FOUNDATIONONE®**CDx**

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 20 September 1940
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Mediastinum
SPECIMEN ID 19-31010 (013870941.1)
SPECIMEN TYPE Block
DATE OF COLLECTION 19 December 2019
SPECIMEN RECEIVED 17 February 2022

Biomarker Findings
Tumor Mutational Burden - 11 Muts/Mb
Microsatellite status - MS-Stable

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

MET exon 14 splice site (3028+1G>A)
CDK4 amplification
KRAS amplification
MDM2 amplification
TET2 S424fs*3

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

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† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Atezolizumab** (p. 7), **Cemiplimab** (p. 8), **Durvalumab** (p. 10), **Nivolumab** (p. 11), **Nivolumab + Ipilimumab** (p. 12), **Pembrolizumab** (p. 13), **Capmatinib** (p. 8), **Crizotinib** (p. 9), **Tepotinib** (p. 14)

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 16)

- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: *TET2* **S424fs*3** (p. 6)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 11 Muts/Mb	Atezolizumab	1	Avelumab
	Cemiplimab	1	
	Durvalumab	1	
	Nivolumab	1	
	Nivolumab + Ipilimumab	1	
	Pembrolizumab	1	
10 Trials see p. 16	Dostarlimab		
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section		

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

COUNTRY CODE
PE

ORDERED TEST #
ORD-1306872-01

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MET - exon 14 splice site (3028+1G>A)	Capmatinib	2A	Cabozantinib
	Crizotinib	2A	
	Tepotinib	2A	
10 Trials see p. 23			
CDK4 - amplification	none		none
10 Trials see p. 18			
KRAS - amplification	none		none
10 Trials see p. 20			
MDM2 - amplification	none		none
4 Trials see p. 22			

☐ *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

TET2 - S424fs*3 .... p. 6

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

TET2 - S424fs*3 .... p. 6

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.

Electronically signed by Erik Williams, M.D. | 25 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

BIOMARKER
Tumor Mutational Burden

RESULT
11 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1 therapies[1-4], and combination nivolumab and ipilimumab[5-10]. 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);[1-2,5-7,11-18]. Improved OS of patients with

NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[19], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[20], 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[21]. 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[22]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[23-24], several other large studies did find a strong association with increased TMB[25-28]. 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[29]. 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)[23]. 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[30]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[30-31].

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[32-33] and cigarette smoke in lung cancer[11,34], treatment with temozolomide-based chemotherapy in glioma[35-36], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[37-41], and microsatellite instability (MSI)[37,40-41]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,5-7,11-18,22,42-51].

BIOMARKER
Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[52-54], including approved therapies nivolumab and pembrolizumab[55]. 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)[56].

FREQUENCY & PROGNOSIS
MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[57-62], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[63-66]. 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[57]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2021).

FINDING SUMMARY
Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[67]. 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[67-69]. 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[70-72]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[67,69,71-72].

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

GENOMIC FINDINGS

ORDERED TEST # ORD-1306872-01

GENE
MET

ALTERATION
exon 14 splice site (3028+1G>A)

TRANSCRIPT ID
NM_000245

CODING SEQUENCE EFFECT
3028+1G>A

VARIANT ALLELE FREQUENCY (% VAF)
26.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, savolitinib, and foretinib have provided benefit for patients with MET-mutated papillary renal cell carcinoma (RCC)[73-76], histiocytic sarcoma[77], and non-small cell lung cancer (NSCLC) of varied histologies[78-82]. 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[83]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations[84], and yielded a PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC[85]. 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[73]. Savolitinib yielded ORRs of 49% (30/61) in patients with MET exon 14 mutated NSCLC[86] and

numerically higher ORR for patients with MET-driven papillary RCC compared to sunitinib (27% [9/33] vs. 7.4% [2/27])[76]. 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)[87]. 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 non-small cell lung cancer (NSCLC) reported that 52% (16/31) of patients achieved a PR[88]. In the Phase 1 CHRYSALIS study, patients with NSCLC harboring MET exon 14 skipping mutations treated with amivantamab achieved a 64% (9/14; 5 PRs confirmed, 4 PRs pending) unconfirmed ORR; 4 out of 7 patients previously treated with MET TKIs responded (Spira et al., 2021 WCLC Abstract OA15.03).

— Potential Resistance —

KRAS amplification may be associated with resistance to crizotinib in the context of MET exon 14 mutation, and was detected as an emergent alteration in 3 patients with NSCLC and acquired resistance to crizotinib[89].

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[90]. In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[77]. In TCGA datasets, MET mutation has

been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[91-92]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[93-100], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[101]. 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[102]. 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[103-104]. 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)[83].

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[105-106]. Certain MET alterations have been associated with the removal of exon 14[79,107-111] and/or loss of a binding site for the ubiquitin ligase CBL, an enzyme that targets MET for degradation[107,112-114]. 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[107,111,113-117]; 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[77,79,118-122].

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PATIENT

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

REPORT DATE
25 Feb 2022

GENOMIC FINDINGS

ORDERED TEST # ORD-1306872-01

GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —
CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[123-126]. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib[127],

palbociclib[123,128], and ribociclib[129].

FREQUENCY & PROGNOSIS
In the TCGA datasets, CDK4 amplification or mutation occurs in 7% and 1% of lung adenocarcinoma cases, respectively[130]; however, neither were detected in any of the lung squamous cell carcinoma cases[92]. CDK4 amplification correlated with high CDK4 gene and protein expression in lung tumors[131]. High CDK4 protein expression has been detected in 23-47% of non-small cell lung cancers, specifically in 38% (18/47) of lung adenocarcinomas, 44% (4/9) of lung squamous cell carcinomas, and 83% (10/12) of large cell lung cancers[131-133]. A preclinical study suggests targeting of CDK4 as a potential strategy against KRAS-driven lung adenocarcinomas[134].

High CDK4 protein expression predicted poor overall survival in patients with lung cancer in one study[133].

FINDING SUMMARY
CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[135]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[136-137]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[123,131,138-143].

GENE
KRAS

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —
Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[144-149]. Multiple clinical studies have reported either low response rates or response rates similar to those of chemotherapy in patients with KRAS-mutated NSCLC receiving MEK inhibitors as a monotherapy[150-152]. In a Phase 3 study, the addition of selumetinib to docetaxel did not significantly improve the PFS or OS of patients with KRAS-mutant NSCLC relative to docetaxel alone[153]. In a Phase 1/1b study evaluating trametinib with either docetaxel or pemetrexed, responses were independent of KRAS mutation status[154]. Combinatorial approaches involving MEK inhibitors and other targeted therapies, including PI3K or EGFR inhibitors, have

generally had limited clinical efficacy in patients with NSCLC and have been associated with high toxicity[155-157] despite preclinical evidence supporting the effectiveness of combinatorial strategies involving inhibitors of PI3K[158-159], RAF[160], pan-ERBB[161], or BCL2[162-163]. Clinical evidence that KRAS amplification in the absence of a concurrent KRAS activating mutation is sensitive to MEK inhibitors is limited. A Phase 2 study of selumetinib plus docetaxel in patients with gastric cancer reported 1/2 patients with KRAS amplification experienced a PR[164]. A patient with cervical cancer harboring both KRAS and PIK3CA amplification treated with the combination of trametinib and the AKT inhibitor GSK2141795 achieved a SD[165].

— Potential Resistance —
KRAS amplification may be associated with resistance to crizotinib in the context of MET exon 14 mutation, and was detected as an emergent alteration in 3 patients with NSCLC and acquired resistance to crizotinib[89].

FREQUENCY & PROGNOSIS
KRAS amplification has been observed in 1.1-6.1%

of lung adenocarcinoma cases[15,130] and 2.3-3.7% of lung squamous cell carcinoma (SCC) cases[92,130]. In one study of 55 patients with lung adenocarcinoma, KRAS mutations, especially in combination with TP53 alterations, correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab, likely as a consequence of association with some immunogenic features such as tumor mutation burden[166]. KRAS amplification associated with increased invasiveness of lung adenocarcinomas in one study[167].

FINDING SUMMARY
KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[145,168]. In numerous cancer type-specific studies as well as a large-scale pan-cancer analysis, KRAS amplification was shown to correlate with increased expression[169-172]. Additionally, KRAS amplification correlated with sensitivity of cancer cell lines to KRAS knockdown, suggesting that amplified KRAS is an oncogenic driver[172].

ORDERED TEST # ORD-1306872-01

GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[173]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[174-175]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[176-177]. A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients

with urothelial carcinoma; and 2 out of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[178]. 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[179-180]; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[181]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[182]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[183-184].

FREQUENCY & PROGNOSIS
In the TCGA datasets, amplification of MDM2 has been reported in 8% of lung adenocarcinoma cases[91] and 2% of lung squamous cell carcinoma cases[92]. 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[185-187]. 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[185,187-189].

FINDING SUMMARY
MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[190-192]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[193-194]. Overexpression or amplification of MDM2 is frequent in cancer[195]. 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[196] and 2/3 patients with MDM2 or MDM4 amplification[197] 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)[15]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[15].

GENE
TET2

ALTERATION
S424fs*3

TRANSCRIPT ID
NM_001127208

CODING SEQUENCE EFFECT
1270delA

VARIANT ALLELE FREQUENCY (% VAF)
9.8%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS
TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2022)[198-199]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2022).

FINDING SUMMARY
TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[200-201]. Alterations such as seen here may disrupt TET2 function or expression[202-206].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS
Variants seen in this gene have been reported to

occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[207-212]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[207-208]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[213]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[211,214-215]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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PATIENT

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

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THERAPIES WITH CLINICAL BENEFIT   IN PATIENT'S TUMOR TYPE

Atezolizumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,46,216] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA

In the Phase 3 IMpower131 study, addition of atezolizumab to first-line carboplatin and paclitaxel improved median PFS for patients with squamous NSCLC compared with chemotherapy alone (6.3 vs. 5.6 months, HR=0.71); longer PFS was observed across PD-L1 expression subgroups[217]. In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[218-220] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[219]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[218]. In IMpower132, the

addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[220]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (mOS; 20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38% vs. 29%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[221]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in mOS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[222], confirming previous Phase 2 trial data[223-224] . In the OAK trial, improved OS was observed for patients, regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was reported for patients with high PD-L1 tumor cell (>50%) or tumor-infiltrating immune cell (>10%) expression (HR=0.41) compared with those possessing <1% expression on either cell type (HR=0.75)[222]. Retrospective analyses of the OAK trial also identified clinical benefit for patients receiving atezolizumab and metformin compared with atezolizumab alone (ORR of 25% vs. 13%)[225], and for patients with 2 or more mutations in DNA damage response and repair pathway genes compared with those without (durable clinical benefit rate of 57% vs. 31%, p=0.003)[226]. The Phase 3 IMpower010 study of adjuvant atezolizumab treatment following adjuvant chemotherapy for patients with resected Stage II-IIIA NSCLC reported improved median disease-free survival compared with best supportive care (42.3 vs. 35.3 months, HR=0.79), with the greatest benefit observed for patients with PD-L1 tumor cell expression of ≥1% (not reached vs. 35.3 months, HR=0.66)[227]. In the randomized Phase 2 CITYSCAPE study of treatment-naive advanced NSCLC, the addition of tiragolumab to atezolizumab showed clinically meaningful improvement in ORR (37% [25/67] vs. 21% [14/68]) and PFS (5.6 vs. 3.9 months, HR=0.58), with greater ORR (66% [19/29] vs. 24% [7/29]) and PFS (not reached vs. 4.1 months, HR=0.30) observed for patients with PD-L1 tumor proportion scores (TPS) ≥50%[228].

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PATIENT

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THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Capmatinib

Assay findings association

MET
exon 14 splice site (3028+1G>A)

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

GENE ASSOCIATION
Based on extensive clinical data in NSCLC[84,86,229-232], MET mutations associated with exon 14 skipping may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA
A patient with KRAS-mutated NSCLC harboring a MET exon 14 splicing mutation achieved CR from the combination of capmatinib and erlotinib[233]. Capmatinib monotherapy has demonstrated clinical activity for patients with advanced NSCLC harboring MET exon 14 skipping alterations and lacking EGFR mutations or ALK rearrangements[234-235] . 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[229]. Additionally, this study recorded a 53.8% (7/13) intracranial response rate and 92.3% (12/13) intracranial DCR[234]. 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[236]. 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)[237], gastric cancer (n=9), or other advanced solid tumors (n=24)[238-239] .

Cemiplimab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE
Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with NSCLC with high PD-L1 expression (TPS ≥ 50%), cutaneous squamous cell carcinoma (CSCC), or basal cell carcinoma (BCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical data across solid tumors[2-4,46,216] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA
The Phase 3 EMPOWER-Lung 1 trial for treatment-naive advanced non-small cell lung cancer (NSCLC) reported that cemiplimab improved median PFS (mPFS, 8.2 vs. 5.7 months, hazard ratio [HR]=0.54), median OS (mOS, not reached vs. 14.2 months, HR=0.57), and ORR (39% vs. 20%) compared with chemotherapy in patients with high PD-L1 expression (TPS ≥ 50%); improved mPFS (6.2 vs. 5.6 months, HR=0.59), mOS (22.1 vs. 14.3 months, HR=0.68), and ORR (37% vs. 21%) were also reported for cemiplimab over chemotherapy in the intention-to-treat population[240]. In a Phase 2 trial of cemiplimab-containing regimens as second-line therapy for NSCLC, cemiplimab combined with ipilimumab elicited a numerically higher ORR (46% [5/11]) compared with high-dose (11% [1/9]) and standard-dose cemiplimab monotherapy (0% [0/8])[241].

FOUNDATIONONE®**CDx**

PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Crizotinib

Assay findings association

MET
exon 14 splice site (3028+1G>A)

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)[242-246], gastric cancer[247], gastroesophageal cancer[248], glioblastoma[249], and carcinoma of unknown primary[250], as well as in patients with MET-mutated cancers, including NSCLC[77,79-82,251], renal cell carcinoma (RCC)[75], and histiocytic sarcoma[77]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[77,79-83] . Limited clinical and preclinical data suggest KRAS amplification may be associated with resistance to crizotinib in the context of

MET exon 14 mutation[89,252] . KRAS amplification was detected as an emergent alteration in 3 patients with MET exon 14 mutations and NSCLC who acquired resistance to crizotinib[89].

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[253]. 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[254-255] . A retrospective study reported median PFS of 7.4 months in patients with MET exon 14-altered NSCLC treated with crizotinib[256]. 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[243]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[257-261] , ROS1 rearrangements[255,262-265] , an NTRK1 fusion[266], or MET activation[79-82,110,242-246,251,267-272] .

Dostarlimab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE
Dostarlimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor response. It is FDA approved to treat patients with mismatch repair deficient recurrent or advanced endometrial cancer or solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical data across solid tumors[2-4,46,216] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been

observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

SUPPORTING DATA
In the Phase 1 GARNET trial of dostarlimab, patients with non-small cell lung cancer (NSCLC) experienced an immune-related ORR (irORR) of 27% with 2 CRs[273]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[274-276] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[274,277] .

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PATIENT

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

REPORT DATE
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THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Durvalumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,46,216], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable non-small cell lung cancer (NSCLC) who did not have progression on chemoradiotherapy, durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; median PFS (mPFS) was 23.9 versus 5.6 months (HR=0.49) for patients with PD-L1 expression ≥1% and 10.7 versus 5.6 months (HR=0.79) for patients with PD-L1 expression <1%. Median OS (mOS) benefit was observed for patients with PD-L1 expression ≥1% (57.4 vs. 29.6 months, HR=0.60), but not for those with PD-L1 expression <1% (33.9 vs. 43.0 months, HR=1.05)[278-279]. In the Phase 3 ARCTIC study for patients with metastatic NSCLC who had progressed on 2 or fewer prior therapies, single-agent durvalumab improved OS (11.7 vs. 6.8 months, HR=0.63) and PFS (3.8 vs. 2.2 months, HR=0.71) versus the investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[280]. However, for patients in cohort B (PD-L1 <25%), durvalumab plus tremelimumab did not significantly improve OS (11.5 vs. 8.7 months, HR=0.80) or PFS (3.5 vs. 3.5 months, HR=0.77) compared with SOC[280]. In the Phase 3 MYSTIC trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC and PD-L1 expression ≥25%, neither durvalumab monotherapy nor durvalumab plus tremelimumab improved OS versus chemotherapy (HR=0.76 vs. HR=0.85)[281]. The addition of durvalumab and tremelimumab to chemotherapy improved mOS (14.0 vs. 11.7 months, HR=0.77) and mPFS (6.2 vs. 4.8 months, HR=0.72) relative to chemotherapy in the Phase 3 POSEIDON trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC[282]. In a Phase 2 study, the addition of radiotherapy to durvalumab and tremelimumab did not improve the activity or efficacy relative to the doublet combination for patients with NSCLC[283]. In Phase 2 trials for patients with advanced or relapsed NSCLC treated with single-agent durvalumab, increased tumor cell PD-L1 positivity corresponded with improved ORR[284-285] and OS[284]; patients with very high PD-L1 expression (≥90%) had an ORR of 31% (21/68) compared with ORRs of 16% (24/146) for patients with ≥25% PD-L1 expression and 7.5% (7/93) for patients with <25% PD-L1 expression[285]. Retreatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR-negative or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25% (10/40) of patients[286].

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PATIENT

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

REPORT DATE
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| THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE |

Nivolumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved as monotherapy in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma or squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). It is also approved in combination with cabozantinib to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,46,216], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

In patients with advanced non-small cell lung cancer (NSCLC) and at least 5% PD-L1 expression, although first-line nivolumab did not improve median PFS (4.2 vs. 5.9 months, HR=1.15) or OS (14.4 vs. 13.2 months, HR=1.02) in the overall population as compared with investigator's choice of platinum-based doublet chemotherapy, patients with elevated TMB (TMB ≥13 muts/Mb) experienced more benefit from nivolumab than from chemotherapy (PFS of 9.7 vs. 5.8 months, ORR of 47% vs. 28%)[14]. A study of neoadjuvant nivolumab for patients with resectable NSCLC reported that major pathologic responses occurred in 45.0% (9/20) of patients and significantly correlated with TMB[16]. For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (mOS; 12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40-0.59)[287]. In advanced squamous NSCLC, second-line nivolumab resulted in longer mOS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[288-289]. Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[290]. In the CheckMate 227 study, the combination of nivolumab and platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[291], despite Phase 1 results in the same setting suggesting improved ORR and OS[292]. In the Phase 3 CheckMate 816 study, the combination of nivolumab and platinum-based doublet chemotherapy did show benefit as a neoadjuvant treatment for patients with resectable NSCLC, reporting a pathological CR (pCR) rate of 24% versus 2.2% for chemotherapy alone, and the benefit was consistent across subgroups stratified by PD-L1 expression, stage of disease, or tumor mutational burden (TMB)[293]. A Phase 1 study of nivolumab combined with the immunostimulatory therapy bempegaldesleukin for immunotherapy-naive patients with NSCLC reported an ORR of 60% (3/5; 2 CRs) and mPFS of 18.0 months[294].

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PATIENT

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

REPORT DATE
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ORDERED TEST # ORD-1306872-01

Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response, and ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. The combination is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), and pleural mesothelioma. Furthermore, nivolumab is approved in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[5-6,295], a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

The Phase 3 CheckMate 227 study of nivolumab plus ipilimumab for patients with advanced non-small cell lung cancer (NSCLC) reported improved median OS relative to chemotherapy (17.1 vs. 13.9 months, HR=0.73) regardless of PD-L1 positivity, histology, tumor mutational burden (TMB) status, or brain metastases[20,296-297], despite earlier analysis of this trial that suggested improved PFS only for patients with TMB ≥10 Muts/Mb (as measured by this assay)[6]. Similar results were observed in the Phase 3 CheckMate 9LA study, which reported significantly improved 2-year OS (38% vs. 26%), median PFS (6.7 months vs. 5.3 months), and ORR (38% vs. 25%) for patients treated with nivolumab plus ipilimumab in combination with chemotherapy when compared with patients treated with chemotherapy alone[298].

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PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Pembrolizumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with tumor mutational burden (TMB)-high (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or mismatch repair-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), cervical cancer, or esophageal cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma, and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or gastroesophageal junction cancer, renal cell carcinoma, TNBC, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,46,216], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

The superiority of pembrolizumab over platinum chemotherapy as first-line treatment for patients with PD-L1-positive non-small cell lung cancer (NSCLC) lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[299] and ≥50% (26.3 vs. 13.4 months, HR=0.62-0.69)[300], with estimated 5-year OS rates of 32% versus 16% in the KEYNOTE-024 study[300]. In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of PD-L1 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[301]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS of 90-100% relative to those with TPS of 50-89% (not reached vs. 15.9 months, HR=0.39)[302]. Phase 3 studies showed that the addition of pembrolizumab to chemotherapy is superior to chemotherapy alone in the first-line setting for patients with either non-squamous (KEYNOTE-189)[303] or squamous (KEYNOTE-407)[304-305] NSCLC, regardless of PD-L1 or tumor mutational burden (TMB) status[19]. An exploratory analysis of KEYNOTE-189 demonstrated the superiority of the pembrolizumab combination therapy, regardless of blood TMB (bTMB) status[306]. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+22%, p=0.011)[307]. In the Phase 2/3 KEYNOTE-010 study, pembrolizumab extended mOS relative to docetaxel (10.4-12.7 vs. 8.2 months) for patients with previously treated PD-L1-positive NSCLC[308]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single agent and in combination with chemotherapy, to treat patients with NSCLC and brain metastases[309-311]. Clinical activity has also been achieved with pembrolizumab in combination with the AXL inhibitor bemcentinib[312], the anti-CTLA-4 antibody ipilimumab[313], the anti-TIGIT antibody vibostolimab[314], the HDAC inhibitor vorinostat[315], the multikinase inhibitor lenvatinib[316], and the PARP inhibitor niraparib[317].

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PATIENT

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

REPORT DATE
25 Feb 2022

THERAPIES WITH CLINICAL BENEFIT   IN PATIENT'S TUMOR TYPE

Tepotinib

Assay findings association

MET
exon 14 splice site (3028+1G>A)

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[84,86,229-232], MET mutations associated with exon 14 skipping 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[84,232]. Among patients with brain metastases, tepotinib yielded an ORR of 57% (8/14)[318], median DOR of 9.5 months, and median PFS of 10.9 months[84]. Tepotinib has primarily been investigated in non-small cell lung cancer (NSCLC) and has demonstrated efficacy as a single agent for patients with MET amplification[319] and MET exon 14-skipping alterations[84,232]. Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[320-321]. A case study reported 1 PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC metastatic to the brain[85].

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PATIENT

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

REPORT DATE
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ORDERED TEST # ORD-1306872-01

Avelumab

Assay findings association

Tumor Mutational Burden
11 Muts/Mb

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,46,216], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

SUPPORTING DATA

In the Phase 3 JAVELIN Lung 200 study for patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum therapy, avelumab did not improve median OS (mOS) when compared with docetaxel (11.4 vs. 10.6 months; HR=0.87) for patients with PD-L1 expression in ≥1% of tumor cells; a prespecified exploratory analysis at higher PD-L1 expression cutoffs showed improved mOS for PD-L1 ≥50% (13.6 vs. 9.2 months; HR=0.67) and ≥80% (17.1 vs. 9.3 months; HR=0.59)[322], and improved 2-year OS rates of 30% versus 21% (≥1% PD-L1), 36% versus 18% (≥50% PD-L1), and 40% versus 20% (≥80% PD-L1)[323]. A post-hoc analysis of this study suggested that a relatively high proportion of patients in the docetaxel arm received subsequent immune checkpoint inhibitor treatment, which may have confounded the outcomes of this study[324]. A Phase 1 study evaluating single-agent avelumab to treat patients with advanced NSCLC reported an ORR of 20%, median PFS (mPFS) of 4.0 months, and mOS of 14.1 months in the first-line setting[325]. A Phase 2 study of avelumab with axitinib to treat advanced NSCLC reported an ORR of 32% (13/41) and mPFS of 5.5 months; tumor reduction was observed for PD-L1-negative and -positive (≥1% PD-L1) samples[326]. A Phase 1b/2 study of avelumab combined with the anti-semaphorin 4D antibody pepinemab to treat advanced NSCLC reported an ORR of 24% (5/21) and DCR of 81% for immunotherapy-naive patients, and ORR of 6.9% (2/29) and DCR of 59% for patients who had disease progression on prior immunotherapy treatment[327]. A study of neoadjuvant avelumab plus chemotherapy to treat early-stage resectable NSCLC reported an ORR of 27% (4/15), which was not considered an enhancement over chemotherapy alone[328].

Cabozantinib

Assay findings association

MET
exon 14 splice site (3028+1G>A)

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[79,329], as well as by extensive preclinical data[330-336].

SUPPORTING DATA

Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[79]. 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[337]. 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[338]. 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[339].

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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PATIENT

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

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CLINICAL TRIALS

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.

BIOMARKER
Tumor Mutational Burden

RESULT
11 Muts/Mb

RATIONALE
Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT03800134	PHASE 3

A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer

TARGETS
PD-L1

LOCATIONS: San Isidro (Peru), Lima (Peru), Bellavista (Peru), San Salvador de Jujuy (Argentina), Viña del Mar (Chile), Santiago (Chile), San José (Costa Rica), Rosario (Argentina), Pergamino (Argentina), Temuco (Chile)

NCT03735121	PHASE 3

A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer

TARGETS
PD-L1, VEGFA

LOCATIONS: Arequipa (Peru), Lima (Peru), Salta (Argentina), La Rioja (Argentina), Vina Del Mar (Chile), Recoleta (Chile), Temuco (Chile), Ijui (Brazil), Guatemala (Guatemala), Ciudad de Guatemala (Guatemala)

NCT04385368	PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Lima (Peru), Bellavista (Peru), Trujillo (Peru), Rosario (Argentina), São José do Rio Preto (Brazil), Cipolletti (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Ciudad de Buenos Aires (Argentina), Caba (Argentina), Blumenau (Brazil)

NCT04380636	PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Lima (Peru), Arequipa (Peru), Antofagasta (Chile), Vina del Mar (Chile), Santiago (Chile), Temuco (Chile), Orizaba (Mexico), Florida, Tlalpan (Mexico)

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

CLINICAL TRIALS

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: San Isidro (Peru), Ijui (Brazil), Cdmx (Mexico), Mexico (Mexico), Florida, Monterrey (Mexico), Tennessee, Virginia

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NCT04521621

PHASE 1/2

A Study of V937 in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/ Metastatic Solid Tumors (V937-013)

TARGETS
PD-1

LOCATIONS: Lima (Peru), Taichung (Taiwan), New Jersey, Toronto (Canada), Montreal (Canada), Oregon, Porto (Portugal), Madrid (Spain), Barcelona (Spain), Villejuif (France)

NCT03976375

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) With Lenvatinib (E7080/MK-7902) vs. Docetaxel in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease (PD) After Platinum Doublet Chemotherapy and Immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Rosario (Argentina), Caba (Argentina), Buenos Aires (Argentina), Ponce (Puerto Rico)

NCT04738487

PHASE 3

Vibostolimab (MK-7684) With Pembrolizumab as a Coformulation (MK-7684A) Versus Pembrolizumab (MK-3475) Monotherapy for Programmed Cell Death 1 Ligand 1 (PD-L1) Positive Metastatic Non-Small Cell Lung Cancer (MK-7684A-003)

TARGETS
TIGIT, PD-1

LOCATIONS: La Serena (Chile), Providencia (Chile), Talca (Chile), Temuco (Chile), Puerto Montt (Chile), Guatemala (Guatemala), Guatemala City (Guatemala), Oaxaca (Mexico), Merida (Mexico), Mexico city (Mexico)

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

TARGETS
PD-1, PD-L1, CTLA-4

LOCATIONS: Vina del Mar (Chile), Santiago de Chile (Chile), Rio Cuarto (Argentina), Ijui (Brazil), Cuiudad Autonoma De Buenos Aires (Argentina), Buenos Aires (Argentina), Barretos (Brazil), Porto Alegre - Rs (Brazil), Blumenau (Brazil), Hato Rey (Puerto Rico)

NCT04513925

PHASE 3

A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

TARGETS
TIGIT, PD-L1

LOCATIONS: Cordoba (Argentina), Sao Jose do Rio Preto (Brazil), Buenos Aires (Argentina), Ciudad Autonoma Buenos Aires (Argentina), Barretos (Brazil), Curitiba (Brazil), Porto Alegre (Brazil), Sao Paulo (Brazil), Florida, Fortaleza (Brazil)

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

CLINICAL TRIALS

ORDERED TEST # ORD-1306872-01

GENE
CDK4

RATIONALE
CDK4 amplification may predict sensitivity to   CDK4/6 inhibitors.

ALTERATION
amplification

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

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

NCT03994796 — PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Florida, Louisiana, Texas, Mississippi, Georgia

NCT04801966 — PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04553133 — PHASE 1/2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Texas, Massachusetts, Michigan

NCT03310879 — PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

CLINICAL TRIALS

NCT03297606 — PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04557449 — PHASE 1

Study to Test the Safety and Tolerability of PF-07220060 in Participants With Advance Solid Tumors

TARGETS
CDK4, Aromatase, ER

LOCATIONS: Texas, Tennessee, Connecticut, Massachusetts, Michigan

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NCT03065062 — PHASE 1

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

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

LOCATIONS: Massachusetts

NCT02896335 — PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT04000529 — PHASE 1

Phase Ib Study of TNO155 in Combination With Spartalizumab or Ribociclib in Selected Malignancies

TARGETS
PD-1, SHP2, CDK6, CDK4

LOCATIONS: Massachusetts, Barcelona (Spain), Bruxelles (Belgium), Koeln (Germany), Westmead (Australia), Chuo ku (Japan), Chengdu (China), Hong Kong (Hong Kong), Singapore (Singapore)

FOUNDATION**ONE**®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

CLINICAL TRIALS

ORDERED TEST # ORD-1306872-01

GENE
KRAS

ALTERATION
amplification

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS alterations are not predictive biomarkers for MEK inhibitor monotherapy in NSCLC and combinatorial approaches may yield improved efficacy.

NCT03600701

PHASE 2

Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer

TARGETS
PD-L1, MEK

LOCATIONS: Florida, Alabama, North Carolina, Virginia, District of Columbia, Oklahoma, Ohio, Pennsylvania, Michigan

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03337698

PHASE 1/2

A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)

TARGETS
PD-L1, MEK, CEA, CXCR4, EZH2, MDM2, ADORA2A

LOCATIONS: Tennessee, Ohio, Nevada, Malaga (Spain), Madrid (Spain), Valencia (Spain), Pamplona (Spain), Saint Herblain (France), Barcelona (Spain), Toulouse (France)

NCT03170206

PHASE 1/2

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor Binimetinib (MEK162) for Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer

TARGETS
MEK, CDK4, CDK6

LOCATIONS: Massachusetts

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Randwick (Australia), Blacktown (Australia), Melbourne (Australia), Nedlands (Australia)

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

FOUNDATION**ONE**®**CDx**

PATIENT

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

REPORT DATE
25 Feb 2022

CLINICAL TRIALS

ORDERED TEST # ORD-1306872-01

NCT04803318   PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid
Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs,
KIT, MEK

LOCATIONS: Guangzhou (China)

NCT04800822   PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

TARGETS
SHP2, ROS1, ALK, MEK, BRAF, EGFR

LOCATIONS: Texas, Tennessee, New York, Michigan, California

NCT03991819   PHASE 1

Study of Binimetinib in Combination With Pembrolizumab in Advanced Non-Small Cell Lung Cancer

TARGETS
MEK, PD-1

LOCATIONS: Toronto (Canada)

NCT02407509   PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

FOUNDATION**ONE**®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

CLINICAL TRIALS

ORDERED TEST # ORD-1306872-01

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.

NCT04589845
PHASE 2

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

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

LOCATIONS: Sao Paulo (Brazil), San Juan (Puerto Rico), Florida, Alabama, Texas, Georgia, South Carolina

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, Virginia, Arkansas, District of Columbia, Pennsylvania, Missouri

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), Barcelona (Spain), Leuven (Belgium), Tübingen (Germany), Berlin (Germany), 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

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

CLINICAL TRIALS

ORDERED TEST # ORD-1306872-01

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

ALTERATION
exon 14 splice site (3028+1G>A)

NCT04427072 — PHASE 3

Study of Capmatinib Efficacy in Comparison With Docetaxel in Previously Treated Participants With Non-small Cell Lung Cancer Harboring MET Exon 14 Skipping Mutation

TARGETS
MET

LOCATIONS: Barretos (Brazil), Sao Paulo (Brazil), Lisboa (Portugal), Matosinhos (Portugal), Porto (Portugal), La Coruna (Spain), Malaga (Spain), Oviedo (Spain), Madrid (Spain), Valencia (Spain)

NCT03906071 — PHASE 3

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

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

LOCATIONS: Florida

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

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

NCT04310007 — PHASE 2

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

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

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

NCT03539536 — PHASE 2

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

TARGETS
MET

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

NCT03175224 — PHASE 1/2

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

TARGETS
MET

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

FOUNDATION**ONE**®**CDx**

PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

CLINICAL TRIALS

NCT04077099 | PHASE 1/2

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

TARGETS
MET

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

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

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

NCT03170960 | PHASE 1/2

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

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

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

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NCT03297606 | PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

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.

BRCA2 K2673R	*CIC* E1263Q	*DAXX* R299Q	*DDR1* A533S
EZH2 E404K	*MAP3K1* L78P	*MED12* Q2076_Y2077insQ and Q2076_Y2077insQQ	*MST1R* R1079Q
NOTCH2 G2239R	*PALB2* A503P	*SMARCA4* R370H	*TSC1* K587R
XPO1 R340I			

PATIENT

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

REPORT DATE
25 Feb 2022

FOUNDATIONONE®CDx

ORDERED TEST # ORD-1306872-01

APPENDIX   Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	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)

FOUNDATIONONE®CDx

PATIENT

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

REPORT DATE
25 Feb 2022

ORDERED TEST # ORD-1306872-01

APPENDIX   About FoundationOne®CDx

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table
Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

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

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.

5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.

6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

MR Suite Version 6.0.0

The median exon coverage for this sample is 844x

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Lung non-small cell lung carcinoma (NOS)

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PATIENT

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

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APPENDIX   References

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