FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Sample, Jane	Lung adenocarcinoma	01 Jan 2018

PRF#
XXXXXXXX

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 adenocarcinoma
NAME Not Given
DATE OF BIRTH Not Given
SEX Not Given
MEDICAL RECORD # Not Given

PHYSICIAN

ORDERING PHYSICIAN Not Given
MEDICAL FACILITY Not Given
ADDITIONAL RECIPIENT Not Given
MEDICAL FACILITY ID Not Given
PATHOLOGIST Not Given

SPECIMEN

SPECIMEN SITE Not Given
SPECIMEN ID Not Given
SPECIMEN TYPE Not Given
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - TMB-Low (4 Muts/Mb)

Gene Alterations

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

ALK EML4-ALK fusion (Variant 1)
CCND1 amplification
FGF19 amplification
FGF3 amplification
FGF4 amplification
NFKBIA amplification
NKX2-1 amplification
TP53 R306*

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

6 Therapies Approved in the EU
0 Therapies with Lack of Response
14 Clinical Trials

GENOMIC SIGNATURES	ACTIONABILITY	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Genomic Signatures section	
Tumor Mutational Burden - TMB-Low (4 Muts/Mb)	No therapies or clinical trials. see Genomic Signatures section	
GENE ALTERATIONS	**THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)**	**THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)**
***ALK* -** EML4-ALK fusion (Variant 1) **10 Trials** see p. 11	Alectinib Ceritinib Crizotinib	None
***CCND1* -** amplification **4 Trials** see p. 14	None	Abemaciclib Palbociclib Ribociclib

GENE ALTERATIONS 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 Gene Alterations section.

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

Therapies contained in this report may have been approved through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

GENOMIC SIGNATURE

Microsatellite status

CATEGORY

MS-Stable

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 inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4-5]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[6]. Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%)[5]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without[4].

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[13]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[13-15]. The tumor seen here is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[16-18]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[13,15,17-18]

GENOMIC SIGNATURE

Tumor Mutational Burden

CATEGORY

TMB-Low (4 Muts/Mb)

POTENTIAL TREATMENT STRATEGIES

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4[19], anti-PD-L1[20-23], and anti-PD-1 therapies[5,24-25]; 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)[25]. 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[5,24-25]. 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[26] or nivolumab[27], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab[28], 2 pediatric patients with biallelic mismatch repair deficiency-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[29], and 2 patients with microsatellite-stable rectal cancers, 1 who achieved an ongoing PR to pembrolizumab and the other an ongoing complete response to nivolumab[30]. For patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[19,31] and anti-PD-1/anti-PD-L1 treatments[21]. For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load (12.4 mutations [muts] per megabase [Mb]) compared to nonresponders (6.4 muts/Mb)[20], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival[22]. In a retrospective analysis of 17 solid tumor types (comprised of 47% NSCLC, 40% mUC, and 13% encompassing 15 other solid tumors), a TMB of ≥16 muts/Mb associated with an objective response rate to atezolizumab of 30% vs. 14% for chemotherapy alone[32].

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 9017). Intermediate TMB was frequently observed in NSCLC with BRAF (31%) or KRAS (39%) mutation (Spigel et al., 2016; ASCO Abstract 9017). Although some studies have reported a lack of association between smoking and mutational burden in NSCLC (Schwartz et al., 2016; ASCO Abstract 8533)[66,67], several other large studies did find a strong association with increased Low TMB is observed more commonly in nonsmall 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[33]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[34-36], several other large studies did find a strong association with increased TMB[37-40]. 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)[35].

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[41-42] and cigarette smoke in lung cancer[25,43], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[44-48], and microsatellite instability (MSI)[44,47-48]. The tumor seen here harbors a low TMB. Compared to patients with tumors harboring higher TMB levels, patients with tumors harboring low TMB levels have experienced lower rates of clinical benefit from treatment with immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma[19], anti-PD-L1 therapy in urothelial carcinoma[20], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer[5,25].

GENE
ALK

ALTERATION
EML4-ALK fusion (Variant 1)

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 rearrangement[49-50,51-56]. As first-line treatment, crizotinib improved overall survival (OS) relative to chemotherapy (HR=0.35) for patients with ALK+ advanced NSCLC[57]. Crizotinib has also shown activity in ALKmutant neuroblastoma[58-59]. Preclinically, ALK activating point mutations are crizotinibsensitive[60-61]. 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% (92/163) and PFS of 6.9 months for those who were previously treated[62]. 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, respectively[53]. Antitumor activity was also seen in the central nervous system (CNS), a common site of failure during crizotinib treatment[53,63-64]. Alectinib combined with atezolizumab led to an ORR of 81% (17/21) as first-line treatment for PD-L1 unselected, ALK+ NSCLC[65]. 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, respectively[66]. 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 mutation[67]; G1202 therefore does not appear to represent a major mechanism of lorlatinib resistance[68-69]. Lorlatinib led to complete resolution of intrathecal metastases and stabilization of CNS metastases for a heavily pretreated patient with ALK+ NSCLC[70], and its use in the fourth-line setting led to disappearance of leptomeningeal disease for a patient with ALK-rearranged metastatic inflammatory myofibroblastic sarcoma[71]. 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 treated[72]. 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, respectively[73]. 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 ALK F1245V mutant neuroblastoma but in 0/13 patients with ALK fusion-positive tumors previously treated with an ALK inhibitor and in none of the other patients with ALK non-fusion alterations[74]. A Phase 2 trial of the HSP90 inhibitor ganetespib reported PRs in a small number of patients with ALK-rearranged NSCLC[75].

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 heritage[76-82]. Other rearrangements involving ALK have also been described in lung cancer[83-84]. EML4-ALK fusions have been reported to be a significant indicator of poor prognosis in advanced stage NSCLC[82].

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 proliferation[85]. Different EML4-ALK variants have been identified in cancer, all of which contain the intracellular tyrosine kinase domain of ALK[86]. 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 3 a/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 5 a/b, 1-2% of cases)[87,92-94], and exon 17 (variant 8 a/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 ceritinib[88,90,96]; however, variants 3a/b are less sensitive to crizotinib in vitro[88]. Although EML4-ALK variant 1 was associated with significantly longer median progression-free survival (11 months vs. 4.2 months) in a small study of crizotinib-treated non-small cell lung cancer (NSCLC)[97], other studies have not found a correlation between EML4-ALK variants and response to crizotinib in NSCLC[52,89].

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 ribociclib98-99 100-101102-105. 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 adenocarcinomas108-109. 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.

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 HCC116. Preliminary results from the dose escalation part of a Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, 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 datasets, FGF19 amplification has been reported with highest incidence in esophageal carcinoma (35%), 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, FGF4, 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.

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, FGF4, 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.

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies129-130 and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)129. Therefore, investigation in clinical trials in multiple tumor types. FGF4 amplification may confer sensitivity to sorafenib, which is FDA approved to treat HCC, renal cell carcinoma, and differentiated thyroid carcinoma. Sorafenib is under

FREQUENCY & PROGNOSIS
This chromosomal region is frequently amplified in a diverse range of malignancies112 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
FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth131 and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development132. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers112,129,133-136 and may confer sensitivity to the multi-kinase inhibitor sorafenib129.

GENE
NFKBIA

ALTERATION
amplification

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

FREQUENCY & PROGNOSIS
In the TCGA datasets, amplification of NFKBIA has been reported with the highest incidence in lung adenocarcinoma (11.7%)107, esophageal carcinoma (3.8%), uterine carcinosarcoma (3.6%), lung squamous cell carcinoma (3.4%), and ovarian serous cystadenocarcinoma (2.6%) (cBioPortal, 2017). Amplification or increased expression of NFKBIA in EGFR-mutant lung cancer has been reported to predict improved response to EGFR tyrosine kinase inhibitors137-138. Certain NFKBIA polymorphisms, which may affect IkBa expression levels, have been studied as risk factors for some cancer types, although the data are mixed and conflicting139-141.

FINDING SUMMARY
NFKBIA encodes IkBa, an inhibitor of the NF-kappaB (NFkB)/REL complex. It has been reported to act as a tumor suppressor in Hodgkin's lymphoma 395-399 and in glioblastoma 392,400-401. NFKBIA has been reported to be amplified in cancer 227 and may be biologically relevant in this context 228-229. In contrast, truncating mutations that result in loss of the majority of the IkBa protein are predicted to be inactivating.

GENE
NKX2-1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies or trials that target tumors with TTF-1 amplification or overexpression. Lung cancer cell lines that express both TTF-1 and NKX2-8, which is located in the same amplicon as NKX2-1, have demonstrated resistance to cisplatin therapy152, although conflicting data has also been reported153.

FREQUENCY & PROGNOSIS
Putative amplification of NKX2-1 has been reported with the highest incidence in lung cancer, and has been observed in 14% of adenocarcinomas107 and 5% of squamous cell carcinomas (SCC)154 as well as other tumor types including prostate adenocarcinomas (6%)155, and poorly differentiated and anaplastic thyroid cancers (4%)156. NKX2-1 mutation has been observed in 9% of acinar cell carcinomas of the pancreas157, 5% of uterine carcinosarcomas158, and is infrequent in other tumor types (cBioPortal, COSMIC, 2018). TTF-1 is expressed in a majority of lung adenocarcinomas and small cell carcinomas, as well as in a subset of thyroid and CNS tumors159-161. Cytoplasmic TTF-1 expression has been reported as an adverse prognostic factor in breast carcinoma162-163. However, whether amplification and/or expression status of NKX2-1 have prognostic implications for patients with lung cancer is controversial152-153,164-167. TTF-1 has been observed to have tumor-promoting as well as anti-oncogenic roles168-169.

FINDING SUMMARY
NKX2-1 (NK2 homeobox 1) encodes the thyroid transcription factor TTF-1170. Amplification of NKX2-1 results in overexpression of TTF-1 and upregulated transcription of downstream target genes171.

GENE
TP53

ALTERATION
R306*

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[172-175] or p53 gene therapy and immunotherapeutics such as SGT-53[176-180] and ALT-801[181]. In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53-wild-type[182]. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer[183]. Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel[184]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage[180]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[185]. 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 adenocarcinoma[192]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[24].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[193]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[194-196]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[197-202]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[203] to 1:20,000[202], and in the appropriate clinical context, germline testing of TP53 is recommended.

Alectinib

Assay findings associations

ALK
EML4-ALK fusion (Variant 1)

AREAS OF THERAPEUTIC USE

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. It is available in the EU to treat patients with ALK-positive advanced non-small cell lung cancer (NSCLC) as first-line therapy or after prior treatment with crizotinib.

GENE ASSOCIATION

Activating ALK alterations may predict sensitivity to alectinib on the basis of extensive clinical evidence in ALK-rearranged NSCLC51,20456,205-206.

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+ NSCLC65. In the context of crizotinib resistance, the Phase 3 ALUR trial for patients with ALK+ NSCLC reported that 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 9.4% and median duration of response in patients with CNS disease at baseline for 17.3 months versus 5.5 months207. A Phase 2 study of alectinib for crizotinib-refractory, 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.

Ceritinib

Assay findings associations

ALK
EML4-ALK fusion (Variant 1)

AREAS OF THERAPEUTIC USE

Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is available in the EU to treat advanced ALK-positive non-small cell lung carcinoma (NSCLC) either as first-line treatment or following crizotinib therapy.

GENE ASSOCIATION

On the basis of strong clinical data demonstrating benefit to patients with crizotinib-naïve lung cancer62,223-224 or those previously treated with crizotinib225-22655,62,227, 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 in the ASCEND-4 Phase 3 study, 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 platinumbased chemotherapy224. A Phase 3 study of ceritinib for ALK inhibitor-naïve patients with ALK+ NSCLC observed a whole-body (WB) objective response rate (ORR) of 63.7%, a WB disease control rate (DCR) of 89.5%, and progression-free survival (PFS) of 11.1 months223. The ASCEND-5 Phase 3 study comparing ceritinib to chemotherapy for patients with ALK+ NSCLC previously treated with crizotinib and chemotherapy also reported a significant benefit for ceritinib in ORR (39% vs. 7%) and median PFS (5.4 vs. 1.6 months); there was no improvement of median OS (18.1 vs. 20.1 months), which may be due to the crossover of patients to the ceritinib arm226. The ASCEND-1 Phase 1 study of ceritinib for patients with ALK+ NSCLC reported an ORR of 72%, median PFS of 18.4 months, and 12-month overall survival (OS) of 83%62. Earlier Phase 1 and 2 studies reported similar clinical benefit as measured by ORR (39-57%), median PFS (5.7-6.9 months), and median OS of 16.7 months55,62,227; for patients with brain metastases, an intracranial ORR of 39% and duration of response of 12.8 months were achieved225. Case studies have also reported responses to ceritinib in patients with ALK+ NSCLC and ALK missense mutation after disease progression on crizotinib228 or alectinib229-230.

Crizotinib

Assay findings associations

ALK

EML4-ALK fusion (Variant 1)

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) whose tumors are positive for ALK either as first-line or following previous treatment. It is also available to treat patients with ROS1-positive advanced NSCLC.

GENE ASSOCIATION

ALK activation may predict sensitivity to crizotinib. In patients with ALK-rearranged NSCLC, crizotinib improved outcomes in both the first-line[231-232] and second-line[54] 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 treatment[97]. 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 lymphoma[58,233-234].

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 carboplatin[232]. 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 ALKpositive advanced NSCLC and prior platinum-based therapy (NCT00932893), crizotinib significantly improved median PFS (7.7 months vs. 3.0 months), ORR (65% vs. 20%), and quality of life as compared with chemotherapy[54,235]. 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 treatment[231,236232]. 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 chemotherapy[237]. 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 metastases[238]. 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 OS[239]. Upon disease progression, further survival benefit can be derived for patients with ALK-positive NSCLC who continue crizotinib treatment[240].

IMPORTANT Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 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. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

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 HSP90 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "alectinib", "AF802", "CH5424802", "ceritinib", "LDK378", "crizotinib", "PF-02341066", "CEP-37440", "dalantercept", "gilteritinib", "ASP2215", "PF-06463922", "RXDX-101", "TSR-011", "X-396", "lung", "solid tumor", and/or "advanced cancer".

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 Assay Screening Trial)

TARGETS
ALK, PD-L1, RET

LOCATIONS: Okayama (Japan), Shizuoka (Japan), Saga (Japan), Aichi (Japan), Hiroshima (Japan), Kurralta Park (Australia), Rio de Janeiro (Brazil), California, Krakow (Poland), Moscovskaya Oblast (Russian Federation), CD Mexico (Mexico), Kyoto (Japan), Malaga (Spain), Connecticut, San Luis Potosí (Mexico), Miyagi (Japan), Gdańsk (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), Hospitalet de Llobregat (Spain), Poitiers (France), Pennsylvania, 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 [illegible] to [illegible] in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

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

LOCATIONS: Pergamino (Argentina), Virginia, Changchun (China), Barcelona (Spain), Wisconsin, Nanchang (China), São Paulo (Brazil), Changsha (China), Bristol (United Kingdom), Santo André (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), Ostrava-Vitkovice (Czechia), Gdańsk (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)

NCT02568267

PHASE 2

An Open-Label, Multicenter, Global Phase 2 Basket Study of [illegible] for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements

TARGETS
ALK, ROS1, TRKC, TRKB, TRKA

LOCATIONS: Hyogo (Japan), London (United Kingdom), Lyon (France), Leiden (Netherlands), Taipei City (Taiwan), Cambridge (United Kingdom), Florida, Toulouse (France), Oklahoma, Kashiwa-shi (Japan), Washington, Lille (France), Michigan, Illinois, Gdansk (Poland), Barcelona (Spain), Ehime (Japan), Wisconsin, Georgia, Taipei (Taiwan), Köln (Germany), Albury (Australia), Maryland, Göttingen (Germany), Genova (Italy), Warszawa (Poland), Utah, North Carolina, Oregon, New Hampshire, Missouri, Padova (Italy), Madrid (Spain), Bedford Park (Australia), Gliwice (Poland), Tainan (Taiwan), Chang Hua (Taiwan), Hawaii, Amsterdam (Netherlands), Torino (Italy), Massachusetts, Orbassano (Italy), Roma (Italy), Arizona, Shatin (Hong Kong), Taichung (Taiwan), Villejuif cedex (France), Singapore (Singapore), Connecticut, Aichi (Japan), Marseille cedex 5 (France), Shizuoka (Japan), Otwock (Poland), Pisa (Italy), Poznań (Poland), Cheongju-si (Korea, Republic of), Candiolo (Italy), Nevada, Kowloon (Hong Kong), Bordeaux (France), Dresden (Germany), Virginia, Paris (France), Napoli (Italy), District of Columbia, Heidelberg (Australia), New Lambton Heights (Australia), Malaga (Spain), Montpellier cedex 5 (France), Berlin (Germany), Colorado, Paris cedex 15 (France), Miyagi (Japan), Texas, California, Liverpool (Australia), Manchester (United Kingdom), Ohio, Sevilla (Spain), Fukuoka (Japan), Osaka (Japan), Minnesota, Marseille (France), Fuenlabrada (Spain), Milano (Italy), Niigata (Japan), Perugia (Italy), New York, Seoul (Korea, Republic of), Hong Kong (Hong Kong)

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 [illegible] in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)

TARGETS
ALK, ROS1, TRKC, TRKB, TRKA

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

NCT00585195

PHASE 1

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

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

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

NCT02693535

PHASE 2

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
ABL, CDK4, PARP, EGFR, DDR2, PDGFRs, VEGFRs, CTLA-4, ROS1, CSF1R, ERBB2, PD-1, ERBB3, MEK, RAF1, KIT, AXL, SMO, TRKC, mTOR, TRKA, MET, ALK, BRAF, RET, SRC, FLT3, CDK6

LOCATIONS: North Dakota, Washington, Illinois, California, Pennsylvania, Georgia, Arizona, Utah, North Carolina, Oklahoma, Alabama, South Dakota, Florida, Michigan, Oregon, Virginia, Texas, Nebraska

NCT01625234

PHASE 1 / 2

Phase 1/2, First-in-Human, Dose-Escalation Study of [illegible] in Patients With Advanced Solid Tumors and Expansion Phase in Patients With ALK-positive Non-Small Cell Lung Cancer

TARGETS
ABL, MET, ALK, ROS1, AXL

LOCATIONS: California, Oregon, Wisconsin, Tennessee, New York, Missouri, Maryland, South Carolina, Pennsylvania, Massachusetts, Texas, Virginia, Ohio, West Virginia

NCT02706626

PHASE 2

Phase 2 Trial of [illegible] After Treatment With Second-Generation ALK Inhibitors in Refractory ALK Rearranged Non-Small Cell Lung Cancer (NSCLC)

TARGETS
EGFR, ALK, ROS1

LOCATIONS: Colorado, Tennessee, Texas, North Carolina

NCT02321501

PHASE 1

A Phase I/Ib Dose Escalation and Biomarker Study of [illegible] in Combination With Everolimus in Patients With Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ALK, ROS1, mTOR

LOCATIONS: Texas

NCT02227940

PHASE 1

A Phase I Study of [redacted] a Novel ALK Inhibitor, in Combination With [redacted] Based Chemotherapy in Patients With Advanced Solid Tumors

TARGETS
ALK, ROS1

LOCATIONS: New York

GENE

CCND1

ALTERATION

amplification

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 trial website clinicaltrials.gov using keyword terms such as "CDK4", "CDK6", "palbociclib", "PD-0332991", "abemaciclib", "LY2835219", "ribociclib", "LEE011", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

NCT03099174

PHASE 1

An Open Label, Phase Ib Dose-escalation Study Evaluating the Safety and Tolerability of [illegible] 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

TARGETS
CDK4, Aromatase, ER, IGF-2, IGF-1, CDK6

LOCATIONS: Nevada, Madrid (Spain), Connecticut, Pozuelo de Alarcón (Spain), Paris (France), Marseille (France), Barcelona (Spain), California, Minnesota

NCT02897375

PHASE 1

A Phase 1 Study of [illegible] in Combination With [illegible] or [illegible] in Advanced Solid Malignancies

TARGETS
CDK4, CDK6

LOCATIONS: Georgia

NCT01037790

PHASE 2

Phase II Trial of the Cyclin-Dependent Kinase Inhibitor [illegible] in Patients With Cancer

TARGETS
CDK4, CDK6

LOCATIONS: Pennsylvania

NCT03065062

PHASE 1

Phase I Study of the CDK4/6 Inhibitor [illegible] in Combination With the PI3K/mTOR Inhibitor [illegible] for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

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

LOCATIONS: Massachusetts

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.

ASXL1 N986S	***CREBBP*** K2075R	***ERBB2*** E503K	***FANCC*** C206F
KDM5C R1435C	***MEN1*** amplification	***NOTCH1*** D1953H	***SMARCA4*** Q347K

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*	*ATRX*	*AMER1 (FAM123B)*
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*	*PARK2*
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*	*PDGFRB*
PDK1	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*	*POLD1*
POLE	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*	*PTEN*
PTPN11	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*	*RAD51D*
RAD52	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*	*RICTOR*
RNF43	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX2*
SOX9	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*	*SYK*
TBX3	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*
TSC2	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WHSC1L1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*KIT*	*EGFR*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*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 GENOMIC SIGNATURES

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

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) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with 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 PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using 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 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*: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Alterations and Therapies

Genomic Signatures
Appear at the top of the report, but are not ranked higher than Gene Alterations.

Gene Alterations
Therapies approved in the EU (In Patient's Tumor Type) → Therapies approved in the EU (In Other Tumor Type) → Clinical Trial Options → No Known Options (If multiple findings exist within any of these categories, the results are listed alphabetically by gene name.)

Therapies
Sensitizing therapies → Resistant therapies. (If multiple therapies exist within any of these categories, they are listed alphabetically by therapy name.)

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

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

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

The median exon coverage for this sample is 733X

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