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

PATIENT

DISEASE Lung cancer (NOS)
NAME
DATE OF BIRTH
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID
SPECIMEN TYPE Blood
DATE OF COLLECTION
SPECIMEN RECEIVED
MEDIAN EXON COVERAGE

Biomarker Findings

MSI Status Undetermined.

Genomic Findings

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

ATM I1469M
STK11 G276fs*11

5 Therapies with Clinical Benefit
0 Therapies with Lack of Response
19 Clinical Trials

BIOMARKER FINDINGS

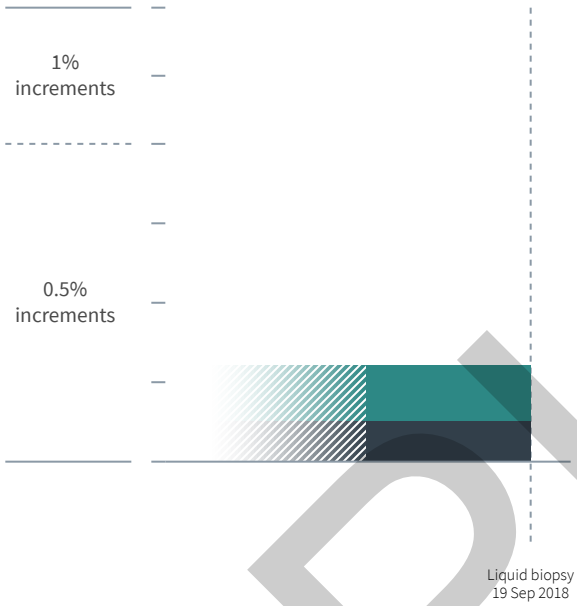
ACTIONABILITY

MSI Status Undetermined

GENOMIC FINDINGS	MAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ATM - I1469M	0.26%	None	Niraparib
			Olaparib
			Rucaparib
10 Trials see p. 7			
STK11 - G276fs*11	0.35%	None	Everolimus
			Temsirolimus
10 Trials see p. 9			

NOTE Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. In the appropriate clinical context, germline testing of *APC*, *BRCA1*, *BRCA2*, *CDH1*, *NF1*, *PALB2*, *RB1*, *RET*, *STK11*, and *TP53* is recommended.

Mutant Allele Frequency is not applicable for copy number amplifications or rearrangements.



HISTORIC PATIENT FINDINGS		TEST 1 MAF%
ATM	● I1469M	0.26%
STK11	● G276fs*11	0.35%

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

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

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

GENE
ATM

ALTERATION
I1469M

POTENTIAL TREATMENT STRATEGIES

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair, and may predict sensitivity to PARP inhibitors [1] such as olaparib, rucaparib, and niraparib. Several preclinical studies have shown that loss of functional ATM confers moderate sensitivity to PARP inhibitors [2-6], with some studies reporting increased sensitivity specifically in cells with loss of both ATM and TP53 [7-8]; one preclinical study reported that ATM depletion did not increase sensitivity to PARP inhibitors [9]. In a Phase 2 trial, 4/5 patients with ATM-mutated castration-resistant prostate cancer benefited from olaparib treatment [10]. In a Phase 2 study of patients with gastric cancer, the combination of olaparib with paclitaxel resulted in improved overall survival versus paclitaxel alone, both in the overall patient population and the patient population with low ATM protein expression [11]. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells, and were active in a lymphoma mouse model lacking ATM activity, suggesting a potential therapeutic strategy for tumors with inactivating ATM mutations [12]. 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

ATM mutations have been reported in 8-11% of lung adenocarcinomas [13-15] and 5% of lung squamous cell carcinomas (SCCs)[16]. Expression of ATM protein has been reported to be significantly higher in non-small cell lung carcinoma samples than in normal tissues [17]. In one study, higher ATM protein levels in lung SCC, but not in lung adenocarcinoma, significantly correlated with shorter disease-free and overall survival of patients treated with cisplatin [18].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response [19]. Loss of functional ATM promotes tumorigenesis [20] and mutations in ATM underlie the rare autosomal recessive inherited disorder ataxia-telangiectasia that is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer [19]. 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.

GENE
STK11

ALTERATION
G276fs*11

POTENTIAL TREATMENT STRATEGIES

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations [21-25]. The mTOR inhibitors everolimus and temsirolimus are FDA approved for the treatment of other tumor types, and are being investigated in clinical trials for several indications [26-29]. A PJS patient with pancreatic cancer and an STK11 mutation experienced a partial response to the mTOR inhibitor everolimus [30]. Loss of STK11 also leads to activation of the downstream kinase SRC, suggesting that inhibitors such as dasatinib or bosutinib may be relevant for the treatment of LKB1-deficient tumors [31].

FREQUENCY & PROGNOSIS

Several clinical studies have found STK11 mutation to be common in non-small cell lung cancer (NSCLC) (15-35%), with alterations more prevalent in lung adenocarcinomas (13-34%) than in lung squamous cell carcinoma (2-19%) [15-16,22,32-35]. In the TCGA datasets, STK11 homozygous deletion was observed in 1% of lung adenocarcinoma cases [13] and was not observed in any of 178 lung squamous cell carcinoma cases [16]. Strongly decreased or absent expression of LKB1 correlated with inferior outcome in patients with NSCLC treated with bevacizumab-containing chemotherapy; expression of LKB1 was not prognostic in patients treated with chemotherapy without bevacizumab [36]. STK11 mutations in NSCLC often co-occur with activating KRAS mutations [34-35]. In transgenic mouse models, animals expressing mutant KRAS developed lung adenocarcinomas, whereas the KRAS-mutant/LKB1-deficient mice developed an expanded histological spectrum of tumors that included large cell and squamous cell carcinomas [22].

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels [21]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis [31,37]. Functional disruption of the STK11 kinase domain (amino acids 49-309) or STRAD binding domain (amino acids 320-343) through mutation or loss, such as observed here, is predicted to be inactivating [38-49]. Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation [50]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers [50-52], and individuals with this syndrome have a 30-50% risk of developing breast cancer [50,52]. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

Everolimus

Assay findings association

STK11
G276fs*11

APPROVED INDICATIONS

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract; and, in association with tuberous sclerosis complex (TSC), renal angiomyolipoma and subependymal giant cell astrocytoma. Everolimus is also approved to treat hormone receptor-positive, HER2-negative advanced breast cancer in combination with exemestane following prior therapy with letrozole or anastrozole, as well as in combination with the multikinase inhibitor lenvatinib to treat advanced RCC following prior antiangiogenic therapy.

GENE ASSOCIATION

Increased mTOR signaling is present in LKB1-deficient tumors[21-22 23,53 25]; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[21]. Everolimus elicited clinical responses lasting >6 months in 2 patients with pancreatic cancer[30,54] and 1 patient with atypical pituitary adenoma[55], all of whom harbored STK11 alterations in their tumors.

SUPPORTING DATA

A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity[56], but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population[57]. A Phase 1 study evaluated the addition of everolimus to carboplatin and paclitaxel +/- bevacizumab in advanced NSCLC and found the combinations produced 1 complete response and 10 partial responses (n=52), although treatments were not well tolerated[58]. A Phase 1 study in patients with advanced NSCLC of the combination of everolimus and erlotinib reported 9 objective responses and 28 patients experiencing stable disease (n=74), but a Phase 2 study found the combination inefficacious at tolerated doses[59-60]. A trial of combination treatment with sorafenib and everolimus that included 2 patients with lung adenocarcinoma reported a partial response in one patient and stable disease in the other, with both patients experiencing progression-free survival of more than 4 months[61]. A Phase 1b trial of a combination of trametinib and everolimus in patients with solid tumors reported frequent adverse events and the study was unable to identify a recommended Phase 2 dose and schedule for the combination[62].

Niraparib

Assay findings association

ATM
I1469M

APPROVED INDICATIONS

The PARP inhibitor niraparib is FDA approved for the maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. Clinical benefit of various PARP inhibitors has been associated with ATM alterations in prostate cancer[10], gastric cancer[11], and papillary renal cell carcinoma[63]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with solid tumors, 2/2 patients with non-small cell lung cancer achieved stable disease; 1/2 patients harbored a BRCA2 mutation[64].

Olaparib

Assay findings association

ATM
I1469M

APPROVED INDICATIONS

The PARP inhibitor olaparib is FDA approved to treat advanced ovarian cancer with deleterious or suspected deleterious germline BRCA mutations after 3 or more prior lines of chemotherapy and for maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Olaparib is also approved to treat patients with HER2-negative metastatic breast cancer and deleterious or suspected deleterious germline BRCA mutations who have been previously treated with chemotherapy; patients with hormone receptor-positive breast cancer should have been previously treated with, or considered inappropriate for, endocrine therapy.

GENE ASSOCIATION

Loss or inactivation of ATM may predict sensitivity to olaparib[2,10 3]. In a Phase 2 study of patients with gastric cancer, the combination of olaparib with paclitaxel resulted in improved overall survival versus paclitaxel alone, both in the overall patient population and the patient population with low ATM protein expression[11]. Furthermore, 4/5 patients with ATM-mutated castration-resistant prostate cancer were reported to benefit from olaparib treatment[10] and a patient with ATM-mutated papillary renal cell carcinoma benefited from PARP inhibitor veliparib for 7 months[63]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

In a Phase 2 study, the addition of olaparib to gefitinib did not significantly increase either median PFS (10.9 vs. 12.8 months; HR 0.75, p=0.12) or median OS (23.1 vs. 23.3 months; HR 1.22, p=0.346) in patients with EGFR-mutant NSCLC, unselected for other mutations; the ORR for patients treated with the combination (71%, 60/84) was similar to that of those treated with single-agent gefitinib (68%, 61/90)[65].

Rucaparib

Assay findings association

ATM
I1469M

APPROVED INDICATIONS

The PARP inhibitor rucaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations who have been previously treated with two or more chemotherapies. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. Clinical benefit of various PARP inhibitors has been associated with ATM alterations in prostate cancer[10], gastric cancer[11], and papillary renal cell carcinoma[63]. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of non-small cell lung carcinoma are limited (PubMed, Sep 2018). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median progression-free survival was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[66]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[67]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved stable disease (SD) lasting 12 weeks or more[68]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[69]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 complete response (CR), 2/19 partial response (PR; one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[70]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[71]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[72]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[73].

Temsirolimus

Assay findings association

STK11
G276fs*11

APPROVED INDICATIONS

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma.

GENE ASSOCIATION

Increased mTOR signaling is present in LKB1-deficient tumors[21-22 23,53 25]; therefore, therapies targeting mTOR may be relevant for tumors with STK11 alterations[21].

SUPPORTING DATA

In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), front-line temsirolimus monotherapy demonstrated some clinical benefit but failed to meet the trial's primary end point[74]. In a Phase 1 trial of temsirolimus and radiation in patients with NSCLC, of 8 evaluable patients, 3 exhibited a partial response and 2 exhibited stable disease[75].

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

IMPORTANT Clinical trials are ordered by gene and prioritized in the following descending order: pediatric trial qualification → Geographical proximity → Later 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. This is not meant to be a complete list of available trials and does not necessarily indicate that the patient will meet clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov.

GENE
ATM

ALTERATION
I1469M

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors or inhibitors of DNA-PKcs. 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.

NCT02264678 — **PHASE 1/2**

A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD6738 in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies.

TARGETS ATR, PARP, PD-L1

LOCATIONS: California, New York, MARSEILLE Cedex 5 (France), Villejuif (France), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)

NCT02412371 — **PHASE 2**

A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination With Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects With Stage III Non-Small Cell Lung Cancer (NSCLC)

TARGETS PARP

LOCATIONS: California, Delaware, Illinois, Maryland, Massachusetts, New York, North Carolina, Rhode Island, Texas, Virginia

NCT02498613 — **PHASE 2**

A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors

TARGETS PARP, VEGFRs

LOCATIONS: Vancouver (Canada), California, Connecticut, Florida, Michigan, Toronto (Canada), Tennessee, Texas, Virginia

NCT02154490 — **PHASE 2/3**

A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (Lung-MAP)

TARGETS PARP, CTLA-4, PD-1

LOCATIONS: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Hamilton (Canada), Ottawa (Canada), Toronto (Canada), Oregon, Pennsylvania, Rhode Island, Regina (Canada), South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, Wyoming

NCT02921919 — **PHASE 2**

A Single-arm, Open-label, Multicenter, Extended Treatment, Safety Study In Patients Treated With Talazoparib

TARGETS PARP

LOCATIONS: Edmonton (Canada), California, Florida, Indiana, Michigan, New Jersey, Hamilton (Canada), Montreal (Canada), Sutton (United Kingdom), Texas, Yaroslavl (Russian Federation), Budapest (Hungary), Chisinau (Moldova, Republic of), Moscow (Russian Federation), Saint-Petersburg (Russian Federation)

NCT02997176 — **PHASE 1**

A Phase I Open-label Pharmacokinetics And Safety Study Of Talazoparib (mdv3800) In Patients With Advanced Solid Tumors And Normal Or Varying Degrees Of Hepatic Impairment

TARGETS PARP

LOCATIONS: California, Florida, Massachusetts, Texas

NCT02079636	PHASE 1
A Phase 1b Study of LY2835219 in Combination With Multiple Single Agent Options for Patients With Stage IV NSCLC	**TARGETS** CDK4, CDK6, VEGFR2, PD-1, DNA-PK, PI3K, mTOR

LOCATIONS: Arkansas, California, Indiana, New Jersey, New Mexico, North Carolina, Tennessee, Madrid (Spain), Majadahonda (Spain), Sevilla (Spain)

NCT02693535	PHASE 2
Targeted Agent and Profiling Utilization Registry (TAPUR) Study	**TARGETS** VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, RAF1, PARP, PD-1

LOCATIONS: Arizona, Georgia, Illinois, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, South Dakota, Utah, Washington

NCT01012817	PHASE 1/2
A Phase I/II Trial of ABT-888, an Inhibitor of Poly(ADP-Ribose) Polymerase (PARP), and Topotecan (TPT) in Patients With Solid Tumors (Phase I) and Relapsed Ovarian Cancer or Primary Peritoneal Cancer (Phase II) After Prior Platinum Containing First-Line Chemotherapy	**TARGETS** TOP1, PARP

LOCATIONS: Arizona, California, Florida, Illinois, Kansas, Minnesota, Pennsylvania

NCT02289690	PHASE 2
A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination With Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer	**TARGETS** PARP, TOP2

LOCATIONS: Arizona, Colorado, Georgia, Illinois, North Carolina, Ohio, Pennsylvania, Texas, Albury (Australia), Douglas (Australia), Frankston (Australia), Wollongong (Australia), Brussels (Belgium), Edegem (Belgium), Liege (Belgium), Mons (Belgium), Namur (Belgium), Calgary (Canada), Edmonton (Canada), Hamilton (Canada), Montreal (Canada), Nova Ves Pod Plesi (Czech Republic), Novy Jicin (Czech Republic), Ostrava (Czech Republic), Pardubice (Czech Republic), Nova Ves Pod Plesi (Czechia), Novy Jicin (Czechia), Ostrava (Czechia), Pardubice (Czechia), Creteil (France), Le Mans (France), Limoges (France), Limousin (France), Budapest (Hungary), Debrecen (Hungary), Farkasgyepu Kulterulet (Hungary), Gyor (Hungary), Matrahaza (Hungary), Szekesfehervar (Hungary), Szolnok (Hungary), Szombathely (Hungary), Busan (Korea, Republic of), Chungcheongbuk-do (Korea, Republic of), Jeonnam (Korea, Republic of), Seoul (Korea, Republic of), Groningen (Netherlands), Harderwijk (Netherlands), Heerlen (Netherlands), Nijmegen (Netherlands), Rotterdam (Netherlands), Utrecht (Netherlands), Zwolle (Netherlands), Belgorod (Russian Federation), Ekaterinburg (Russian Federation), Moscow (Russian Federation), Murmansk (Russian Federation), Saint Petersburg (Russian Federation), Saransk (Russian Federation), Volgograd (Russian Federation), Barcelona (Spain), Madrid (Spain), Madrid (Espana) (Spain), Majadahonda, Madrid (Spain)

GENE
STK11

ALTERATION
G276fs*11

RATIONALE
Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations. In addition, analysis in lung tumors indicate that loss of LKB1 function may result in SRC activation, suggesting inhibitors of the SRC kinases may be clinically beneficial when LKB1 is inactive.

NCT02750514 — **PHASE 2**

A Phase 2, Fast Real Time Assessment of Combination Therapies in Immuno-Oncology Study in Subjects With Advanced Non-Small Cell Lung Cancer (FRACTION-Lung)

TARGETS
CTLA-4, LAG-3, ABL, DDR2, KIT, PDGFRs, SRC, PD-1

LOCATIONS: Edmonton (Canada), California, Colorado, Connecticut, District of Columbia, Georgia, London (United Kingdom), Kansas, Maryland, Massachusetts, Michigan, Missouri, Nevada, New York, North Carolina, Ohio, Hamilton (Canada), Ottawa (Canada), Oregon, Pennsylvania, Tennessee, Texas, Utah, Clayton (Australia), Virginia, Washington, Salzburg (Austria), Copenhagen (Denmark), Paris (France), Toulouse (France), Toulouse Cedex 9 (France), Villejuif (France), Villejuif Cedex (France), Milan (Italy), Milano (Italy), Rozzano (Italy), Amsterdam (Netherlands), Oslo (Norway), Madrid (Spain), Pamplona (Spain), Stockholm (Sweden), Lausanne (Switzerland)

NCT01920061 — **PHASE 1**

A Phase 1b Open-label Three-arm Multi-center Study To Assess The Safety And Tolerability Of Pf-05212384 (pi3k/Mtor Inhibitor) In Combination With Other Anti-tumor Agents

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, EGFR, ERBB2, ERBB4

LOCATIONS: Alabama, Vancouver (Canada), California, Colorado, Massachusetts, Michigan, Toronto (Canada), Pennsylvania, South Carolina, Milan (Italy), Roma (Italy), Barcelona (Spain), Madrid (Spain), London (United Kingdom), Oxford (United Kingdom)

NCT02079636 — **PHASE 1**

A Phase 1b Study of LY2835219 in Combination With Multiple Single Agent Options for Patients With Stage IV NSCLC

TARGETS
CDK4, CDK6, VEGFR2, PD-1, DNA-PK, PI3K, mTOR

LOCATIONS: Arkansas, California, Indiana, New Jersey, New Mexico, North Carolina, Tennessee, Madrid (Spain), Majadahonda (Spain), Sevilla (Spain)

NCT01737502 — **PHASE 1/2**

A Phase I-II Trial of Combined PKCι and mTOR Inhibition for Patients With Advanced or Recurrent Lung Cancer (NSCLC and SCLC) Without Standard Treatment Options

TARGETS
mTOR

LOCATIONS: Arizona

NCT02719691 — **PHASE 1**

A Phase Ib Study of the Combination of MLN0128 (Dual TORC1/2 Inhibitor) and MLN8237 (Aurora A Inhibitor, Alisertib) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Triple-negative Breast Cancer (TNBC)

TARGETS
mTORC2, mTORC1, Aurora kinase A

LOCATIONS: Colorado

NCT02576444 — **PHASE 2**

A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors

TARGETS
PARP, AKTs, WEE1, mTORC1, mTORC2

LOCATIONS: Connecticut, Massachusetts, Tennessee

NCT01884285 — **PHASE 1**

A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Anti-tumour Activity of AZD8186 in Patients With Advanced Castration-resistant Prostate Cancer (CRPC), Squamous Non-Small Cell Lung Cancer (sqNSCLC), Triple Negative Breast Cancer (TNBC) and Patients With Known PTEN-deficient/Mutated or PIK3CB Mutated/ Amplified Advanced Solid Malignancies as Monotherapy and in Combination With Abiraterone Acetate or AZD2014

TARGETS
PI3K-beta, CYP17, mTORC1, mTORC2

LOCATIONS: Massachusetts, Michigan, New York, Toronto (Canada), Washington, Wisconsin, Barcelona (Spain), London (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)

NCT01529593 — **PHASE 1**

Phase I Study of Temsirolimus in Combination With Metformin in Patients With Advanced Cancers

TARGETS
AMPK, mTOR

LOCATIONS: Texas

NCT01552434 — **PHASE 1**

A Phase I Trial of Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT01582191 — **PHASE 1**

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

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.

ATM	*CHEK2*
Y1470C	R346C

FoundationOne Liquid interrogates the complete exonic sequence of 35 genes, introns of 7 genes involved in rearrangements, and select exons of an additional 35 genes. 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

APC	*AR*	*ATM*	*BRCA1*	*BRCA2*	*CCND1*	*CD274 (PD-I1)*	*CDH1*	*CDK4*
CDK6	*CDK12*	*CDKN2A*	*CHEK2*	*CRKL*	*EGFR*	*ERBB2*	*ERRFI1*	*FGFR1*
FGFR2	*FOXL2*	*KRAS*	*MDM2*	*MET*	*MYC*	*MYCN*	*NF1*	*PALB2*
PDCD1LG2 (PD-L2)	*PTEN*	*PTPN11*	*RB1*	*SMO*	*STK11*	*TP53*	*VEGFA*	

DNA GENE LIST: SELECT EXONIC SEQUENCE OF THE DETECTION OF BASE SUBSTITUTIONS, INSERTIONS/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1 *Exons 4-9*	*AKT1* *Exon 3*	*ALK* *Exons 20-29*	*ARAF* *Exons 4, 5, 7, 11, 13, 15, 16*	*BRAF* *Exons 11-18*	*BTK* *Exons 2, 15*	*CTNNB1* *Exon 3*	*DDR2* *Exons 5, 17, 18*	*ESR1* *Exons 4-8*
EZH2 *Exons 4, 16, 18*	*FGFR3* *Exons 7, 9, 14*	*FLT3* *Exons 14, 15, 20*	*GNA11* *Exons 4, 5*	*GNAQ* *Exons 4, 5*	*GNAS* *Exons 1, 8*	*HRAS* *Exons 2, 3*	*IDH1* *Exon 4*	*IDH2* *Exon 4*
JAK2 *Exon 14*	*JAK3* *Exons 5, 11-13, 15, 16*	*KIT* *Exons 8, 9, 11-13, 17*	*MAP2K1 (MEK1)* *Exons 2, 3*	*MAP2K2 (MEK2)* *Exons 2-4, 6, 7*	*MPL* *Exon 10*	*MTOR* *Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56*	*MYD88* *Exon 4*	*NPM1* *Exons 4-6, 8, 10*
NRAS *Exons 2, 3*	*PDGFRA* *Exons 12, 18*	*PDGFRB* *Exons 12-21, 23*	*PIK3CA* *Exons 2, 3, 5-8, 10, 14, 19, 21*	*RAF1* *Exons 3-7, 10, 14, 15, 17*	*RET* *Exons 11, 13-16*	*ROS1* *Exons 36-38, 40*	*TERT* *(Promoter only)*	

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*EGFR*	*FGFR2*	*FGFR3*	*PDGFRA*	*RET*	*ROS1*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite Status (MS)

The median exon coverage for this sample is 5,176x

PERFORMANCE SPECIFICATIONS			
	Mutant Allelle Frequency (MAF) / Tumor Fraction‡	Sensitivity*	Positive Predictive Value (PPV)*
Base Substitutions	>0.5%	99.9% (99.7%-99.9%)	100% (99.9%-100%)
	0.25%-0.5%	95.8% (94.5%-96.9%)	99.8% (99.3%-99.9%)
	<0.25%	68.4% (65.7%-70.9%)	96.1% (94.8%-97.1%)
Insertions/Deletions†	>0.5%	99.7% (98.7%-99.9%)	100% (99.3%-100%)
	0.25%–0.5%	87.7% (81.1%-92.2%)	98.8% (95.4%-99.8%)
	<0.25%	60.5% (52.7%-67.7%)	96.8% (92.3%-98.8%)
Rearrangements**	>0.5%	100% (85.9%-100%)	100% (85.9%-100%)
	0.25%–0.5%	89.4% (65.5%-98.2%)	100% (77.1%-100%)
	<0.25%	68.4% (43.5%-86.4%)	100% (71.7%-100%)
Copy Number Amplifications§	≥20%	95.3% (82.9%-99.2%)	97.6% (85.9%-99.9%)
	<20%	Varies depending on amplitude of CNA and ctDNA fraction	
MSI¶	>2.0%	92.0% (72.5%-98.6%)	100% (82.2%-100%)
Reproducibility (average concordance between replicates)			
97.7% inter-batch precision		95.9% intra-batch precision	

*95% confidence intervals. Sensitivity assessment for <0.25% bin restricted to alterations in the 0.125%-0.25% expected allele frequency range.

†Deletions up to 2kb and insertions up to 40bp are detected. Sensitivity is lower for indels in repetitive regions.

**Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced.

‡Sensitivity for MSI and copy number amplifications was determined using contrived samples with tumor fraction >20%. Most clinical samples will have less than 20% tumor fraction.

§Copy-number ≥8.

¶Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at a subset of homopolymer repeat loci covered by the assay. Microsatellite status is assayed for all FoundationOne®Liquid samples and will only be reported if MSI-High is determined.

Assay specifications are based on samples meeting a minimum coverage threshold (>85% of targeted regions must have >2500× redundant coverage). Specimens with higher input mass typically obtain higher coverage and have higher sensitivity for low-frequency alterations.

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

ABOUT FOUNDATIONONE®LIQUID

FoundationOne Liquid was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Liquid may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

DIAGNOSTIC SIGNIFICANCE

FoundationOne Liquid identifies alterations to select cancer-associated genes or portions of genes (biomarkers).

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls. The threshold used in FoundationOne Liquid for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. For copy number amplifications, the equivocal status may be applied to calls in samples with calculated tumor fraction <30% but above the noise threshold. In addition, copy number amplifications in genes with three (3) baited exons are also marked as equivocal.

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. 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.

RANKING OF ALTERATIONS AND THERAPIES

Biomarker Findings

Appear at the top of the report, but are not ranked higher than Genomic Findings.

Genomic Findings

Therapies with Clinical Benefit In Patient's Tumor Type → Therapies with Clinical Benefit 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 in alphabetical order.)

Clinical Trials

Pediatric trial qualification → Geographical Proximity → Later trial phase.

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 Liquid.

TREATMENT DECISIONS ARE THE 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid is performed using cell-free DNA, and as such germline events may not be reported. The following target typically has low coverage resulting in a reduction in sensitivity: *TP53* exon 1 and *PDGFRA* exon 12.

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

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