PATIENT
DISEASE Lung adenocarcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

NO REPORTABLE ALTERATIONS WITH COMPANION DIAGNOSTIC (CDx) CLAIMS

See professional services section for additional information

No alterations associated with companion diagnostic indications were detected. Please consider confirmation with tumor tissue testing, such as FoundationOne®CDx, if possible.

Other Short Variants Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
See *professional services* section for information on the alterations listed in this section as well as any additional detected copy number alterations, gene rearrangements, or biomarkers.

BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE IN TISSUE SUPPORTED BY ANALYTICAL VALIDATION USING cfDNA

MET splice site 3025_3028+3delGAAGGTA

OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

BRCA2 S353*
DNMT3A Q842* #
RB1 splice site 1333-40_1333-2del39
TP53 R337C #

 # Refer to appendix for limitation statement relating to detection of alterations in ASXL1, ATM, CBL, CHEK2, DNMT3A, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2, TP53, and U2AF1.

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

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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Note: The intended use (IU) statement and claims made on this sample report may not be up to date. For the latest version of the FoundationOne Liquid CDx claims and IU, please see the current label: www.foundationmedicine.com/f1lcdx

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT

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Biomarker Findings

Blood Tumor Mutational Burden - 16 Muts/Mb
Microsatellite status - Cannot Be Determined
Tumor Fraction - Cannot Be Determined

Genomic Findings

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

MET exon 14 splice site (3025_3028+3delGAAGGTA)
BRCA2 S353*
DNMT3A Q842*
RB1 splice site 1333-40_1333-2del39
TP53 R337C

13 Therapies with Clinical Benefit
0 Therapies with Lack of Response

27 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 16 Muts/Mb	Atezolizumab 1 Durvalumab 1 Nivolumab 1 Pembrolizumab 1	Avelumab Cemiplimab
10 Trials see p. 17		
Microsatellite status - Cannot Be Determined	Unable to determine Microsatellite status due to insufficient evidence of genomic instability.	
Tumor Fraction - Cannot Be Determined	Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.	

GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
MET - exon 14 splice site (3025_3028+3delGAAGGTA)	8.6%	Capmatinib 2A Crizotinib 2A	Cabozantinib
10 Trials see p. 21			

NCCN category

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GENOMIC FINDINGS		VAF %
BRCA2 -	S353*	1.0%

10 Trials see p. 19

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
None	Niraparib
	Olaparib
	Rucaparib
	Talazoparib

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

IMPORTANT NOTE Genomic alterations detected may be associated with activity of certain FDA-approved drugs, however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the clinical 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. In the appropriate clinical context, germline testing of *APC*, *BRCA1*, *BRCA2*, *BRIP1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

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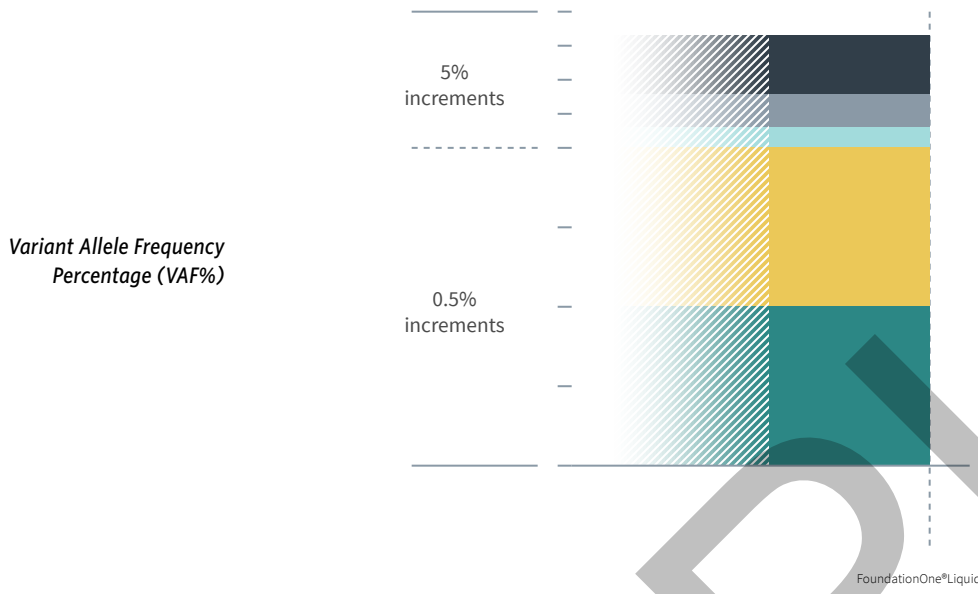

HISTORIC PATIENT FINDINGS		VAF%
Blood Tumor Mutational Burden		16 Muts/Mb
Microsatellite status		Cannot Be Determined
Tumor Fraction		Cannot Be Determined
MET	exon 14 splice site (3025_3028+3delGAAGGTA)	8.6%
BRCA2	S353*	1.0%
DNMT3A	Q842*	1.2%
RB1	splice site 1333-40_1333-2del39	2.8%
TP53	R337C	4.8%

IMPORTANT NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

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Not Detected = baited but not detected on test
Detected = present (VAF% is not applicable)
VAF% = variant allele frequency percentage
Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
16 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in NSCLC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. A retrospective analysis of 2 large randomized trials demonstrated patients with NSCLC and a bTMB ≥10 Muts/Mb achieved greater clinical benefit following treatment with atezolizumab than those with bTMB <10 Muts/Mb[1]; similar results have been reported in additional clinical trials using either PD-1 or PD-L1 inhibitors and at higher bTMB cutpoints for patients with NSCLC[3-4] . In a small study, treatment with PD-1 or PD-L1 inhibitors resulted in improved PFS for patients with NSCLC and bTMB ≥6 Muts/Mb as compared to patients with bTMB <6 Muts/Mb[2].

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[3]. Published data investigating the prognostic implications of bTMB levels in lung cancer are limited (PubMed, Jul 2020). 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)[5]. 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[6]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[6-7].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[8-9] and cigarette smoke in lung cancer[10-11], treatment with temozolomide-based chemotherapy in glioma[12-13], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[14-18], and microsatellite instability (MSI)[14,17-18]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3].

BIOMARKER

Tumor Fraction

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

There are currently no targeted approaches to address specific tumor fraction levels; however, on the basis of emerging clinical evidence, changes in tumor fraction may correlate with treatment duration and clinical response and may be a useful indicator for cancer management[19-24].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels has been reported in a variety of tumor types, with higher tumor fraction levels reported in patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal cancer[31], and gastrointestinal cancer[32].

FINDING SUMMARY

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. Tumor cells in most advanced solid tumor types may shed ctDNA through the process of apoptosis or necrosis[25,33-34]. Tumor fraction has been proposed to be a noninvasive surrogate biomarker of disease burden dynamics. Elevated tumor fraction levels have been associated with inferior prognosis, and therapeutic resistance to treatment in certain tumor types[22,28,31], whereas reduced levels have been correlated with tumor shrinkage and improved clinical outcome in patients with non-small cell lung cancer, urothelial cancer, and melanoma treated with immunotherapy[20,24,35]. Tumor fraction estimate is computationally derived from observed aneuploid instability in the sample. However, the tumor fraction estimate in this sample could not be determined with confidence.

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GENE
MET

ALTERATION
exon 14 splice site (3025_3028+3delGAAGGTA)

TRANSCRIPT ID
NM_000245

CODING SEQUENCE EFFECT
3025_3028+3delGAAGGTA

POTENTIAL TREATMENT STRATEGIES

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. A Phase 1 study for patients with MET-altered NSCLC treated with MET inhibitor bozitinib monotherapy reported an overall ORR of 30.6% (11/36) and DCR of 97.2% (35/36) with MET overexpression, amplification, and exon 14 skipping demonstrating ORRs of 35.7% (5/14), 41.2% (7/17), and 66.7% (10/15), respectively; increased ORRs were observed in patients with both exon 14 skipping and amplification (100%, 4/4) and with both amplification and overexpression (50%, 3/6)[36]. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, savolitinib, and foretinib have provided benefit for patients with MET-mutated papillary renal cell carcinoma (RCC)[37-40], histiocytic sarcoma[41], and non-small cell lung cancer (NSCLC) of varied histologies[42-46]. 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[47]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations[48]. 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[37]. Higher ORR was observed between patients with MET-driven papillary RCC treated with savolitinib (27.3%, 9/33 PRs) compared to sunitinib (7.4%, 2/27 PRs), though no significant difference in PFS was observed between groups (7.0 vs. 5.6 months; p=0.31)[40]. A Phase 2 study evaluating the MET inhibitor savolitinib for patients with MET exon 14 splice site mutation-positive pulmonary sarcomatoid carcinoma and other types of NSCLCs reported 16/31 (52%) of patients achieved a PR[49].

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[50]. In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[41]. In TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[51-52]. Studies on the effect of MET amplification on prognosis in NSCLC have yielded conflicting results[53-60], although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[61]. 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[62]. 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[63-64]. 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)[47].

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[65-66]. Certain MET alterations have been associated with the removal of exon 14[43,67-71] and/or loss of a binding site for the ubiquitin ligase CBL, an enzyme that targets MET for degradation[67,72-74]. 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[67,71,73-77]; 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[41,43,78-82].

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GENE
BRCA2

ALTERATION
S353*

TRANSCRIPT ID
NM_000059

CODING SEQUENCE EFFECT
1058C>G

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[83-100] or to ATR inhibitors[101-102]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[84,89,92,99-100] and for patients with platinum-resistant or -refractory disease[83,88,95,98]. In a case study, a patient with therapy-induced neuroendocrine prostate cancer and an inactivating BRCA2 rearrangement experienced a CR ongoing for 20 months to the ATR inhibitor berzosertib[102]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[103], ovarian carcinoma[104], and triple-negative breast cancer (TNBC)[105] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA2-deficient cells to ATR inhibitors. Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lurbinectedin, and the platinum chemotherapies cisplatin and carboplatin[106-116].

FREQUENCY & PROGNOSIS

In the TCGA datasets, BRCA2 mutation was found in 5% of lung adenocarcinomas[51] and 6% of lung squamous cell carcinomas[52]. BRCA2 mutations are infrequent in non-small cell lung cancer (NSCLC); however, loss of heterozygosity (LOH) of the BRCA2 region on chromosome 13q has been observed in up to 70% of cases studied[117]. Loss of BRCA2 protein expression has been reported in 34% of NSCLC cases and was more frequent in adenocarcinomas (44% of cases) than in squamous cell carcinomas (24% of cases); reduction in protein expression was associated with promoter hypermethylation[118]. Published data investigating the prognostic implications of BRCA2 mutation or loss in lung cancer are limited (PubMed, Mar 2020).

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[119]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[120]. BRCA2 alterations that disrupt PALB2 binding (aa 21-39)[121], the BRC repeats (aa 1002-2085), the DNA binding domain (aa 2479-3192), and/or the C-terminal RAD51 binding domain, as observed here, are predicted to be inactivating[119,122-137]. One or more of the BRCA2 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Mar 2020)[138]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[139-140], and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >80% and 23%, respectively[141]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[142]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[141,143-148]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

GENE
DNMT3A

ALTERATION
Q842*

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
2524C>T

POTENTIAL TREATMENT STRATEGIES

While DNA methyltransferase (DNMT) inhibitors such as azacitidine and decitabine have shown clinical benefit in hematological malignancies, clinical utility in solid tumors has not been demonstrated.

FREQUENCY & PROGNOSIS

DNMT3A mutations have been reported in 13% of hematopoietic and lymphoid malignancies and at lower frequencies in solid tumors, including those of the peritoneum (3%), skin (3%), urinary tract (3%), large intestine (3%), small intestine (3%), and lung (2%) (COSMIC, 2020). The role of DNMT3A alterations in solid tumors is unclear. Multivariate analysis showed strong DNMT3A protein expression to be an independent prognostic marker for improved survival in patients with lung adenocarcinoma[149]. Variants seen in this gene have been reported to occur in clonal hematopoiesis of indeterminate potential (CHIP), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[150-155]. CHIP is associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[150-151]. Clinical management of patients with CHIP may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[156]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CHIP[154,157-158]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CHIP.

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[159-160]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[161-166]. Alterations that result in loss or disruption of the C-terminal catalytic domain (amino acids 627-912), such as observed here, are expected to be inactivating[167-170].

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