**ABOUT THE TEST**

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

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### PATIENT

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### BIOMARKER FINDINGS

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - TMB-Low (4 Muts/Mb)

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### GENOMIC FINDINGS

**ALK** - EML4-ALK fusion (Variant 1)

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

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### ACTIONABILITY

**Biomarker Findings**

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<tr>
<td>Tumor Mutational Burden</td>
<td>TMB-Low (4 Muts/Mb)</td>
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No therapies or clinical trials. see Biomarker Findings section

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### THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)

- **ALK** EML4-ALK fusion (Variant 1)
  - Alectinib
  - Brigatinib
  - Ceritinib
  - Crizotinib

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### THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)

- None

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**CCND1** - amplification

4 Trials see p. 14

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**10 Trials** see p. 11

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**0** Therapies with Lack of Response

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**14** Clinical Trials

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Electronically Signed by Julia A. Elvin, M.D., Ph.D. • Jeffrey S. Ross, M.D., Medical Director • 01 January 2018
Foundation Medicine, Inc. • 1-888-988-3639

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

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

**FGF19** - amplification ........................................ p. 5  
**FGF3** - amplification ........................................ p. 5  
**FGF4** - amplification ........................................ p. 6  
**NFKBIA** - amplification ...................................... p. 6  
**NKX2-1** - amplification ...................................... p. 6  
**TP53** - R306* .................................................. p. 7

**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.
**BIOMARKER FINDINGS**

**Biomarker**

<table>
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**Potential Treatment Strategies**

On the basis of clinical evidence, microsatellite stable (MSS) tumors are significantly less likely than MSI-high (MSI-H) tumors to respond to anti-PD-1 immune checkpoint inhibitors1-3, including approved therapies nivolumab and pembrolizumab4-5. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, \(p=0.001\))6. Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%)5. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without4.

**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 tumor13. 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 PMS213-15. The tumor seen here is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers16-18. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins13,15,17-18.
Tumor Mutational Burden

**CATEGORY**
TMB-Low (4 Muts/Mb)

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**POTENTIAL TREATMENT STRATEGIES**

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapies. FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) for patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19) in studies of patients with either NSCLC or colorectal cancer (CRC). Patients whose tumors harbored elevated mutational burden reported higher overall response rates to pembrolizumab. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses (PRs) following treatment with pembrolizumab or nivolumab, a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab, and 2 pediatric patients with biallelic mismatch repair deficiency-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab, and 2 patients with microsatellite-stable rectal cancers, who achieved an ongoing PR to pembrolizumab and the other an ongoing complete response to nivolumab. For patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab and anti-PD-1/anti-PD-L1 treatments. For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load (12.4 mutations [Muts] per megabase [Mb]) compared to nonresponders (6.4 Muts/Mb). A TMB of >16 Muts/Mb was associated with significantly longer overall survival. In a retrospective analysis of 17 solid tumor types (comprised of 47% NSCLC, 40% uMUC, and 13% encompassing 15 other solid tumors), a TMB of >16 Muts/Mb was associated with an objective response rate to atezolizumab of 30% vs. 14% for chemotherapy alone.

**FREQUENCY & PROGNOSIS**

Intermediate TMB has been reported in 30-31% of non-small cell lung carcinomas (NSCLC), including 30% of adenocarcinomas and 41% of squamous cell carcinomas (SCC) (Spigel et al., 2016; ASCO Abstract 907). Intermediate TMB was frequently observed in NSCLC with BRAF (31%) or KRAS (39%) mutation (Spigel et al., 2016; ASCO Abstract 907). Although some studies have reported a lack of association between smoking and mutational burden in NSCLC, several other large studies did find a strong association with increased TMB. In multiple solid tumor types, a TMB of >16 Muts/Mb was associated with significantly longer overall survival (14.5 vs. 3.4-3.7 months).

**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, cigarette smoke in lung cancer, and microsatellite instability (MSI) in colorectal cancer (CRC). The tumor seen here harbors a higher TMB, which is associated with clinical benefit from treatment with immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma, anti-PD-L1 therapy in urothelial carcinoma, and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer.

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

**ALTERATION**  
EML4-ALK fusion (Variant 1)

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**POTENTIAL TREATMENT STRATEGIES**

The ALK inhibitors crizotinib, ceritinib, brigatinib, and alectinib have shown significant clinical activity for patients with non-small cell lung cancer (NSCLC) whose tumors test positive for ALK rearrangement49-50 51-56. As first-line treatment, crizotinib improved overall survival (OS) relative to chemotherapy (HR=0.35) for patients with ALK+ advanced NSCLC57. Crizotinib has also shown activity in ALKmutant neuroblastoma8-59. Preclinically, ALK activating point mutations are crizotinib-sensitive60-61. A Phase 1 study of ceritinib in ALK-rearranged NSCLC reported overall survival (OS) of 72% (60/83) for patients who were ALK inhibitor-naive and median progression-free survival (PFS) of 18.4 months, versus an OS of 56% (92/169) and PFS of 6.9 months for those who were previously treated62. A Phase 1/2 study of brigatinib for patients with ALK-rearranged NSCLC reported confirmed ORRs of 62% (44/71) and 100% (8/8) for crizotinib-treated and crizotinib-naive patients, respectively53. Antitumor activity was also seen in the central nervous system (CNS), a common site of failure during crizotinib treatment53,63-64. Alectinib combined with axolotilumb led to an ORR of 81% (17/21) as first-line treatment for PD-L1 unselected, ALK+ NSCLC65. Lorlatinib led to an ORR of 73% (43/59), 39% (11/28), and 39% (43/111), and intracranial ORR of 68% (25/37), 46% (6/13), and 47% (38/81), for patients with NSCLC previously treated with crizotinib, one prior ALK inhibitor, or 2-3 prior ALK inhibitors, respectively66. For patients whose tumors harbored one or more ALK kinase domain mutations, lorlatinib led to responses for 64% (29/45), including 58% (11/19) for those with the ALK G1202R resistance mutation67. G1202 therefore does not appear to represent a major mechanism of lorlatinib resistance68-69. Lorlatinib led to complete resolution of intrathecal metastases and stabilization of CNS metastases for a heavily pretreated patient with ALK+ NSCLC70, and its use in the fourth-line setting led to disappearance of leptomeningeal disease for a patient with ALK-rearranged metastatic inflammatory myofibroblastic sarcoma71. The combination of lorlatinib and the PD-L1 inhibitor avelumab led to a confirmed response rate of 46.4% [12 partial responses (PRs), 1 complete response] for the 28 patients with ALK+ NSCLC who were treated72. Ensartinib treatment for ALK+ NSCLC led to ORRs of 80%, 69%, and 64% for patients who were treatment-naive, crizotinib refractory, or for intracranial metastases, respectively73. Phase 1 studies of the ALK/ROS1/TRK inhibitor entrectinib have reported responses for 4/7 (57%) kinase inhibitor-naive patients with ALK-rearranged solid tumors, including patients with NSCLC, renal cell carcinoma, and colorectal cancer; as well as for 1 patient with NSCLC, renal cell carcinoma, and colorectal cancer; as well as for 1 patient with NSCLC, renal cell carcinoma, and colorectal cancer. The EML4-ALK gene fusion has been observed in approximately 3-7% of non-small cell lung cancer (NSCLC)52,87-88,90,96; however, variants 3a/b are less sensitive to activating and sensitive to ALK inhibitors, including crizotinib and ceritinib88,90,96; however, variants 3a/b are less sensitive to crizotinib in vitro88. Although EML4-ALK variant 1 was associated with significantly longer median progression-free survival (13 months vs. 4.2 months) in a small study of crizotinib-treated non-small cell lung cancer (NSCLC)74, other studies have not found a correlation between EML4-ALK variants and response to crizotinib in NSCLC52,87,94.

**FINDING SUMMARY**

ALK encodes a receptor tyrosine kinase, a member of the insulin receptor superfamily, whose activation induces the downstream pathways associated with cell survival, angiogenesis, and cell proliferation85. Different EML4-ALK variants have been identified in cancer, all of which contain the intracellular tyrosine kinase domain of ALK86. The most commonly observed rearrangements consist of ALK exon 20 fused to a variety of breakpoints in EML4: exon 13 (variant 1, 33-54% of cases)87-89, exon 20 (variant 2, 10-12% of cases)87-89, exon 6 (variant 3a/b, 26-30% of cases)52,87-88,90, exon 15 (variant 4, 2% of cases)76,91-92, exon 18 (variant 5, 1.6-3% of cases)89,91, exon 2 (variant 5a/b, 1-2% of cases)87,92-94, and exon 17 (variant 8a/b, <1%)89,91-95. All of these variants have been characterized as, or are predicted to be, activating and sensitive to ALK inhibitors, including crizotinib and ceritinib88,90,96; however, variants 3a/b are less sensitive to crizotinib in vitro88. Although EML4-ALK variant 1 was associated with significantly longer median progression-free survival (13 months vs. 4.2 months) in a small study of crizotinib-treated non-small cell lung cancer (NSCLC)74, other studies have not found a correlation between EML4-ALK variants and response to crizotinib in NSCLC52,87,94.

**FREQUENCY & PROGNOSIS**

The EML4-ALK gene fusion has been observed in approximately 3-7% of non-small cell lung cancer (NSCLC) cases, more frequently in younger patients, non-smokers, males, and patients of Asian heritage76-82. Other rearrangements involving ALK have also been described in lung cancer83-84. EML4-ALK fusions have been reported to be a significant indicator of poor prognosis in advanced stage NSCLC82.
GENE

**CCND1**

**ALTERATION**

amplification

**POTENTIAL TREATMENT STRATEGIES**

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as FDA-approved abemaciclib, palbociclib, and ribociclib.98-99 100-101 102-105. Clinical benefit has been reported for patients with solid tumors with CCND1 amplification or expression in response to treatment with palbociclib106, ribociclib98-99 100,104, and abemaciclib105.

**FREQUENCY & PROGNOSIS**

In the TCGA dataset, amplification of CCND1 has been found in 4.3% of lung adenocarcinoma cases107. Other studies have reported CCND1 amplification in 3-25% of lung adenocarcinoma108-109. Expression of cyclin D1 has been reported in 59% (36/61) of non-small cell lung cancer tumors analyzed but was not reported to be associated with clinicopathologic parameters110.

**FINDING SUMMARY**

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression111 and may lead to excessive proliferation112-113.

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GENE

**FGF19**

**ALTERATION**

amplification

**POTENTIAL TREATMENT STRATEGIES**

There are no targeted therapies that directly address genomic alterations in FGF19. However, amplification of FGF19 predicts sensitivity to inhibitors of FGFR4 in liver cancer cell lines114. In one preclinical study, selective inhibition of FGFR4 reduced tumor burden in an FGF19-amplified HCC xenograft model115. A Phase 1 study of the FGFR4 inhibitor BLU-554 for previously treated HCC (11/14 sorafenib) reported 1 partial response and 1 stable disease (SD) in patients with FGF19-positive HCCs16. Preliminary results from the dose escalation part of a Phase 1/2 study evaluating another FGFR4 inhibitor, FGFr401, showed an overall response rate of 8% (4/53), 53% (28/53) SDs, and a median time to progression of 4.1 months; responses were observed in both FGF19-positive and -negative cases117. In one clinical study, a trend toward response to sorafenib treatment and FGF19 copy number gain was observed in patients with HCC, and 2 patients harboring FGF19 copy number gain experienced a complete response118. Multiple therapies targeting FGF19 or FGFR4 signaling are in preclinical development119, and clinical trials evaluating inhibitors of FGFR4 are under way for patients with solid tumors.

**FREQUENCY & PROGNOSIS**

In the TCGA dataset, FGF19 amplification has been reported with highest incidence in esophageal carcinoma (55%), head and neck squamous cell carcinoma (28%), breast carcinoma (16%), lung squamous cell carcinoma (12%), bladder urothelial carcinoma (12%), and cholangiocarcinoma (11%) (cBioPortal, 2017). In HCC, FGF19 is an important driver gene115,120-121, and FGF19 protein expression correlates with tumor progression and poorer prognosis122. Exogenous FGF19 has been shown to promote prostate cancer tumorigenesis in a preclinical study123, and the presence of FGF19-positive tissues is an independent factor for worse prognosis following radical prostatectomy124.

**FINDING SUMMARY**

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver115,125. FGF19 lies in a region of chromosome 11q13 frequently amplified in a diverse range of malignancies that also contains FGF3, FGFR4, and CCND1126. Correlation between FGF19 amplification and protein expression has been demonstrated in hepatocellular carcinoma (HCC)127 but was not observed in several other tumor types120.

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GENE

**FGF3**

**ALTERATION**

amplification

**POTENTIAL TREATMENT STRATEGIES**

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers.

**FREQUENCY & PROGNOSIS**

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGFR4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies112.

**FINDING SUMMARY**

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures128.
investigation in clinical trials in multiple tumor types. FGFR amplification may confer sensitivity to sorafenib, which is FDA approved to treat HCC, renal cell carcinoma, and differentiated

**FREQUENCY & PROGNOSIS**

This chromosomal region is frequently amplified in a diverse range of malignancies including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 28%), breast invasive carcinoma (16%), lung squamous cell carcinoma (12%), bladder urothelial carcinoma (12%), ovarian serous cystadenocarcinoma (8%), stomach adenocarcinoma (7%), skin melanoma (6%), and hepatocellular carcinoma (HCC; 5%) (cBioPortal, 2017).

**FINDING SUMMARY**

FGFR encodes fibroblast growth factor 4, which plays a central role in development of the teeth and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development. FGFR lies in a region of chromosome 11q13 that also contains FGFR1, FGFR3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression.

Amplification of FGFR, along with that of FGFR1, FGFR3, and CCND1, has been reported in a variety of cancers and has been correlated with patient response to sorafenib (p=0.006). Therefore, thyroid carcinoma. Sorafenib is under investigation in clinical trials in multiple tumor types. FGFR amplification may confer sensitivity to sorafenib, which is FDA approved to treat HCC, renal cell carcinoma, and differentiated

**GENE**

**FGFR**

**ALTERATION**

amplification

**POSSIBLE TREATMENT STRATEGIES**

FGFR amplification and overexpression was associated with cell sensitivity to the multi-kinase inhibitor sorafenib in preclinical studies and amplification of FGFR/FGR3 in HCC significantly correlated with patient response to sorafenib (p=0.006). Therefore, thyroid carcinoma. Sorafenib is under investigation in clinical trials in multiple tumor types. FGFR amplification may confer sensitivity to sorafenib, which is FDA approved to treat HCC, renal cell carcinoma, and differentiated

**POSSIBLE TREATMENT STRATEGIES**

There are no approved therapies or trials that target tumors with FGFR amplification or overexpression. Lung cancer cell lines that express both FGFR1 and NKX2-2 are resistant to cisplatin therapy. Although conflicting data has also been reported, the expression level of FGFR amplification has been observed to be associated with improved response to EGFR inhibitors. Certain FGFR polymorphisms, which may affect IkBα expression levels, have been studied as risk factors for some cancer types, although the data are mixed and conflicting.

**GENE**

**NFKBIA**

**ALTERATION**

amplification

**POSSIBLE TREATMENT STRATEGIES**

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

**FREQUENCY & PROGNOSIS**

In the TCGA datasets, amplification of NFKBIA has been reported with the highest incidence in lung adenocarcinoma (11.7%), esophageal carcinoma (9.8%), uterine carcinosarcoma (5.6%), lung squamous cell carcinoma (3.4%), and ovarian serous cystadenocarcinoma (2.6%) (cBioPortal, 2017). Amplification or increased expression of NFKBIA in EGFR-mutant lung cancer has been reported to predict improved response to EGFR tyrosine kinase inhibitors. Certain NFKBIA polymorphisms, which may affect IkBα expression levels, have been studied as risk factors for some cancer types, although the data are mixed and conflicting.

**FINDING SUMMARY**

NFKBIA encodes IkBα, an inhibitor of the NF-kappaB (NFκB/REL complex). It has been reported to act as a tumor suppressor in Hodgkin’s lymphoma and in glioblastoma. Amplification of NFKBIA has been reported to be amplified in cancer and may be biologically relevant in this context. Truncating mutations that result in loss of the IkBα protein are predicted to be inactivating.

**GENE**

**NKX2-1**

**ALTERATION**

amplification

**POSSIBLE TREATMENT STRATEGIES**

There are no approved therapies or trials that target tumors with NKX2-1 amplification or overexpression. Lung cancer cell lines that express both NKX2-1 and NKX2-2 are resistant to cisplatin therapy. Although conflicting data has also been reported, the expression level of NKX2-1 has been observed in 14% of adenocarcinomas and in 5% of squamous cell carcinomas (SCC) as well as in a subset of thyroid and CNS tumors. NKX2-1 encodes the thyroid transcription factor TTF-1. Amplification of NKX2-1 has been reported as an adverse prognostic factor in breast carcinoma and may be controversial. However, whether amplification and/or expression of NKX2-1 have prognostic implications for patients with lung cancer is controversial. TTF-1 has been observed to have tumor-promoting and anti-oncogenic roles.

**FREQUENCY & PROGNOSIS**

Putative amplification of NKX2-1 has been reported with the highest incidence in lung cancer, and has been observed in 14% of adenocarcinomas and 5% of squamous cell carcinomas (SCC) as well as in a subset of thyroid and CNS tumors. Cytoplasmic TTF-1 expression has been reported as an adverse prognostic factor in breast carcinoma and may be controversial. However, whether amplification and/or expression of NKX2-1 have prognostic implications for patients with lung cancer is controversial. TTF-1 has been observed to have tumor-promoting and anti-oncogenic roles.

**FINDING SUMMARY**

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

**TP53**

**ALTERATION**

R306*

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**POTENTIAL TREATMENT STRATEGIES**

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor AZD1775 or p53 gene therapy and immunotherapeutics such as SGT-53 or ALT-801. In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53-wild-type182. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer183. Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel184. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage180. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model185. Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

**FREQUENCY & PROGNOSIS**

TP53 is one of the most commonly mutated genes in lung cancer. TP53 mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)107,154,186-191. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma192. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study24. Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers193. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis194-196. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers197-202. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000203 to 1:20,000202, and in the appropriate clinical context, germline testing of TP53 is recommended.
Alectinib

**AREAS OF THERAPEUTIC USE**
Alectinib is a tyrosine kinase inhibitor that targets ALK and RET and is FDA approved to treat patients with ALK positive, metastatic non-small cell lung cancer (NSCLC).

**GENE ASSOCIATION**
Activating ALK alterations may predict sensitivity to alectinib on the basis of extensive clinical evidence in ALK-rearranged NSCLC.

**SUPPORTING DATA**
Alectinib has been primarily studied for the treatment of ALK-rearranged NSCLC. In the Phase 3 ALEX study comparing alectinib with crizotinib in ALK-rearranged, inhibitor-naive NSCLC, patients treated with alectinib experienced significantly improved progression-free survival (PFS), 68.4% versus 48.7% (hazard ratio [HR]=0.47); median PFS was not reached in the alectinib arm and was 11.1 months in the crizotinib arm; and median overall survival (OS) was not reached in either arm at 2 years207. Similar results have been reported in the J-ALEX trial for inhibitor-naive Japanese patients with ALK-positive NSCLC208. Alectinib combined with atezolizumab led to an objective response rate (ORR) of 81% (17/21) as first-line treatment for PD-L1 unselected, ALK+ NSCLC209. In the context of crizotinib resistance, the Phase 3 ALUR trial for patients with ALK+ NSCLC progressed on or are intolerant to crizotinib reported alectinib significantly improved PFS relative to chemotherapy (7.1 vs. 1.6 months; HR=0.32)209. Phase 1/2 and Phase 2 trials of alectinib in ALK-rearranged NSCLC refractory to crizotinib reported ORRs of 45-55%56,206,210, with a reported median duration of response of 11.2–17 months56,210-211. Alectinib has demonstrated significant activity against central nervous system (CNS) metastases, such as leptomeningeal metastases, for patients with NSCLC56,204-207,210,212-216. In the ALUR trial, alectinib significantly improved ORR for CNS metastases relative to chemotherapy (54.2% vs. 0%)209. In the ALEX study, alectinib showed superior efficacy in CNS compared with crizotinib, with 12-month progression rate with CNS disease of 41.4% versus 4.4% and median duration of response in patients with CNS disease at baseline for 173 months versus 5.5 months207. A Phase 2 study of alectinib for crizotinib-resistant, ALK rearranged NSCLC reported 27% of patients achieving a CNS-specific CR, and an overall CNS disease control rate of 83% (95% confidence interval, 74% to 91%)56. In a preliminary study of alectinib in four cases of metastatic, RET-rearranged NSCLC, three of whom had previously been treated with cabozantinib, PRs were observed in two patients (one confirmed and one unconfirmed), with an additional patient exhibiting SD for 6 weeks and one case of progressive disease; improvement in CNS disease was observed in one patient after dose increase217.

Brigatinib

**AREAS OF THERAPEUTIC USE**
Brigatinib is a kinase inhibitor that targets ALK, ROS1, and mutant EGFR and is FDA approved to treat patients with metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

**GENE ASSOCIATION**
Activating ALK alterations may predict sensitivity to brigatinib based on strong clinical218-219 and preclinical220-221 evidence.

**SUPPORTING DATA**
Brigatinib has been studied primarily for the treatment of ALK-rearranged NSCLC. In the randomized Phase 2 ALTA study, 222 patients with ALK-rearranged NSCLC who progressed on crizotinib were treated with brigatinib and experienced overall response rates (ORRs) of 48-53% (with 5 CR, 4 PR) and progression-free survival (PFS) rates of 9.2-15.6 months (hazard ratio of 0.55)219,222. In addition, brigatinib demonstrated activity against brain metastasis of patients with ALK-rearranged NSCLC, with 23% (18/79; 2 CR, 7 PR) of patients in the 90 mg dose arm achieving a mean intracranial PFS of 15.6 months (hazard ratio of 0.66), although the intracranial PFS was not reached in 18% (13/72, 12 PR) of patients in the 180 mg dose arm of the study222. In the expansion stage of a Phase 1/2 study, responses to brigatinib were observed in ALK-rearranged NSCLC cases that were ALK-inhibitor naive (4/4 patients, 100% ORR) or previously treated with crizotinib (31/42 patients, 74% ORR) but not in the single case of EGFR T790M-positive NSCLC with resistance to previous EGFR tyrosine kinase inhibitor53. Brigatinib was associated with an ORR of 17% (3/18 patients) in other solid tumors with ALK/ROS1/EGFR alterations53.
**Ceritinib**

**AREAS OF THERAPEUTIC USE**
Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is FDA approved to treat metastatic nonsmall cell lung cancer (NSCLC) in patients whose tumors are positive for ALK rearrangements or ROS1 rearrangements.

**GENE ASSOCIATION**
On the basis of strong clinical data demonstrating benefit to patients with ceritinib-naïve lung cancer and those previously treated with crizotinib-225 to 227, ALK rearrangements may predict sensitivity to ceritinib.

**SUPPORTING DATA**
Multiple Phase 3 studies have reported clinical benefit from ceritinib for patients with advanced ALK-rearranged (ALK+) NSCLC. As a first-line treatment for patients with ALK+ NSCLC, ceritinib monotherapy significantly increased the median progression-free survival (PFS) to 16.6 months, compared to a median PFS of 8.1 months in patients with platinum-based chemotherapy224. A Phase 3 study of ceritinib for ALK inhibitor-naïve patients with ALK+

**Crizotinib**

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

**GENE ASSOCIATION**
ALK activation may predict sensitivity to crizotinib. In patients with ALK-rearranged NSCLC, crizotinib improved outcomes in both the first-line231-232 and second-line245 settings compared with chemotherapy. Retrospective analysis of 35 patients with NSCLC indicated that compared with other EML4-ALK variants, EML4-ALK variant 1 was an independent predictor of improved median PFS (11.0 vs. 4.2 months, hazard ratio of 0.35) on crizotinib treatment97. ALK inhibitors have also demonstrated clinical activity in the context of several other cancer types with activating ALK alterations, including thyroid carcinoma, inflammatory myofibroblastic tumors, and anaplastic large cell lymphoma58,233-234.

**SUPPORTING DATA**
The Phase 3 PROFILE 1014 study for patients with ALK positive non-squamous NSCLC reported significantly prolonged progression-free survival [PFS, 10.9 vs. 7.0 months, hazard ratio (HR) 0.45] and higher objective response rate (ORR, 74% vs. 45%) with first-line crizotinib compared with pemetrexed and cisplatin or carboplatin232. A similar Phase 3 study for East Asian patients confirmed that crizotinib is superior to chemotherapy in this setting (PFS of 11.1 vs. 6.8 months, HR 0.40; ORR of 87.5% vs. 45.6%)231. In the ongoing Phase 3 PROFILE 1007 study for patients with ALK-positive advanced NSCLC and prior platinum-based therapy (NCT00932893), crizotinib significantly improved median PFS (77 months vs. 3.0 months), ORR (65% vs. 20%), and quality of life as compared with chemotherapy54,235. The three Phase 3 studies observed numerical, but not statistically significant, improvement of overall survival (OS) with crizotinib (HR of 0.82-0.90), although most patients (70-89%) crossed over from the chemotherapy groups to crizotinib treatment231,236232. The efficacy of crizotinib in patients with brain metastases has also been examined. Prospective comparison of the intracranial efficacy in patients with stable treated brain metastases included in PROFILE 1014 reported significantly prolonged intracranial disease control rate (DCR) at 24 weeks (56% vs. 25%) and PFS (9.0 vs. 4.0 months, HR 0.40) for patients treated with first-line crizotinib as compared with chemotherapy237. Pooled retrospective analysis of patients with ALK-rearranged NSCLC and concurrent brain metastases from the PROFILE 1007 and 1005 studies reported 12-week intracranial DCRs of 56% vs. 62% and intracranial ORR of 18% vs. 33% in patients with previously untreated versus previously treated brain metastases238. In a retrospective study of patients with brain metastases from ALK rearranged NSCLC, the majority of whom were treated with radiotherapy and crizotinib, the median OS after diagnosis of brain metastasis was 49.5 months; lack of prior targeted therapy, absence of extracranial metastasis, and a Karnofsky performance score of 90 or higher were significantly associated with improved OS239. Upon disease progression, further survival benefit can be derived for patients with ALK-positive NSCLC who continue crizotinib treatment240.
Abemaciclib

**AREAS OF THERAPEUTIC USE**
Abemaciclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor-positive (HR+), HER2-negative (HER2–) advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women, in combination with fulvestrant for women who have progressed on endocrine therapy, or as monotherapy for adults who have progressed on endocrine therapy and chemotherapy in the metastatic setting.

**GENE ASSOCIATION**
On the basis of clinical data in breast cancer and mantle cell lymphoma, CCND1 amplification or activation may be associated with response to abemaciclib. In a Phase 1 study, 4/10 patients with CCND1-amplified breast cancer responded to single-agent abemaciclib, with all of the responders having HR+ tumors.

**SUPPORTING DATA**
Abemaciclib has been investigated primarily in the context of breast cancer103,241-242. In a Phase 1 study evaluating abemaciclib as monotherapy, patients with NSCLC experienced a disease control rate of 49% (50% for KRAS wild-type tumors and 55% for KRAS-mutant tumors), with 2 partial responses (PRs)243. A Phase 1 study of abemaciclib in combination with ramucirumab in metastatic NSCLC reported 2 unconfirmed PRs243.

Palbociclib

**AREAS OF THERAPEUTIC USE**
Palbociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor-positive (HR+), HER2-negative (HER2–) advanced or metastatic breast cancer in combination with an aromatase inhibitor as first-line therapy for postmenopausal women or in combination with fulvestrant following progression on endocrine therapy.

**GENE ASSOCIATION**
Clinical studies in liposarcoma and mantle cell lymphoma as well as responses in patients with breast cancer or melanoma indicate that activation of cyclin D-CDK4/6 may predict sensitivity to therapies such as palbociclib99,106,244.

**SUPPORTING DATA**
Palbociclib has been studied primarily for the treatment of ER+ breast cancers103,245-246. A Phase 2 study of palbociclib in patients with recurrent or metastatic non-small cell lung cancer (NSCLC) and loss of p16INK4a reported no responses in any of the 16 evaluable patients but stable disease (SD) in 8 (50%) patients247. A trial of the CDK4/6 inhibitor abemaciclib in patients with NSCLC reported a disease control rate of 51% (57% for patients with KRAS wild-type tumors and 54% for patients with KRAS-mutant tumors), with one confirmed PR248.

Ribociclib

**AREAS OF THERAPEUTIC USE**
Ribociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved in combination with an aromatase inhibitor as first-line therapy to treat women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced or metastatic breast cancer. Ribociclib is also approved in combination with fulvestrant to treat postmenopausal women with HR+, HER2– advanced or metastatic breast cancer, either as first-line therapy or following disease progression on endocrine therapy.

**GENE ASSOCIATION**
On the basis of clinical responses for 3 patients with bladder cancer, BRAF/NRAS-wild-type melanoma, or ER positive breast cancer, CCND1 amplification may predict sensitivity to CDK4/6 inhibitors such as ribociclib. In a prospective trial, 1 out of 12 patients with CCND1-amplified solid tumors responded to ribociclib99.

**SUPPORTING DATA**
The Phase 1 Signature study of ribociclib for the treatment of patients with CDK4/6 pathway-activated tumors reported clinical benefit for 18.4% (19/103) of cases, 58% (11/19) of whom had p16INK4a mutation or loss; antitumor activity was observed in 3 patients99. Phase 1 studies of ribociclib for the treatment of patients with Rb+ advanced solid tumors reported 2.4% partial responses and 23.5-34.4% stable diseases (SD)104,249; the 3 responders had alterations in the CDK4/6 pathway104. Another Phase 1 study of ribociclib monotherapy reported some efficacy in pediatric patients with neuroblastoma [4 SD, including 2 for >280 days, and 4 progressive disease (PD)] and CNS rhadoblast tumors, including ATRT [1 SD (ongoing after 444 days) and 9 PD], although RBs status was not determined in any of the patients; of the patients with CDK4-amplified tumors (all neuroblastoma), 1 achieved SD (for >280 days) and 2 exhibited PD250.

**NOTE**
Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient’s tumor type.
QRF# XXXXXXX

**GENE**

**ALK**

**ALTERATION**

EML4-ALK fusion (Variant 1)

**RATIONALE**

ALK rearrangements, activating mutations, or amplification may be associated with increased activity in the ALK kinase. Therefore, drugs that inhibit ALK kinase may be relevant. Additionally, patients who have become resistant to crizotinib may harbor sensitivity to newer ALK inhibitors or to HS590 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the website clinicaltrials.gov using keyword terms such as "alectinib", "AF802", "CHS5424802", "ceritinib", "LDK378", "crizotinib", "PF-02341066", "CEP-70440", "dalantercept", "gilteritinib", "ASP2215", "PF-06463922", "RXDX-101", "X-396", "lung", "solid tumor", and/or "advanced cancer".

**CLINICAL TRIALS**

**NCT03178552**

**PHASE 2 / 3**

A Phase II/III Multicenter Study Evaluating the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring Actionable Somatic Mutations Detected in Blood (B-FAST: Blood-First Assaying Screening Trial)

**LOCATIONS:**

Okayama (Japan), Shizuoka (Japan), Saga (Japan), Aichi (Japan), Hiroshima (Japan), Kurultai Park (Australia), Rio de Janeiro (Brazil), California, Krakow (Poland), Moscovskaya Oblast (Russian Federation), CD Mexico (Mexico), Kyoto (Japan), Malaga (Spain), Connecticut, San Luis Potosi (Mexico), Miyagi (Japan), Gdansk (Poland), Santiago de Compostela (Spain), Warszawa (Poland), Madrid (Spain), Osaka (Japan), Esslingen (Germany), Bunkyo-ku (Japan), Ijui (Brazil), Ishikawa (Japan), Yamaguchi (Japan), Alicante (Spain), Barcelona (Spain), Shatin (Hong Kong), Hospital de Lllobregat (Spain), Poitiers (France), Pennsylvanie, Tokyo (Japan), Valencia (Spain), Toronto (Canada), Fukuoka (Japan), New York, Wakayama (Japan), Milano (Italy), Beer Sheva (Israel), Olsztyn (Poland), Florida, Illinois, Niigata (Japan), Ehime (Japan), Kanagawa (Japan), Otwock (Poland)

**NCT02767804**

**PHASE 3**

Phase 3 Randomized Study Comparing X-396 (Ensartinib) to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

**LOCATIONS:**

Pergamino (Argentina), Virginia, Changchun (China), Barcelona (Spain), Wisconsin, Nanchang (China), Sao Paulo (Brazil), Changsha (China), Bristol (United Kingdom), Santo Andre (Brazil), Jerusalem (Israel), Tianjin (China), New York, Warsaw (Poland), Rosario (Argentina), Oregon, Florida, Montpellier (France), Palma de Mallorca (Spain), Edirne (Turkey), Sondrio (Italy), Shenyang (China), Plesice (Czechia), Brussels (Belgium), Osthra-Vitkovice (Czechia), Gdansk (Poland), Hong Kong (Hong Kong), Haifa (Israel), Nottingham (United Kingdom), Qingdao (China), Moscow (Russian Federation), Hangzhou (China), Ravenna (Italy), Aviano (Italy), Missouri, Tennessee, Meldola (Italy), Nanjing (China), Idaho, Georgia, Hefei (China), Istanbul (Turkey), Legnago (Italy), Berlin (Germany), Usti nad Labem (Czechia), Beijing (China), Omsk (Russian Federation), Guangzhou (China), Buenos Aires (Argentina), Michigan, Milano (Italy), Lima (Peru), Saint Petersburg (Russian Federation), Pamplona (Spain), Madrid (Spain), Wuhan (China), Izmir (Turkey), Seoul (Korea, Republic of), Caba (Argentina)

**NCT03093116**

**PHASE 1 / 2**

A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)

**LOCATIONS:**

Massachusetts, Colorado, New York, Seoul (Korea, Republic of), California

**NCT00585195**

**PHASE 1**

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

**LOCATIONS:**

New York, Michigan, Colorado, Ohio, Pennsylvania, California, Kashiwa (Japan), Nagoya (Japan), Akashi (Japan), Massachusetts, Melbourne (Australia), North Carolina, Seoul (Korea, Republic of), Vermont, Sapporo (Japan), Osakasayama (Japan)
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NCT02227940

A Phase I Study of Ceritinib (LDK378), a Novel ALK Inhibitor, in Combination With Gemcitabine-Based Chemotherapy in Patients With Advanced Solid Tumors

LOCATIONS: New York
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<th>GENE</th>
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<tr>
<td>ALTERATION</td>
<td>amplification</td>
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**RATIONALE**
CCND1 amplification may activate CDK4/6 and may predict sensitivity to CDK4/6 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the [ClinicalTrials.gov](https://clinicaltrials.gov) using keyword terms such as "CDK4", "CDK6", "palbociclib", "PD-032991", "abemaciclib", "LY2835219", "ribociclib", "LEE011", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

### Clinical Trials

<table>
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<th>NCT Number</th>
<th>Phase</th>
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<td>An Open Label, Phase Ib Dose-escalation Study Evaluating the Safety and Tolerability of BI 836845 and Abemaciclib in Patients With Locally Advanced or Metastatic Solid Tumors and in Combination With Endocrine Therapy in Patients With Locally Advanced or Metastatic Hormone Receptor-positive Breast Cancer, Followed by Expansion Cohorts</td>
<td>CDK4, Aromatase, ER, IGF-2, IGF-1, CDK6</td>
<td>Nevada, Madrid (Spain), Connecticut, Pozuelo de Alarcón (Spain), Paris (France), Marseille (France), Barcelona (Spain), California, Minnesota</td>
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<td>NCT02897375</td>
<td>PHASE 1</td>
<td>A Phase 1 Study of Palbociclib in Combination With Cisplatin or Carboplatin in Advanced Solid Malignancies</td>
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<td>Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer</td>
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<td>NCT03065062</td>
<td>PHASE 1</td>
<td>Phase I 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 &amp; Neck and Other Solid Tumors</td>
<td>CDK4, mTORC1, PI3K-gamma, mTORC2, PI3K-alpha, CDK6</td>
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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.

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

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

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**DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS**

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*TERC is an ncRNA
**Promoter region of TERT is interrogated

**ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS**

Microsatellite (MS) status
Tumor Mutational Burden (TMB)
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, homologous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

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.

Limitations
1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established.

2. TMB by F1CDx is defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
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

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>DEFINITION</th>
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<td>CR</td>
<td>Complete response</td>
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<tr>
<td>DCR</td>
<td>Disease control rate</td>
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<td>DNMT</td>
<td>DNA methyltransferase</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>ITD</td>
<td>Internal tandem duplication</td>
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<td>MMR</td>
<td>Mismatch repair</td>
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<tr>
<td>muts/Mb</td>
<td>Mutations per megabase</td>
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<td>NOS</td>
<td>Not otherwise specified</td>
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<tr>
<td>ORR</td>
<td>Objective response rate</td>
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<td>OS</td>
<td>Overall survival</td>
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<td>PD</td>
<td>Progressive disease</td>
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<td>PFS</td>
<td>Progression-free survival</td>
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<tr>
<td>PR</td>
<td>Partial response</td>
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<tr>
<td>SD</td>
<td>Stable disease</td>
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<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
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The median exon coverage for this sample is 733X


Legrand et al., 2018; ASCO Abstract 12000

Schwartz et al., 2016; ASCO Abstract 8533


Camidge et al., 2011; ASCO Abstract 2501

Bang et al., 2010; ASCO Abstract 3

Gandi et al., 2015; ASCO Abstract 8019


Moss et al., 2012; ASCO 9500


Huber et al., 2018; ASCO Abstract 9061

Kim et al., 2018; ASCO Abstract 9009

Besse et al., 2018; ASCO Abstract 9032

Shaw et al., 2018; AACR Abstract CT044


Kim et al., 2016; EORTC–NCI–AACR Symposium Abstract 105A.

Chan et al., 2017; AACR Abstract CT06/24.


181. Hajdijberg et al., 2012; ASCO Abstract e1050
183. Oza et al., 2015; ASCO Abstract 5506
184. Leijen et al., 2015; ASCO Abstract 2507

APPENDIX References


REPORT DATE
01 Jan 2018

Patient Information

Patient: Sample, Jane

TUMOR TYPE Lung adenocarcinoma

Foundation Medicine, Inc. • 1-888-988-3639

Sample Preparation: ISS Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 2020027531

Sample Analysis: ISS Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 2020027531
NSCLC - are TKIs Changing the Treatment Strategy? Anticancer


with diffuse leptomeningeal carcinomatosis. Oncologist 20(2):232-6

non-small cell lung cancer patient who progressed on crizotinib and is sensitive to ceritinib. Lung Cancer 10(2):232-6

and Other Solid Tumors. Clin Cancer Res


Lin et al., 2018; ASCO Abstract 9093


Felip et al., 2015; ASCO Abstract 8506


Felip et al., 2015; ELCC Abstract 147D

Scaglioni et al., 2016; ESMO Abstract LA848_PR


Lu SH, Greenbowe J, Khan ZU, et al. (2015) I1171 missense mutation (particularly I1171N) is a common resistance mutation in ALK-positive NSCLC patients who have progressive disease while on crizotinib and is sensitive to ceritinib. Lung Cancer 88(2):231-4

Li et al., 2016; ASCO Abstract 9058


Shaw et al., 2016; ASCO Abstract 9066


Kim et al., 2015; ASCO Abstract 8047


Gopalan et al., 2014; ASCO Abstract 8077

Goldman et al., 2014; ASCO Abstract 8026

Yamada et al., 2015; AACR-NCI-EORTC Abstract B31


Electronically Signed by Julia A. Elvin, M.D., Ph.D. • Jeffrey S. Ross, M.D., Medical Director • 01 January 2018