazières J, et al. J. Clin. Oncol. (2015) pmid: 25667280
362. Scheffler M, et al. Oncotarget (2015) pmid: 25868855
363. Vaishnavi A, et al. Nat. Med. (2013) pmid: 24162815
364. Drilon et al., 2016; ASCO Abstract 108
365. Camidge et al., 2014; ASCO Abstract 8001
366. Schrock AB, et al. J Thorac Oncol (2016) pmid: 27343443
367. Jorge SE, et al. Lung Cancer (2015) pmid: 26791794
368. Mahjoubi L, et al. Invest New Drugs (2016) pmid: 26892698
369. Zhang Y, et al. J Thorac Oncol (2016) pmid: 26724472
370. Caparica R, et al. J Thorac Oncol (2017) pmid: 27664533
371. York ER, et al. J Thorac Oncol (2017) pmid: 28274743
372. Dagogo-Jack I, et al. Clin Cancer Res (2020) pmid: 32086345
373. Viteri et al., 2020; ESMO Abstract 1286P
374. Klempner SJ, et al. J Thorac Oncol (2017) pmid: 27693535
375. Yakes FM, et al. Mol. Cancer Ther. (2011) pmid: 21926191
376. Weber H, et al. J Biomol Screen (2014) pmid: 25260782
377. Navis AC, et al. PLoS ONE (2013) pmid: 23484006
378. Yeh I, et al. Nat Commun (2015) pmid: 26013381
379. Lee YH, et al. Cancers (Basel) (2014) pmid: 25534569
380. Torres KE, et al. Clin. Cancer Res. (2011) pmid: 21540237
381. Sameni M, et al. Clin. Cancer Res. (2016) pmid: 26432786
382. Hellerstedt BA, et al. Clin Lung Cancer (2019) pmid: 30528315
383. Neal JW, et al. Lancet Oncol. (2016) pmid: 27825638
384. Nokihara H, et al. Clin Lung Cancer (2019) pmid: 30718102

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