FOUNDATIONONE®CDx

PATIENT

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

COUNTRY CODE
PE

REPORT DATE
19 Mar 2021

ORDERED TEST #
ORD-1039682-01

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

PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)

DATE OF BIRTH 19 March 1939
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Oncologia Patologica
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 320946
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID BE21-00686-1A (H21-5332)
SPECIMEN TYPE Block
DATE OF COLLECTION 11 February 2021
SPECIMEN RECEIVED 11 March 2021

Biomarker Findings

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

Genomic Findings

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

NF1 Y489C
EGFR V292L
RAD21 amplification - equivocal†
SRC amplification - equivocal†
TP53 E294fs*51

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

† See About the Test in appendix for details.

2 Therapies with Clinical Benefit
0 Therapies with Lack of Response
18 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
***NF1* -** Y489C	none	Selumetinib
10 Trials *see p. 10*		Trametinib
***EGFR* -** V292L	none	none
10 Trials *see p. 8*		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

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

BIOMARKER

Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

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

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GENE
NF1

ALTERATION
Y489C

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
1466A>G

VARIANT ALLELE FREQUENCY (% VAF)
26.4%

POTENTIAL TREATMENT STRATEGIES
On the basis of clinical evidence in neurofibromatosis type 1[63-64] and neurofibromatosis-associated glioma or glioblastoma[65-66], as well as extensive preclinical evidence in several tumor types[67-72], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including the approved agents everolimus and temsirolimus, based on limited clinical data[73-75] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[76-77]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[78]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[79], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[80].

FREQUENCY & PROGNOSIS
In the TCGA datasets, NF1 mutation has been observed in 11% of lung adenocarcinoma cases[81] and 8% of lung squamous cell carcinoma cases[82]. Published data investigating the prognostic implications of NF1 alteration in lung cancer are limited (PubMed, Feb 2021). However, decreased NF1 expression was reported in 2 lung adenocarcinoma samples after disease progression on first generation EGFR inhibitor and afatinib; neither sample harbored EGFR T790M mutation[83].

FINDING SUMMARY
NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[84]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[85]. Alterations such as seen here may disrupt NF1 function or expression[85-94].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the NF1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with neurofibromatosis type 1 (ClinVar, Sep 2020)[95]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[96-98]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[99-100], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE
EGFR

ALTERATION
V292L

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
874G>T

VARIANT ALLELE FREQUENCY (% VAF)
12.0%

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[101], gefitinib[102], afatinib[103], dacomitinib[104], and osimertinib[105]. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M[105-106]. Osimertinib achieved a 61% ORR for T790M-positive cases and a 21% ORR for T790M-negative cases[105]. In a Phase 1 study, the third-generation EGFR inhibitor alflutinib achieved a 77% ORR for the dose expansion cohort, as well as a CNS ORR of 58.8% (10/17) for patients with T790M-positive non-small cell lung cancer (NSCLC)[107]. Resistance to EGFR inhibition may arise by reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may impede the development of acquired resistance to third-generation EGFR inhibitors[108-110]. A Phase 1 trial combining third-generation EGFR inhibitor lazertinib with the EGFR/MET bispecific antibody amivantamab for EGFR-mutated NSCLC elicited an ORR of 35.6% (16/45) for the osimertinib-resistant, chemotherapy-naive cohort, as well as an ORR of 100% (20/20) for the treatment-naive cohort[111]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[112-113] that has also shown benefit in patients with CRC and melanoma[114-115]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[116-119]. Preclinical studies have reported that EGFR-mutant cells[116-118], including cells with exon 20 insertions[120], are sensitive to HSP90 inhibitors. In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 25% (14/56) and a DCR of 69.6% (39/56) for patients with non-small cell lung cancer (NSCLC) previously treated with an EGFR TKI and platinum-based chemotherapy, many of whom displayed TKI resistance alterations[121]. Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[122-123]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases[124]. The reovirus Reolysin targets cells with activated RAS signaling[125-127] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[128-136]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[137]. The Phase 3 IMpower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy in patients with untreated EGFR-mutated or ALK-rearranged metastatic NSCLC[138]; therefore, the patient's clinical context should be considered. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[47,81,139] and in 4% of lung squamous cell carcinomas[82]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[140-145]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[146-147]. In lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival in all patients and of poor overall survival in patients with EGFR mutations[148-149]. Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival[150]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[151] or resected Stage 1 NSCLC[152].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[153]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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GENE
RAD21

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS
RAD21 amplifications, point mutations, and truncating mutations have been reported in various cancers[154]. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes[155-156], including sporadic Grade 3 but not Grade 1 cancers[155], as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers[155]. Furthermore, SNPs in or near RAD21 have been linked with risk of breast cancer development[157-158]. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer[159] and in colorectal cancer (CRC), especially in KRAS-mutant CRC[160]. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer[161]. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression[162]. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic[163]. Downregulation of RAD21 expression resulted in sensitization of cultured breast[156,164] and CRC[160] cells to chemotherapy, thereby suggesting that RAD21 overexpression confers resistance to chemotherapy.

FINDING SUMMARY
RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[165-168]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[169], but also leads to an increase in deletions, insertions, and other rearrangements[170]. High RAD21 expression has also been associated with increased genomic instability[155]. Cohesin complex also organizes chromatin domains and regulates gene expression[171-172]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[173]. RAD21 amplification has been correlated with increased expression in breast[155-156,174] and endometrial[159] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

GENE
SRC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
Dasatinib, a SRC and tyrosine kinase inhibitor, is approved for use in Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL). Bosutinib, which targets both ABL and SRC kinases, is approved to treat Ph+ CML with resistance or intolerance to prior therapy. Clinical trials of these agents and other SRC inhibitors are in progress in various cancer types[175-176]. Overexpression of SRC in colorectal carcinoma may be associated with resistance to chemotherapy[177].

FREQUENCY & PROGNOSIS
In the TCGA datasets, SRC amplification was observed in 1.1% of lung squamous cell carcinomas (SCC)[82] and 1.7% of lung adenocarcinomas[81]. SRC activation has been shown to occur frequently in non-small cell lung cancer (NSCLC) tumors and cell lines, reported in 28-49% of lung tumors in the scientific literature[178-180]. Published data investigating the prognostic implications of SRC alterations in lung cancer are limited (PubMed, Jul 2020).

FINDING SUMMARY
The protein encoded by SRC belongs to a family of related non-receptor tyrosine kinases, members of which have been implicated in the growth and progression of a number of tumors, including breast, colon, and pancreatic cancer[181-183]. SRC has been reported to be amplified in cancer[184] and may be biologically relevant in this context[185-186].

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GENE
TP53

ALTERATION
E294fs*51

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
880delG

VARIANT ALLELE FREQUENCY (% VAF)
34.6%

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 adavosertib[187-190], or p53 gene therapy and immunotherapeutics such as SGT-53[191-195] and ALT-801[196]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[197]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[198]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[199]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[200]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[201]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[202]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[195]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[203]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[204-205]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[206-207]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[81-82,208-213], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[47-48,81-82]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[184,214]. 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[215]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[216]. Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[217-222]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[217-218]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[223]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[221,224-225]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[226]. Alterations such as seen here may disrupt TP53 function or expression[227-231].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[232-234], including sarcomas[235-236]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[237] to 1:20,000[236]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[238]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Selumetinib

Assay findings association

NF1
Y489C

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[63,66] and strong preclinical evidence[68-72] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

In a Phase 2 study of selumetinib monotherapy to treat patients with lung cancer who were selected for mutation in KRAS, HRAS, NRAS, or BRAF, a mPFS of 2.3 months and mOS of 6.5 months was observed[239]. In a Phase 2 study of patients with NSCLC who had failed on at least 2 prior chemotherapeutic regimes, selumetinib as a monotherapy did not improve survival as compared to pemetrexed (67 vs 90 days, HR= 1.08); however, 2 PRs were reported[240]. A Phase 2 study of selumetinib combined with docetaxel in patients with advanced or metastatic KRAS wild-type NSCLC who were previously treated did not report improved survival benefit compared to docetaxel alone[241]. A Phase 2 study of selumetinib combined with pemetrexed and platinum based chemotherapy for treatment of patients with advanced non-squamous NSCLC showed improved ORR (35% with intermittent dosing and 62% for continuous dosing) compared to chemotherapy alone (24%) but did not report a statistically significant improvement in mPFS[242]. The combination of selumetinib with platinum doublet chemotherapy has been studied in a Phase 1 trial for patients with advanced NSCLC in the first line setting and has reported 4/21 PRs in the selumetinib + pemetrexed/carboplatin cohort and 2/15 PRs in the pemetrexed/cisplatin cohort; selumetinib in combination with gemcitabine regimens was not tolerated[243]. A Phase 1b study of selumetinib in combination with osimertinib for patients with EGFR-mutated lung cancer who had progressed on previous TKI treatment reported an ORR of 41.7% (15/36)[244].

Trametinib

Assay findings association

NF1
Y489C

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[63,66] and strong preclinical evidence[68-72] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

For patients with previously treated BRAF V600E-mutated metastatic NSCLC, trametinib in combination with the BRAF inhibitor dabrafenib achieved an ORR of 63% (36/57), including 2 CRs and 34 PRs, a DCR (CRs, PRs, and SD) of 79% (45/57), and a median PFS of 9.7 months[245]. Dabrafenib plus trametinib demonstrated similar activity as first-line therapy for BRAF V600E-mutated metastatic NSCLC, with an ORR of 64% (23/36) and a median PFS of 10.9 months[246]. Phase 1 and 2 monotherapy trials of MEK inhibitors such as trametinib and RO4987655 have shown low response rates in patients with NSCLC, irrespective of KRAS mutation status, and no improvement in PFS compared to docetaxel[247-249] . However, Phase 1 and 2 trials of MEK inhibitors in combination with docetaxel or pemetrexed in NSCLC have shown improved clinical activity and patient survival compared to chemotherapeutics alone, although no association was observed between response and KRAS mutation status[250-252] . In contrast, although 3 objective responses were observed in patients with NSCLC treated with the MEK inhibitor selumetinib in combination with erlotinib in a Phase 2 trial, there was no significant increase in either PFS or OS relative to patients treated with selumetinib alone; further, the combination increased toxicity relative to monotherapy[253]. Preclinical and early clinical studies have shown synergistic antitumorigenic effects when the combination of MEK and PI3K inhibitors was used to treat KRAS-driven NSCLC[254-256] . A Phase 1b combination trial of trametinib and the pan-PI3K inhibitor BKM120 reported a DCR of 59% in patients with NSCLC, including 1 confirmed PR in 17 patients; although the reported adverse effects were prevalent and often severe, the study recommended a Phase 2 dose[257]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[79], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[80].

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

Electronically signed by Chelsea Marcus, M.D. | 19 March 2021
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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
EGFR

ALTERATION
V292L

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Several strategies to overcome resistance are under investigation, including next-generation EGFR TKIs and EGFR inhibitor combinations. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04077463

PHASE 1

A Study of Lazertinib as Monotherapy or in Combination With JNJ-61186372 in Japanese Participants With Advanced Non-small Cell Lung Cancer

TARGETS
EGFR, MET

LOCATIONS: Milano (Italy), Gauting (Germany), Stuttgart (Germany), Lyon Cedex 8 (France), Marseille (France), Napoli (Italy), Halle (Saale) (Germany), Saint Mande (France), Villejuif Cedex (France), Paris (France)

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

LOCATIONS: Lyon Cedex 8 (France), Dijon (France), Marseille (France), Villejuif Cedex (France), Paris (France), Barcelona (Spain), Bordeaux (France), Saint-Herblain Cedex (France), Sutton (United Kingdom), Manchester (United Kingdom)

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

NCT03810066

PHASE 2

Exploring the Theragnostic Value of Osimertinib in EGFR-mutated Lung Cancer (THEROS)

TARGETS
EGFR

LOCATIONS: Essen (Germany)

NCT02099058

PHASE 1

A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors

TARGETS
MET, EGFR, PD-1

LOCATIONS: Marseille CEDEX 05 (France), Massachusetts, New Jersey, Virginia, Michigan, Illinois, Tennessee, Colorado, Texas, Seoul (Korea, Republic of)

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NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT03137771

PHASE 2

Maintenance Chemotherapy With or Without Stereotactic Body Radiation Therapy in Treating Patients With Stage IV Non-small Cell Lung Cancer

TARGETS
EGFR, PD-1

LOCATIONS: Tel Hashomer (Israel), New Hampshire, Vermont, Massachusetts, Ottawa (Canada), New York

NCT03755102

PHASE NULL

A Study of Dacomitinib in Patients With Metastatic EGFR Mutant Lung Cancer Previously Treated With Osimertinib

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: New York, New Jersey

NCT02693535

PHASE 2

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

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

LOCATIONS: Maine, New Hampshire, Pennsylvania, Virginia, Michigan

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

GENE
NF1

ALTERATION
Y489C

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Innsbruck (Austria), Salzburg (Austria), Heidelberg (Germany), Wien (Austria), Köln (Germany), Villejuif (France), Paris (France), Bordeaux (France), Nantes Cedex 1 (France), Montreal (Canada)

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

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

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Massachusetts, New York, Pennsylvania, Maryland, Virginia, Michigan, Ohio, Illinois, Wisconsin, North Carolina

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: New York, New Jersey, Maryland

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT04250545

PHASE 1

Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer

TARGETS
mTORC1, mTORC2, GLS

LOCATIONS: New York, California

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT03600701

PHASE 2

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

TARGETS
PD-L1, MEK

LOCATIONS: District of Columbia, Virginia, Michigan, Ohio, Alabama, Florida, Oklahoma, California

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
amplification

CCND2
R262H

CIC
R600H

DDR1
E818K

EGFR
G1103S

ERBB3
R166K

FGF10
amplification

HGF
D348E

JAK1
N789S

MAP3K1
S939C

MED12
Q2119_Q2120insHQQQ

NBN
S118del

NTRK2
H602N

PALB2
A751V

PDK1
E310G

POLD1
R762Q

RICTOR
amplification

SDHA
amplification

SPEN
T2408A

TET2
N275K

TYRO3
P597R

ZNF217
T198M

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Alterations and Therapies

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

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

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters with no conflicts), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *BAP1, BRCA1, BRCA2, BRIP1, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

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SELECT ABBREVIATIONS

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

MR Suite Version 3.0.0

The median exon coverage for this sample is 825x

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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Warth A, et al. Virchows Arch. (2016) pmid: 26637197
7. Ninomiya H, et al. Br. J. Cancer (2006) pmid: 16641899
8. Vanderwalde A, et al. Cancer Med (2018) pmid: 29436178
9. Zang YS, et al. Cancer Med (2019) pmid: 31270941
10. Dudley JC, et al. Clin. Cancer Res. (2016) pmid: 26880610
11. Takamochi K, et al. Lung Cancer (2017) pmid: 28676214
12. Pylkkänen L, et al. Environ. Mol. Mutagen. (1997) pmid: 9329646
13. Gonzalez R, et al. Ann. Oncol. (2000) pmid: 11061602
14. Chen XQ, et al. Nat. Med. (1996) pmid: 8782463
15. Merlo A, et al. Cancer Res. (1994) pmid: 8174113
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
18. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
19. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
20. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
21. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
22. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
23. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
24. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
25. Cristescu R, et al. Science (2018) pmid: 30309915
26. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
27. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
28. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
29. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
30. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
31. Rizvi NA, et al. Science (2015) pmid: 25765070
32. Colli LM, et al. Cancer Res. (2016) pmid: 27197178
33. Wang VE, et al. J Immunother Cancer (2017) pmid: 28923100
34. Carbone DP, et al. N. Engl. J. Med. (2017) pmid: 28636851
35. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
36. Forde PM, et al. N. Engl. J. Med. (2018) pmid: 29658848
37. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
38. Chae YK, et al. Clin Lung Cancer (2019) pmid: 30425022
39. Paz-Ares et al., 2019; ESMO Abstract LBA80
40. Hellmann MD, et al. N. Engl. J. Med. (2019) pmid: 31562796
41. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
42. Spigel et al., 2016; ASCO Abstract 9017
43. Xiao D, et al. Oncotarget (2016) pmid: 27009843
44. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
45. Govindan R, et al. Cell (2012) pmid: 22980976
46. Ding L, et al. Nature (2008) pmid: 18948947
47. Imielinski M, et al. Cell (2012) pmid: 22980975
48. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
49. Stein et al., 2019; DOI: 10.1200/PO.18.00376
50. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
51. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
52. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
53. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
54. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
55. Johnson BE, et al. Science (2014) pmid: 24336570
56. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
57. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
58. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
59. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
60. Nature (2012) pmid: 22810696
61. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
62. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
63. Dombi E, et al. N. Engl. J. Med. (2016) pmid: 28029918
64. Gross AM, et al. N. Engl. J. Med. (2020) pmid: 32187457
65. Fangusaro J, et al. Lancet Oncol. (2019) pmid: 31151904
66. Ameratunga M, et al. J Clin Pharm Ther (2016) pmid: 26936308
67. Woodfield SE, et al. BMC Cancer (2016) pmid: 26925841
68. Jousma E, et al. Pediatr Blood Cancer (2015) pmid: 25907661
69. Nissan MH, et al. Cancer Res. (2014) pmid: 24576830
70. Jessen WJ, et al. J. Clin. Invest. (2013) pmid: 23221341
71. Chang T, et al. J. Clin. Invest. (2013) pmid: 23221337
72. See WL, et al. Cancer Res. (2012) pmid: 22573716
73. Lim SM, et al. Oncotarget (2016) pmid: 26859683
74. Weiss B, et al. Neuro-oncology (2015) pmid: 25314964
75. Janku F, et al. Oncotarget (2014) pmid: 24931142
76. Johannessen CM, et al. Curr. Biol. (2008) pmid: 18164202
77. Johannessen CM, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15937108
78. Malone CF, et al. Cancer Discov (2014) pmid: 24913553
79. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
80. Patterson et al., 2018; AACR Abstract 3891
81. Nature (2014) pmid: 25079552
82. Nature (2012) pmid: 22960745
83. de Bruin EC, et al. Cancer Discov (2014) pmid: 24535670
84. Hattori S, et al. Biochem. Biophys. Res. Commun. (1991) pmid: 1904223
85. Morcos P, et al. Mol. Cell. Biol. (1996) pmid: 8628317
86. Ballester R, et al. Cell (1990) pmid: 2121371
87. Xu GF, et al. Cell (1990) pmid: 2116237
88. Martin GA, et al. Cell (1990) pmid: 2121370
89. Thomas L, et al. Hum. Mutat. (2012) pmid: 22807134
90. Skuse GR, et al. Hum. Mol. Genet. (1997) pmid: 9300663
91. Messiaen LM, et al. Genet. Med. () pmid: 11258625
92. Ars E, et al. Hum. Mol. Genet. (2000) pmid: 10607834
93. Messiaen LM, et al. J. Med. Genet. (2005) pmid: 15863657
94. Poullet P, et al. Mol. Cell. Biol. (1994) pmid: 8264648
95. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
96. Jett K, et al. Genet. Med. (2010) pmid: 20027112
97. Patil S, et al. Oncologist (2012) pmid: 22240541
98. Evans DG, et al. Clin Sarcoma Res (2012) pmid: 23036231
99. Upadhyaya M, et al. J. Med. Genet. (1995) pmid: 8544190
100. Williams VC, et al. Pediatrics (2009) pmid: 19117870
101. Rosell R, et al. Lancet Oncol. (2012) pmid: 22285168
102. Douillard JY, et al. Br. J. Cancer (2014) pmid: 24263064
103. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
104. Mok TS, et al. J. Clin. Oncol. (2018) pmid: 29864379
105. Jänne PA, et al. N. Engl. J. Med. (2015) pmid: 25923549
106. Soria JC, et al. N. Engl. J. Med. (2018) pmid: 29151359
107. Shi Y, et al. J Thorac Oncol (2020) pmid: 32007598
108. Ercan D, et al. Cancer Discov (2012) pmid: 22961667
109. Eberlein CA, et al. Cancer Res. (2015) pmid: 25870145
110. Tricker EM, et al. Cancer Discov (2015) pmid: 26036643
111. Cho et al., 2020; ESMO Abstract 1258O
112. Thatcher N, et al. Lancet Oncol. (2015) pmid: 26045340
113. Paz-Ares L, et al. Lancet Oncol. (2015) pmid: 25701171
114. Elez E, et al. Br. J. Cancer (2016) pmid: 26766738
115. Kuenen B, et al. Clin. Cancer Res. (2010) pmid: 20197484
116. Shimamura T, et al. Cancer Res. (2005) pmid: 16024644
117. Shimamura T, et al. Cancer Res. (2008) pmid: 18632637
118. Sawai A, et al. Cancer Res. (2008) pmid: 18199556
119. Bernardes CE, et al. J Phys Condens Matter (2015) pmid: 25923649
120. Xu W, et al. Br. J. Cancer (2007) pmid: 17712310
121. Yu et al., 2020; ESMO Abstract LBA62
122. Zeng Q, et al. J. Med. Chem. (2015) pmid: 26313252
123. Yang Z, et al. Sci Transl Med (2016) pmid: 27928026
124. Ahn et al., 2019; ASCO 31587882
125. Strong JE, et al. EMBO J. (1998) pmid: 9628872
126. Coffey MC, et al. Science (1998) pmid: 9812900
127. Gong J, et al. Front Oncol (2014) pmid: 25019061
128. Forsyth P, et al. Mol. Ther. (2008) pmid: 18253152
129. Vidal L, et al. Clin. Cancer Res. (2008) pmid: 18981012
130. Gollamudi R, et al. Invest New Drugs (2010) pmid: 19572105
131. Harrington KJ, et al. Clin. Cancer Res. (2010) pmid: 20484020
132. Comins C, et al. Clin. Cancer Res. (2010) pmid: 20926400
133. Lolkema MP, et al. Clin. Cancer Res. (2011) pmid: 21106728
134. Galanis E, et al. Mol. Ther. (2012) pmid: 22871663
135. Karapanagiotou EM, et al. Clin. Cancer Res. (2012) pmid: 22316603
136. Morris DG, et al. Invest New Drugs (2013) pmid: 22886613
137. Villalona-Calero MA, et al. Cancer (2016) pmid: 26709987
138. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
139. Vallee A, et al. Int. J. Oncol. (2013) pmid: 23934203
140. Watzka SB, et al. Eur J Cardiothorac Surg (2010) pmid: 20353893
141. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
142. Grob TJ, et al. Lung Cancer (2013) pmid: 23238037
143. Park S, et al. Histol. Histopathol. (2012) pmid: 22207554
144. Dobashi Y, et al. Hum. Pathol. (2011) pmid: 21040950
145. Ludovini V, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23314677
146. Skrzypski M, et al. Clin Lung Cancer (2013) pmid: 23870818
147. Kim SH, et al. Histol. Histopathol. (2012) pmid: 22419022
148. Lee JS, et al. Ann. Surg. Oncol. (2013) pmid: 23525704
149. Oakley GJ, et al. J Thorac Oncol (2011) pmid: 21587084
150. Traynor AM, et al. Lung Cancer (2013) pmid: 23628526
151. Marks JL, et al. J Thorac Oncol (2008) pmid: 18303429
152. Izar B, et al. Ann. Thorac. Surg. (2013) pmid: 23932319

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153. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
154. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
155. Yan M, et al. Breast Cancer Res. (2012) pmid: 22537934
156. Xu H, et al. Breast Cancer Res. (2011) pmid: 21255398
157. Stevens KN, et al. Breast Cancer Res. Treat. (2011) pmid: 21607584
158. Sehl ME, et al. Clin. Cancer Res. (2009) pmid: 19276285
159. Supernat A, et al. Oncol Lett (2012) pmid: 23205091
160. Deb S, et al. Br. J. Cancer (2014) pmid: 24548858
161. Supernat A, et al. Transl Oncol (2014) pmid: 25048628
162. Porkka KP, et al. Genes Chromosomes Cancer (2004) pmid: 14603436
163. Davis SJ, et al. Mol. Cancer Ther. (2015) pmid: 25852062
164. Atienza JM, et al. Mol. Cancer Ther. (2005) pmid: 15767545
165. Xu H, et al. Nat. Rev. Cancer (2011) pmid: 21326324
166. Hill VK, et al. Biochim. Biophys. Acta (2016) pmid: 27207471
167. Solomon DA, et al. BMB Rep (2014) pmid: 24856830
168. Bauerschmidt C, et al. Nucleic Acids Res. (2010) pmid: 19906707
169. Yun J, et al. Nucleic Acids Res. (2016) pmid: 26420833
170. Gelot C, et al. Nucleus (2016) pmid: 27326661
171. Sofueva S, et al. EMBO J. (2013) pmid: 24185899
172. Deng Z, et al. EMBO J. (2012) pmid: 23010778
173. Yun J, et al. EMBO Rep. (2016) pmid: 27466323
174. Mahmood SF, et al. Carcinogenesis (2014) pmid: 24148822
175. Puls LN, et al. Oncologist (2011) pmid: 21521831
176. Naing A, et al. Invest New Drugs (2013) pmid: 23361621
177. Chen J, et al. Clin Colorectal Cancer (2014) pmid: 24361441
178. Ceppi P, et al. Mol. Cancer Ther. (2009) pmid: 19861409
179. Zhang J, et al. Am. J. Pathol. (2007) pmid: 17200208
180. Leung EL, et al. Mol. Cancer Res. (2009) pmid: 19491201
181. Donahue TR, et al. Clin. Cancer Res. (2012) pmid: 22261810
182. Verbeek BS, et al. J. Pathol. (1996) pmid: 9014858
183. Kim LC, et al. Nat Rev Clin Oncol (2009) pmid: 19787002
184. Gao J, et al. Sci Signal (2013) pmid: 23550210
185. Zack TI, et al. Nat. Genet. (2013) pmid: 24071852
186. Beroukhim R, et al. Nature (2010) pmid: 20164920
187. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
188. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
189. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
190. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
191. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
192. Xu L, et al. Mol. Med. (2001) pmid: 11713371
193. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
194. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
195. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
196. Hajdenberg et al., 2012; ASCO Abstract e15010
197. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
198. Moore et al., 2019; ASCO Abstract 5513
199. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
200. Oza et al., 2015; ASCO Abstract 5506
201. Lee J, et al. Cancer Discov (2019) pmid: 31315834
202. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
203. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
204. Kwok M, et al. Blood (2016) pmid: 26563132
205. Boudny M, et al. Haematologica (2019) pmid: 30975914
206. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
207. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
208. Mogi A, et al. J. Biomed. Biotechnol. (2011) pmid: 21331359
209. Tekpli X, et al. Int. J. Cancer (2013) pmid: 23011884
210. Vignot S, et al. J. Clin. Oncol. (2013) pmid: 23630207
211. Maeng CH, et al. Anticancer Res. (2013) pmid: 24222160
212. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
213. Itakura M, et al. Br. J. Cancer (2013) pmid: 23922113
214. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
215. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
216. Seo JS, et al. Genome Res. (2012) pmid: 22975805
217. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
218. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
219. Xie M, et al. Nat. Med. (2014) pmid: 25326804
220. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
221. Severson EA, et al. Blood (2018) pmid: 29678827
222. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
223. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
224. Chabon JJ, et al. Nature (2020) pmid: 32269342
225. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
226. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
227. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
228. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
229. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
230. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
231. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
232. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
233. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
234. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
235. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
236. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
237. Lalloo F, et al. Lancet (2003) pmid: 12672316
238. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
239. Lopez-Chavez A, et al. J. Clin. Oncol. (2015) pmid: 25667274
240. Hainsworth JD, et al. J Thorac Oncol (2010) pmid: 20802351
241. Soria JC, et al. Ann. Oncol. (2017) pmid: 29045535
242. Melosky B, et al. Lung Cancer (2019) pmid: 31200828
243. Greystoke A, et al. Br. J. Cancer (2017) pmid: 28950288
244. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298
245. Planchard D, et al. Lancet Oncol. (2016) pmid: 27283860
246. Planchard D, et al. Lancet Oncol. (2017) pmid: 28919011
247. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
248. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
249. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
250. Kelly et al., 2013; ASCO Abstract 8027
251. Gandara et al., 2013; ASCO Abstract 8028
252. Jänne PA, et al. Lancet Oncol. (2013) pmid: 23200175
253. Carter CA, et al. Ann. Oncol. (2016) pmid: 26802155
254. Banerji et al., 2014; ASCO Abstract e13559
255. Castellano E, et al. Cancer Cell (2013) pmid: 24229709
256. Ku BM, et al. Invest New Drugs (2015) pmid: 25342139
257. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057

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