FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Smith, James	**10 January 2016**	**Lung adenocarcinoma**

Date of Birth	01 January 1950	**Medical Facility**	Cancer Center	**Specimen Received**	02 January 2016
Sex	Male	**Ordering Physician**	Williams, Jane	**Specimen Site**	Liver
FMI Case #	TRF000000	**Additional Recipient**	Not Given	**Date of Collection**	03 January 2016
Medical Record #	100001	**Medical Facility ID #**	000001	**Specimen Type**	Slide
Specimen ID	SID-00001	**Pathologist**	Not Provided		

ABOUT THE TEST:

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

PATIENT RESULTS

6 genomic alterations

3 therapies associated with potential clinical benefit

0 therapies associated with lack of response

18 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†

ROS1 CD74-ROS1 fusion
CDK4 amplification
MDM2 amplification
RICTOR amplification
APC S688*
FGF10 amplification

Additional Disease-relevant Genes with No Reportable Alterations Identified†

EGFR
KRAS
ALK
BRAF
MET
RET
ERBB2

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
ROS1 CD74-ROS1 fusion	Ceritinib Crizotinib	None	Yes, see clinical trials section
CDK4 amplification	None	Palbociclib	Yes, see clinical trials section
MDM2 amplification	None	None	Yes, see clinical trials section
RICTOR amplification	None	None	Yes, see clinical trials section

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Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
APC S688*	None	None	None
FGF10 amplification	None	None	None

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. 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.

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
● ***ROS1*** CD74-ROS1 fusion	**Gene and Alteration:** The ROS1 oncogene encodes a tyrosine kinase of the insulin receptor family that plays a role in regulating cellular growth and differentiation by activating several signaling pathways, including those involving mitogen-activated protein kinase ERK1/2, phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), STAT3, and VAV3[1]. ROS1 is commonly involved in chromosomal rearrangements that lead to the expression of strongly oncogenic chimeric fusion proteins, such as observed here[2,3,4]. CD74-ROS1 fusions are found in both lung adenocarcinoma and lung squamous cell carcinoma samples[3,4,5,6] and have been reported to be oncogenic[3,4,7]. **Frequency and Prognosis:** ROS1 rearrangements or fusions have been reported in approximately 1-2%of non-small cell lung carcinoma (NSCLC) tumors[2,3,4,8], including in 1-3.4% of lung adenocarcinoma cases[4,5,9,10,11]. CD74-ROS1 fusions accounted for 23% (3/13) to 27% (5/18) of the ROS1 rearrangements identified in two studies of lung cancer[3,5]. In the Lung Adenocarcinoma TCGA dataset, ROS1 point mutations have been detected in 3.5% of cases, whereas ROS1 amplification was not identified[12]. Elevated ROS1 protein levels have been observed in 22% of NSCLC samples evaluated in one study[6]. A study of 1,137 patients with lung adenocarcinoma showed that Stage 4 patients with ROS1 rearrangement had significantly better overall survival (OS) compared to other genetically defined Stage 4 subgroups, with an estimated mean OS of 5.3 years for patients who were treated with chemotherapy and crizotinib[8]. Positive kinase fusion status (ALK, ROS1, or RET) was associated with improved prognosis in lung adenocarcinoma, independently of other prognostic factors[3], although never-smokers with surgically resected lung adenocarcinoma and ALK or ROS1 fusion had significantly shorter disease-free survival (hazard ratio, 2.11)[11]. A study of 208 never-smokers observed an improved objective response rate and longer median progression-free survival (PFS) for ROS-fusion-positive patients treated with pemetrexed but a reduced PFS for ROS1-positive patients treated with EGFR-targeted kinase inhibitors[10]. **Potential Treatment Strategies:** Patients with ROS1-activating rearrangements may benefit from treatment with tyrosine kinase inhibitors with activity against ROS1, such as the approved therapies crizotinib (Moro-Sibilot et al., 2015; ASCO Abstract 8065)[4,5,7,13,14,15,16] and ceritinib[17,18,19,20]. Crizotinib has shown clinical efficacy in ROS1-rearranged non-small cell lung cancer (NSCLC)[8,13]. Ceritinib achieved a partial response for a patient with ROS1-rearranged NSCLC[17]; preclinical data support the sensitivity of ROS1 fusion-positive tumors to certinib[18,19,20]. Crizotinib, ceritinib, and other ROS1-targeted therapies, including AZD3463, brigatinib, cabozantinib, DS-6051-b, entrectinib, foretinib, and lorlatinib, are being investigated in clinical trials[2].
● ***CDK4*** amplification	**Gene and Alteration:** CDK4 encodes cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis [21]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[22,23]. Amplification of CDK4, as a result of chromosomal amplification of the 12q13 region of chromosome 12, has been reported in multiple cancer types, including lung and esophageal cancer and glioblastoma, and correlated with high CDK4 mRNA and protein expression[24,25].

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GENE ALTERATION	INTERPRETATION
	Frequency and Prognosis: In the TCGA datasets, CDK4 amplification has been reported in 7% of lung adenocarcinoma samples analyzed, while CDK4 mutation has been reported in 1% of cases[12]. CDK4 amplification correlated with high CDK4 gene and protein expression in lung tumors[24]. High CDK4 protein expression has been detected in 23-47% of non-small cell lung cancers (NSCLC), specifically in 38% (18/47) of lung adenocarcinomas, 44% (4/9) of lung squamous cell carcinomas, and 83% (10/12) of large cell lung cancers[24,26,27]. High CDK4 protein expression predicted poor overall survival in patients with lung cancer in one study[27]. A preclinical study suggests targeting of CDK4 as a potential strategy against KRAS-driven lung adenocarcinomas[28]. **Potential Treatment Strategies:** CDK4 amplification may predict sensitivity to CDK4/6 inhibitors, such as palbociclib, LEE011, and abemaciclib (Infante et al., 2014; ASCO Abstract 2528, Shapiro et al., 2013; ASCO Abstract 2500) [29,30]. Palbociclib is FDA approved for use in combination with the aromatase inhibitor letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer[31].
● ***MDM2*** amplification	**Gene and Alteration:** MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[32,33]. Overexpression or amplification of MDM2 is frequent in human cancer[34]. **Frequency and Prognosis:** Amplification of MDM2 has been reported in 8% of cases in the Lung Adenocarcinoma TCGA dataset[12]. Separate studies have reported similar incidences of 6-7% in non-small cell lung cancer (NSCLC), mainly in patients with adenocarcinoma, but a higher incidence of 21% has also been observed, with amplification found in various NSCLC subtypes[35,36,37]. The role of MDM2 expression/amplification as a prognostic marker is complex, with some studies showing a negative and others a positive effect on survival in patients with NSCLC[35,37,38,39]. **Potential Treatment Strategies:** MDM2 antagonists disrupt the MDM2-p53 interaction, leading to the stabilization of p53[40]. Preclinical studies have suggested that amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[41,42]. Multiple MDM2 antagonists are under investigation in clinical trials (Beryozkina et al., 2011; ASCO Abstract 3039, Siu et al., 2014; ASCO Abstract 2535).
● ***RICTOR*** amplification	**Gene and Alteration:** RICTOR encodes an mTOR-binding protein that forms part of the rapamycin-insensitive mTORC2 complex, a regulator of cell metabolism and the cytoskeleton[43,44,45]. RICTOR amplification has been reported in cancer (Cheng et al., 2014; ASCO Abstract 8027, Ruder et al., 2015; AACR Abstract 3576, Dabir et al., 2015; ASCO Abstract 7576)[46] and has been associated with clinical response to mTORC1/2 inhibition (Cheng et al., 2014; ASCO Abstract 8027, Kristeleit et al., 2015; ASCO Abstract 2592). **Frequency and Prognosis:** In a genomic study of 1,070 lung cancer cases, focal amplification of RICTOR was detected in 14.6% of small cell lung cancers (7/48), 8.7% of large cell neuroendocrine carcinomas (2/23), 8.4% of adenocarcinomas (61/724), and 7.4% of squamous cell carcinomas (8/108)[47]. RICTOR amplification in lung cancer often co-occurs with mutations in KRAS, EGFR, or the PI3K–AKT–mTOR pathway, but has also been characterized as a driver alteration in lung cancer[47].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: Tumors with RICTOR amplification may be sensitive to inhibitors of mTORC2, the RICTOR-containing complex[48]. In a preclinical study, RICTOR-overexpressing glioma cells were sensitive to RICTOR knockdown[49]. A patient with RICTOR-amplified lung adenocarcinoma experienced stable disease for >18 months upon treatment with dual mTORC1/mTORC2 inhibitors[47], and a patient with RICTOR-amplified metastatic thymus cancer achieved a partial response upon treatment with a pan-PI3K/mTORC1/mTORC2 inhibitor (Kristeleit et al., 2015; ASCO Abstract 2592). Numerous inhibitors that target both mTORC1 and mTORC2 complexes, as well as dual PI3K/mTOR inhibitors, are under preclinical and clinical investigation in multiple tumor types[50,51]. RICTOR alterations, including amplification, have been implicated in resistance to the EGFR tyrosine kinase inhibitor erlotinib in patients with non-small cell lung carcinoma (Ruder et al., 2015; AACR Abstract 3576).
● ***APC*** S688*	**Gene and Alteration:** APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[52]. APC alterations that disrupt the beta-catenin binding domain (amino acids 1020-2035), such as observed here, are likely to impair APC binding to beta-catenin and may upregulate WNT signaling[53,54,55,56,57] and are therefore predicted to be inactivating. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[58,59,60]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[61], and in the appropriate clinical context, germline testing of APC is recommended. **Frequency and Prognosis:** APC mutations have been reported in 4-7% of lung adenocarcinoma cases[12,62,63,64]. In contrast, loss of heterozygosity at the APC/MCC locus has been reported in up to 68% (17/25) of NSCLC, with a higher incidence in squamous cell carcinomas compared to adenocarcinomas[65,66]. APC has been reported to be down-regulated in NSCLC tumors and cell lines[67]. Hypermethylation of APC in NSCLC tumors has been reported in a number of studies[68,69,70]. Hypermethylation of the APC gene and lower APC mRNA expression have been associated with poorer survival in patients with NSCLC[66,71]. **Potential Treatment Strategies:** There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors; however, several potential therapies, including WNT pathway inhibitors and TRAIL agonists, are in clinical trials. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[72]. In addition, the COX-2 inhibitor celecoxib, which is FDA approved for arthritis, was shown to reduce WNT signaling in cancer cell lines[73,74]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[75].
● ***FGF10*** amplification	**Gene and Alteration:** FGF10 encodes fibroblast growth factor 10, a ligand that primarily binds to FGFR2, but also FGFR1[76], with a broad range of functions in development and wound healing. FGF10 has been implicated in regulating the epithelial-mesenchymal transition in cancer cells[77] and during normal development[78]. Germline mutations in FGF10 have been implicated in aplasia of the lacrimal and salivary glands, an autosomal dominant developmental disorder[79]. Amplification of FGF10 has been reported in cancer[80] and may be biologically relevant in this context[34,81].

GENE ALTERATION	INTERPRETATION

Frequency and Prognosis: Infrequent but recurrent amplification of FGF10 has been reported in multiple cancer types, including gallbladder cancer[82], gastric cancer[83], and esophageal squamous cell carcinoma (SCC)[84]; one small-scale study reported FGF10 amplification in 7/7 oral SCC cases[85]. Preclinical studies have shown that increased FGF10 expression and FGF10-FGFR1/2 signaling promotes cancer cell proliferation, invasion, migration, and tumorigenesis in a variety of tumor models[86,87,88,89].

Potential Treatment Strategies: A preclinical study reported that FGF10-driven migration and invasion of pancreatic cancer cell lines could be blocked by inhibitory antibodies targeting FGFR2[88], and a second study found that expression of dominant-negative FGFR1 or FGFR2 led to a decrease in tumor size in a prostate cancer xenograft model driven by FGF10, although the decrease was not statistically significant[87]. Clinical trials are ongoing for multiple inhibitors that target FGFR2 and other kinases, including the FDA-approved agents pazopanib, ponatinib, and lenvatinib, as well as pan-FGFR inhibitors such as AZD4547, BGJ398, CH5183284, and TAS-120; however, these agents have not been comprehensively tested in the context of FGF10 amplification or overexpression.

THERAPIES

FDA-APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Ceritinib	**Approved Indications:** Ceritinib is an inhibitor of the kinases ALK, ROS1, IR, and IGF-1R. It is FDA approved for the treatment of metastatic non-small cell lung cancer (NSCLC) in patients whose tumors are positive for ALK rearrangements, as detected by an FDA-approved test, and who have progressed on or are intolerant to crizotinib. **Gene Association:** Activation of ROS1 may predict sensitivity to ceritinib[17]. **Supporting Data:** A Phase 1 study of ceritinib reported a 58% response rate in 122 NSCLC patients harboring alterations in ALK and a response rate of 56% in 80 of these patients who had previously been treated with crizotinib [90]. Ceritinib has also been shown to inhibit ROS1 in vitro, and clinical trials are currently enrolling NSCLC patients with ROS1 rearrangement (Anjum et al., 2013; ANE Annual Meeting Abstract A98, Zhou et al., 2014; ASCO Abstract TPS8122)[16].
Crizotinib	**Approved Indications:** Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are positive for ALK rearrangements or ROS1 rearrangements. **Gene Association:** Crizotinib has demonstrated clinical efficacy for patients with ROS1-rearranged NSCLC (Ou et al., 2013; ASCO Abstract 8032, Mazieres et al. 2014; ASCO Abstract 11035)[4,5,13,14,15]. **Supporting Data:** Patients with ROS1-rearranged metastatic NSCLC treated with crizotinib achieved an objective response rate (ORR) of 72% (36/50), with 3 complete responses and 33 partial responses; the median progression-free survival (PFS) was 19.2 months, and the median response duration was 17.6 months [13]. Preliminary Phase 2 data confirm a high ORR to crizotinib in ROS1-rearranged NSCLC (Moro-Sibilot et al., 2015; ASCO Abstract 8065). In retrospective studies, crizotinib therapy was associated with an ORR of 80% (24/30) or higher (5/5) and a median PFS of 9.1 months for patients with ROS1-rearranged advanced lung adenocarcinoma[8]. Crizotinib has also demonstrated efficacy in patients with NSCLC and ALK rearrangements[91], an NTRK1 fusion[92], or MET activation[93,94,95,96,97,98].

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Palbociclib	**Approved Indications:** Palbociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination with letrozole as first-line therapy for postmenopausal women or in combination with fulvestrant following progression on endocrine therapy. **Gene Association:** Clinical studies in liposarcoma and mantle cell lymphoma as well as responses in patients with breast cancer or melanoma indicate that activation of cyclin D-CDK4/6 may predict sensitivity to therapies such as palbociclib (Infante et al., 2014; ASCO Abstract 2528)[30,99]. **Supporting Data:** Palbociclib has been studied primarily for the treatment of ER+ breast cancer[31,100,101]. However, a Phase 2 study of palbociclib in patients with recurrent or metastatic non-small cell lung cancer (NSCLC) and loss of p16INK4a reported no responses in any of the 16 evaluable patients but stable disease (SD) in 8 (50%) patients (Gopalan et al., 2014; ASCO Abstract 8077). A trial of the CDK4/6 inhibitor abemaciclib in patients with NSCLC reported a disease control rate of 51% (37% for patients with KRAS-wild-type tumors and 54% for patients with KRAS-mutant tumors), with one confirmed PR (Goldman et al., 2014; ASCO Abstract 8026). For various tumor types, preclinical studies suggest that palbociclib may be useful in combination with other therapies targeting oncogenic drivers such as MEK, BRAF, PI3K, or IGF1R[102,103,104,105,106]. Multiple preclinical studies demonstrate that loss of Rb predicts resistance to palbociclib[107,108,109,110].

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.

CLINICAL TRIALS TO CONSIDER

IMPORTANT: 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. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***ROS1*** CD74-ROS1 fusion	Activating mutations and rearrangements of ROS1 may predict sensitivity to inhibitors of ROS1. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "ROS1", "AKT", "MET", "crizotinib", "ceritinib", "cabozantinib", "AP26113", "LDK378", "PF-06463922", "LY2801653", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase 1 Safety, Pharmacokinetic And Pharmacodynamic Study Of PF-02341066, A c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally To Patients With Advanced Cancer	Phase 1	AXL, ALK, MET, ROS1, RON, TRKs	California, Colorado, Massachusetts, Michigan, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Seoul (Korea, Republic of), Victoria (Australia)	NCT00585195
Phase 1/2 Study Of PF-06463922 (An ALK/ROS1 Tyrosine Kinase Inhibitor) In Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations	Phase 1/Phase 2	ALK, ROS1	Arkansas, California, Colorado, District of Columbia, Massachusetts, Michigan, Missouri, New York, Pennsylvania, Tennessee, Aviano (PN) (Italy), Barcelona (Spain), Chiba (Japan), Fukuoka (Japan), Hyogo (Japan), Koto-ku, Tokyo (Japan), Madrid (Spain), New South Wales (Australia), Osaka (Japan), Paris (France), Perugia (Italy), Queensland (Australia), Singapore (Singapore), Tokyo (Japan), Toulouse (France), Toulouse Cedex 9 (France), Victoria (Australia), Villejuif Cedex (France)	NCT01970865
A Phase 1/2a, Multicenter, Open-Label Study of Oral RXDX-101 in Adult Patients With Locally Advanced or Metastatic Cancer Confirmed to be Positive for TrkA, TrkB, TrkC, ROS1, or ALK Molecular Alterations	Phase 1/Phase 2	ALK, ROS1, TRKA/B/C	California, Colorado, District of Columbia, Florida, Massachusetts, New York, Tennessee, Texas, Barcelona (Spain), Seoul (Korea, Republic of)	NCT02097810
Modular Phase II Study to Link Targeted Therapy to Patients With Pathway Activated Tumors: Module - 7 Ceritinib (LDK378) for	Phase 2	ALK, ROS1, IGF1R, INSR	California, Colorado, Florida, Illinois, Indiana, Maryland, Missouri, Nebraska, Nevada,	NCT02186821

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Patients Whose Tumors Have Aberrations in ALK or ROS1			New Mexico, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, Rhode Island, South Dakota, Tennessee, Texas, Utah, Washington	

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***CDK4*** amplification	Tumors with CDK4 amplification and intact RB1 may be sensitive to CDK4/6 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "CDK4", "PD-0332991", "LEE011", "LY2835219", "palbociclib", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer	Phase 2	CDK4, CDK6	Pennsylvania	NCT01037790
A Phase I Study of the CDK4/6 Inhibitor PD-0332991, 5-Fluorouracil, and Oxaliplatin in Patients With Advanced Solid Tumor Malignancies	Phase 1	CDK4, CDK6	District of Columbia	NCT01522989
A Phase 1b Study of LY2835219 in Combination With Multiple Single Agent Options for Patients With Stage IV NSCLC	Phase 1	CDK4, CDK6, Others	Arkansas, California, Indiana, New Jersey, New Mexico, North Carolina, Tennessee, Madrid (Spain), Majadahonda (Spain), Sevilla (Spain)	NCT02079636
Modular Phase II Study to Link Targeted Therapy to Patients With Pathway Activated Tumors: Module 8 - LEE011 for Patients With CDK4/6 Pathway Activated Tumors	Phase 2	CDK4, CDK6	Alaska, Arizona, California, Colorado, Connecticut, Indiana, Maryland, Missouri, New Mexico, North Carolina, Ohio, Oregon, Rhode Island, South Dakota, Tennessee, Texas, Utah, Virginia, Washington, Wisconsin	NCT02187783

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***MDM2*** amplification	MDM2 overexpression or amplification in the context of wild-type p53 may increase sensitivity to inhibitors of the MDM2-p53 interaction. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "MDM2", "CGM097", "DS-3032b", "RO5503781", "RO6839921", "nutlin", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I, Open-label, Multi-center, Dose Escalation Study of Oral CGM097, a p53/HDM2-interaction Inhibitor, in Adult Patients With Selected Advanced Solid Tumors	Phase 1	MDM2	Massachusetts, Essen (Germany), Köln (Germany), Lyon Cedex (France), Singapore (Singapore), Zürich (Switzerland)	NCT01760525
A Phase 1 Multiple Ascending Dose Study of DS-3032b, an Oral MDM2 Inhibitor, in Subjects With Advanced Solid Tumors or Lymphomas	Phase 1	MDM2	Michigan, New York, Tennessee, Texas	NCT01877382
A Multi-Center, Open-Label, First-in-Human, Phase I Dose-Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RO6839921, An MDM2 Antagonist, Following Intravenous Administration in Patients With Advanced Malignancies, Including Acute Myeloid Leukemia (AML)	Phase 1	MDM2	Colorado, Missouri, South Carolina, Ontario (Canada), Quebec (Canada)	NCT02098967
A Phase I, Open Label, Multicenter, Dose-escalation Study of HDM201 in Adult Patients With Advanced Solid and Hematological Tumors Characterized by Wild-type TP53	Phase 1	MDM2	Massachusetts, New York, Amsterdam (Netherlands), Catalunya (Spain), Essen (Germany), Frankfurt (Germany), Hyogo (Japan), Lyon Cedex (France), Singapore (Singapore), Taiwan ROC (Taiwan), Tokyo (Japan), Utrecht (Netherlands), Würzburg (Germany)	NCT02143635

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***RICTOR*** amplification	RICTOR is a component of the mTORC2 complex, and RICTOR amplification may therefore predict sensitivity to dual mTORC1/mTORC2 inhibitors or dual PI3K/mTOR inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "GDC-0980", "GSK2126458", "PF-04691502", "PF-05212384", "INK-128", "OSI-027", "CC-223", "DS-3078a", "NSCLC", "lung adenocarcinoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Multiarm, Open-label, Phase 1b Study of MLN2480 (an Oral A-, B-, and CRAF Inhibitor) in Combination With MLN0128 (an Oral mTORC 1/2 Inhibitor), or Alisertib (an Oral Aurora A Kinase Inhibitor), or Paclitaxel, in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	mTORC1, mTORC2, RAF, Aurora kinase A	Massachusetts, Pennsylvania, Barcelona (Spain), Oxfordshire (United Kingdom)	NCT02327169
A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	mTORC1, mTORC2	Florida, Oklahoma, Tennessee	NCT02412722
A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	PI3K-alpha, mTORC1, mTORC2	Massachusetts, Tennessee, Texas, Barcelona (Spain), Sutton (United Kingdom)	NCT01899053
TAX-TORC: A Phase I Multi-centre Trial of the Combination of AZD2014 (Dual mTORC1 and mTORC2 Inhibitor) and Weekly Paclitaxel in Patients With Solid Tumours.	Phase 1	mTORC1, mTORC2	Cambridgeshire (United Kingdom), London (United Kingdom), Surrey (United Kingdom)	NCT02193633
A Phase 1 Study of MLN0128 and Bevacizumab in Patients With Recurrent Glioblastoma and Other Solid Tumors	Phase 1	mTORC1, mTORC2, VEGFA	Massachusetts	NCT02142803
Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer	Phase 2	EGFR, VEGFR, RET, MEK, mTORC1, mTORC2, FGFR, AKT, ERBB2, ERBB3	Bordeaux (France), Caen (France), Chartres (France), Clermont-Ferrand (France), Créteil (France), Dijon (France), Grenoble (France), Lille (France), Lyon (France), Marseille (France), Nantes (France), Paris (France), Pierre Bénite (France), Toulon (France), Toulouse (France), Tours (France), Villejuif (France)	NCT02117167

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APPENDIX

VARIANTS OF UNKNOWN SIGNIFICANCE

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 make their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BRD4 P974L	***DOT1L*** G1452_A1458del	***ESR1*** S118P	***FAM46C*** H295Q	***FGF19*** F59L	***FGFR1*** M456I
IL7R amplification	***NFE2L2*** V207F	***PIK3C2B*** T1021A	***PIK3CG*** R359H	***RANBP2*** E744Q	***ROS1*** L2086F
SDHA amplification	***SMARCA4*** D1175G	***SPTA1*** L1646F			

APPENDIX

GENES ASSAYED IN FOUNDATIONONE

FoundationOne is designed to include all 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 315 genes as well as introns of 28 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	*ABL2*	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B)*	*APC*	*AR*
ARAF	*ARFRP1*	*ARID1A*	*ARID1B*	*ARID2*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*
BCORL1	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTK*	*C11orf30 (EMSY)*
CARD11	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CD274*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHD2*	*CHD4*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*
CSF1R	*CTCF*	*CTNNA1*	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR2*	*DICER1*	*DNMT3A*
DOT1L	*EGFR*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*
ERG	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*
FANCG	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*	*FLT1*	*FLT3*
FLT4	*FOXL2*	*FOXP1*	*FRS2*	*FUBP1*	*GABRA6*	*GATA1*	*GATA2*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GLI1*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GRM3*
GSK3B	*H3F3A*	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*HSP90AA1*	*IDH1*	*IDH2*	*IGF1R*
IGF2	*IKBKE*	*IKZF1*	*IL7R*	*INHBA*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*
JAK2	*JAK3*	*JUN*	*KAT6A (MYST3)*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*
KIT	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LMO1*	*LRP1B*	*LYN*	*LZTR1*
MAGI2	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEN1	*MET*	*MITF*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH6*	*MTOR*	*MUTYH*
MYC	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*
NOTCH2	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*	*PAK3*
PALB2	*PARK2*	*PAX5*	*PBRM1*	*PDCD1LG2*	*PDGFRA*	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3CA*
PIK3CB	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PLCG2*	*PMS2*	*POLD1*	*POLE*	*PPP2R1A*	*PRDM1*
PREX2	*PRKAR1A*	*PRKCI*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*	*QKI*	*RAC1*
RAD50	*RAD51*	*RAF1*	*RANBP2*	*RARA*	*RB1*	*RBM10*	*RET*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*RUNX1T1*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SLIT2	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX10*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SPTA1*	*SRC*	*STAG2*	*STAT3*	*STAT4*	*STK11*
SUFU	*SYK*	*TAF1*	*TBX3*	*TERC*	*TERT (promoter only)*	*TET2*	*TGFBR2*	*TNFAIP3*	*TNFRSF14*
TOP1	*TOP2A*	*TP53*	*TSC1*	*TSC2*	*TSHR*	*U2AF1*	*VEGFA*	*VHL*	*WISP3*
WT1	*XPO1*	*ZBTB2*	*ZNF217*	*ZNF703*					

DNA Gene List: For the Detection Select Rearrangements

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*EGFR*	*ETV1*	*ETV4*
ETV5	*ETV6*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*MSH2*	*MYB*	*MYC*	*NOTCH2*
NTRK1	*NTRK2*	*PDGFRA*	*RAF1*	*RARA*	*RET*	*ROS1*	*TMPRSS2*		

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APPENDIX

FOUNDATIONONE PERFORMANCE SPECIFICATIONS

ACCURACY		
Sensitivity: Base Substitutions	At Mutant Allele Frequency ≥10%	>99.9% (CI* 99.6%-100%)
	At Mutant Allele Frequency 5-10%	99.3% (CI* 98.3%-99.8%)
Sensitivity: Insertions/Deletions (1-40 bp)	At Mutant Allele Frequency ≥20%	97.9% (CI* 92.5%-99.7%)
	At Mutant Allele Frequency 10-20%	97.3% (CI* 90.5%-99.7%)
Sensitivity: Copy Number Alterations—Amplifications (ploidy <4, Amplification with Copy Number ≥8)	At ≥30% tumor nuclei	>99.0% (CI* 93.6%-100%)
	At 20% tumor nuclei	92.6% (CI* 66.1%-99.8%)
Sensitivity: Copy Number Alterations—Deletions (ploidy <4, Homozygous Deletions)	At ≥30% tumor nuclei	97.2% (CI* 85.5%-99.9%)
	At 20% tumor nuclei	88.9% (CI* 51.8%-99.7%)
Sensitivity: Rearrangements (selected rearrangements in specimens with ≥20% tumor nuclei)**		>90.0% [1] >99.0% for ALK fusion[2] (CI* 89.1%-100%)
Specificity of all variant types	Positive Predictive Value (PPV)	>99.0%
REPRODUCIBILITY (average concordance between replicates)		96.4% inter-batch precision 98.9% intra-batch precision

*95% Confidence Interval

** 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.

[1] Based on analysis of coverage and re-arrangement structure in the COSMIC database for the solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.

[2] Based on ALK re-arrangement concordance analysis vs. a standard clinical FISH assay described in: Yelensky, R. et al. Analytical validation of solid tumor fusion gene detection in a comprehensive NGS-based clinical cancer genomic test, In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 4699

Assay specifications were determined for typical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

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

APPENDIX

REFERENCES

1 Acquaviva J, Wong R, Charest A (2009) The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. Biochim Biophys Acta 1795(1):37-52.

2 Shaw AT, Hsu PP, Awad MM, et al. (2013) Tyrosine kinase gene rearrangements in epithelial malignancies. Nat Rev Cancer 13(11):772-87.

3 Takeuchi K, Soda M, Togashi Y, et al. (2012) RET, ROS1 and ALK fusions in lung cancer. Nat Med 18(3):378-81.

4 Davies KD, Le AT, Theodoro MF, et al. (2012) Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. Clin Cancer Res 18(17):4570-9.

5 Bergethon K, Shaw AT, Ou SH, et al. (2012) ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 30(8):863-70.

6 Lee HJ, Seol HS, Kim JY, et al. (2013) ROS1 receptor tyrosine kinase, a druggable target, is frequently overexpressed in non-small cell lung carcinomas via genetic and epigenetic mechanisms. Ann Surg Oncol 20(1):200-8.

7 Jun HJ, Johnson H, Bronson RT, et al. (2012) The oncogenic lung cancer fusion kinase CD74-ROS activates a novel invasiveness pathway through E-Syt1 phosphorylation. Cancer Res 72(15):3764-74.

8 Scheffler M, Schultheis A, Teixido C, et al. (2015) ROS1 rearrangements in lung adenocarcinoma: prognostic impact, therapeutic options and genetic variability. Oncotarget 6(12):10577-85.

9 Pan Y, Zhang Y, Li Y, et al. (2014) ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: a comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Lung Cancer 84(2):121-6.

10 Kim HR, Lim SM, Kim HJ, et al. (2013) The frequency and impact of ROS1 rearrangement on clinical outcomes in never smokers with lung adenocarcinoma. Ann Oncol 24(9):2364-70.

11 Kim MH, Shim HS, Kang DR, et al. (2014) Clinical and prognostic implications of ALK and ROS1 rearrangements in never-smokers with surgically resected lung adenocarcinoma. Lung Cancer 83(3):389-95.

12 Cancer Genome Atlas Research Network (2014) Comprehensive molecular profiling of lung adenocarcinoma. Nature 511(7511):543-50.

13 Shaw AT, Ou SH, Bang YJ, et al. (2014) Crizotinib in ROS1-Rearranged Non-Small-Cell Lung Cancer. N Engl J Med ePub Sep 2014.

14 Komiya T, Thomas A, Khozin S, et al. (2012) Response to crizotinib in ROS1-rearranged non-small-cell lung cancer. J Clin Oncol 30(27):3425-6; author reply 3426.

15 Yasuda H, de Figueiredo-Pontes LL, Kobayashi S, et al. (2012) Preclinical rationale for use of the clinically available multitargeted tyrosine kinase inhibitor crizotinib in ROS1-translocated lung cancer. J Thorac Oncol 7(7):1086-90.

16 Marsilje TH, Pei W, Chen B, et al. (2013) Synthesis, structure-activity relationships, and in vivo efficacy of the novel potent and selective anaplastic lymphoma kinase (ALK) inhibitor 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (LDK378) currently in phase 1 and phase 2 clinical trials. J Med Chem 56(14):5675-90.

17 Subbiah V, Hong DS, Meric-Bernstam F (2016) Clinical activity of ceritinib in ROS1-rearranged non-small cell lung cancer: Bench to bedside report. Proc Natl Acad Sci USA ePub Feb 2016.

APPENDIX

REFERENCES

[18] Zou HY, Li Q, Engstrom LD, et al. (2015) PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations. Proc Natl Acad Sci USA 112(11):3493-8.

[19] Katayama R, Kobayashi Y, Friboulet L, et al. (2015) Cabozantinib overcomes crizotinib resistance in ROS1 fusion-positive cancer. Clin Cancer Res 21(1):166-74.

[20] Davare MA, Saborowski A, Eide CA, et al. (2013) Foretinib is a potent inhibitor of oncogenic ROS1 fusion proteins. Proc Natl Acad Sci USA 110(48):19519-24.

[21] Choi YJ, Anders L (2014) Signaling through cyclin D-dependent kinases. Oncogene 33(15):1890-903.

[22] Weinberg RA (1995) The retinoblastoma protein and cell cycle control. Cell 81(3):323-30.

[23] Musgrove EA, Caldon CE, Barraclough J, et al. (2011) Cyclin D as a therapeutic target in cancer. Nat Rev Cancer 11(8):558-72.

[24] Wikman H, Nymark P, Väyrynen A, et al. (2005) CDK4 is a probable target gene in a novel amplicon at 12q13.3-q14.1 in lung cancer. Genes Chromosomes Cancer 42(2):193-9.

[25] Rao SK, Edwards J, Joshi AD, et al. (2010) A survey of glioblastoma genomic amplifications and deletions. J Neurooncol 96(2):169-79.

[26] Borczuk AC, Gorenstein L, Walter KL, et al. (2003) Non-small-cell lung cancer molecular signatures recapitulate lung developmental pathways. Am J Pathol 163(5):1949-60.

[27] Wu A, Wu B, Guo J, et al. (2011) Elevated expression of CDK4 in lung cancer. J Transl Med 9:38.

[28] Puyol M, Martín A, Dubus P, et al. (2010) A synthetic lethal interaction between K-Ras oncogenes and Cdk4 unveils a therapeutic strategy for non-small cell lung carcinoma. Cancer Cell 18(1):63-73.

[29] Flaherty KT, Lorusso PM, Demichele A, et al. (2012) Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. Clin Cancer Res 18(2):568-76.

[30] Dickson MA, Tap WD, Keohan ML, et al. (2013) Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol 31(16):2024-8.

[31] Finn RS, Crown JP, Lang I, et al. (2014) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol ePub Dec 2014.

[32] Brown CJ, Lain S, Verma CS, et al. (2009) Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer 9(12):862-73.

[33] Cordon-Cardo C, Latres E, Drobnjak M, et al. (1994) Molecular abnormalities of mdm2 and p53 genes in adult soft tissue sarcomas. Cancer Res 54(3):794-9.

[34] Beroukhim R, Mermel CH, Porter D, et al. (2010) The landscape of somatic copy-number alteration across human cancers. Nature 463(7283):899-905.

[35] Higashiyama M, Doi O, Kodama K, et al. (1997) MDM2 gene amplification and expression in non-small-cell lung cancer: immunohistochemical expression of its protein is a favourable prognostic marker in patients without p53 protein accumulation. Br J Cancer 75(9):1302-8.

[36] Marchetti A, Buttitta F, Pellegrini S, et al. (1995) mdm2 gene amplification and overexpression in non-small cell lung carcinomas with accumulation of the p53 protein in the absence of p53 gene mutations. Diagn Mol Pathol 4(2):93-7.

APPENDIX

REFERENCES

37 Dworakowska D, Jassem E, Jassem J, et al. (2004) MDM2 gene amplification: a new independent factor of adverse prognosis in non-small cell lung cancer (NSCLC). Lung Cancer 43(3):285-95.

38 Onel K, Cordon-Cardo C (2004) MDM2 and prognosis. Mol Cancer Res 2(1):1-8.

39 Ren YW, Yin ZH, Wan Y, et al. (2013) P53 Arg72Pro and MDM2 SNP309 polymorphisms cooperate to increase lung adenocarcinoma risk in Chinese female non-smokers: a case control study. Asian Pac J Cancer Prev 14(9):5415-20.

40 Cheok CF, Verma CS, Baselga J, et al. (2011) Translating p53 into the clinic. Nat Rev Clin Oncol 8(1):25-37.

41 Ohnstad HO, Castro R, Sun J, et al. (2013) Correlation of TP53 and MDM2 genotypes with response to therapy in sarcoma. Cancer 119(5):1013-22.

42 Gamble LD, Kees UR, Tweddle DA, et al. (2012) MYCN sensitizes neuroblastoma to the MDM2-p53 antagonists Nutlin-3 and MI-63. Oncogene 31(6):752-63.

43 Sarbassov DD, Ali SM, Kim DH, et al. (2004) Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. Curr Biol 14(14):1296-302.

44 Jacinto E, Loewith R, Schmidt A, et al. (2004) Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nat Cell Biol 6(11):1122-8.

45 Pearce LR, Huang X, Boudeau J, et al. (2007) Identification of Protor as a novel Rictor-binding component of mTOR complex-2. Biochem J 405(3):513-22.

46 Ross JS, Wang K, Elkadi OR, et al. (2014) Next-generation sequencing reveals frequent consistent genomic alterations in small cell undifferentiated lung cancer. J Clin Pathol ePub Jun 2014.

47 Cheng H, Zou Y, Ross JS, et al. (2015) RICTOR amplification defines a novel subset of lung cancer patients who may benefit from treatment with mTOR1/2 inhibitors. Cancer Discov ePub Sep 2015.

48 Sparks CA, Guertin DA (2010) Targeting mTOR: prospects for mTOR complex 2 inhibitors in cancer therapy. Oncogene 29(26):3733-44.

49 Masri J, Bernath A, Martin J, et al. (2007) mTORC2 activity is elevated in gliomas and promotes growth and cell motility via overexpression of rictor. Cancer Res 67(24):11712-20.

50 Wander SA, Hennessy BT, Slingerland JM (2011) Next-generation mTOR inhibitors in clinical oncology: how pathway complexity informs therapeutic strategy. J Clin Invest 121(4):1231-41.

51 Schenone S, Brullo C, Musumeci F, et al. (2011) ATP-competitive inhibitors of mTOR: an update. Curr Med Chem 18(20):2995-3014.

52 Logan CY, Nusse R (2004) The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol 20:781-810.

53 Eklof Spink K, Fridman SG, Weis WI (2001) Molecular mechanisms of beta-catenin recognition by adenomatous polyposis coli revealed by the structure of an APC-beta-catenin complex. EMBO J 20(22):6203-12.

54 Liu J, Xing Y, Hinds TR, et al. (2006) The third 20 amino acid repeat is the tightest binding site of APC for beta-catenin. J Mol Biol 360(1):133-44.

55 Dikovskaya D, Li Z, Newton IP, et al. (2010) Microtubule assembly by the Apc protein is regulated by importin-beta--RanGTP. J Cell Sci 123(Pt 5):736-46.

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APPENDIX

REFERENCES

[56] Murphy SJ, McIlhatton B, Logan WP, et al. (2007) A splice-site mutation in exon 4 of the APC gene in a family with attenuated familial adenomatous polyposis. Dig Dis Sci 52(10):2784-7.

[57] Aretz S, Uhlhaas S, Sun Y, et al. (2004) Familial adenomatous polyposis: aberrant splicing due to missense or silent mutations in the APC gene. Hum Mutat 24(5):370-80.

[58] Kerr SE, Thomas CB, Thibodeau SN, et al. (2013) APC germline mutations in individuals being evaluated for familial adenomatous polyposis: a review of the Mayo Clinic experience with 1591 consecutive tests. J Mol Diagn 15(1):31-43.

[59] Fearon ER (2011) Molecular genetics of colorectal cancer. Annu Rev Pathol 6:479-507.

[60] Kastritis E, Murray S, Kyriakou F, et al. (2009) Somatic mutations of adenomatous polyposis coli gene and nuclear b-catenin accumulation have prognostic significance in invasive urothelial carcinomas: evidence for Wnt pathway implication. Int J Cancer 124(1):103-8.

[61] Half E, Bercovich D, Rozen P (2009) Familial adenomatous polyposis. Orphanet J Rare Dis 4:22.

[62] Imielinski M, Berger AH, Hammerman PS, et al. (2012) Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 150(6):1107-20.

[63] Ding L, Getz G, Wheeler DA, et al. (2008) Somatic mutations affect key pathways in lung adenocarcinoma. Nature 455(7216):1069-75.

[64] Ohgaki H, Kros JM, Okamoto Y, et al. (2004) APC mutations are infrequent but present in human lung cancer. Cancer Lett 207(2):197-203.

[65] Sanz-Ortega J, Bryant B, Sanz-Esponera J, et al. (1999) LOH at the APC/MCC gene (5Q21) is frequent in early stages of non-small cell lung cancer. Pathol Res Pract 195(10):677-80.

[66] Poursoltan P, Currey N, Pangon L, et al. (2012) Loss of heterozygosity of the Mutated in Colorectal Cancer gene is not associated with promoter methylation in non-small cell lung cancer. Lung Cancer 77(2):272-6.

[67] Stewart DJ (2014) Wnt signaling pathway in non-small cell lung cancer. J Natl Cancer Inst 106(1):djt356.

[68] Zhang Y, Wang R, Song H, et al. (2011) Methylation of multiple genes as a candidate biomarker in non-small cell lung cancer. Cancer Lett 303(1):21-8.

[69] Virmani AK, Rathi A, Sathyanarayana UG, et al. (2001) Aberrant methylation of the adenomatous polyposis coli (APC) gene promoter 1A in breast and lung carcinomas. Clin Cancer Res 7(7):1998-2004.

[70] Vallböhmer D, Brabender J, Yang D, et al. (2006) DNA methyltransferases messenger RNA expression and aberrant methylation of CpG islands in non-small-cell lung cancer: association and prognostic value. Clin Lung Cancer 8(1):39-44.

[71] Lu Y, Lemon W, Liu PY, et al. (2006) A gene expression signature predicts survival of patients with stage I non-small cell lung cancer. PLoS Med 3(12):e467.

[72] Zhang L, Ren X, Alt E, et al. (2010) Chemoprevention of colorectal cancer by targeting APC-deficient cells for apoptosis. Nature 464(7291):1058-61.

[73] Lu W, Tinsley HN, Keeton A, et al. (2009) Suppression of Wnt/beta-catenin signaling inhibits prostate cancer cell proliferation. Eur J Pharmacol 602(1):8-14.

[74] Tuynman JB, Vermeulen L, Boon EM, et al. (2008) Cyclooxygenase-2 inhibition inhibits c-Met kinase activity and Wnt activity in colon cancer. Cancer Res 68(4):1213-20.

APPENDIX

REFERENCES

[75] Lau T, Chan E, Callow M, et al. (2013) A novel tankyrase small-molecule inhibitor suppresses APC mutation-driven colorectal tumor growth. Cancer Res 73(10):3132-44.

[76] Zhang X, Ibrahimi OA, Olsen SK, et al. (2006) Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. J Biol Chem 281(23):15694-700.

[77] Abolhassani A, Riazi GH, Azizi E, et al. (2014) FGF10: Type III Epithelial Mesenchymal Transition and Invasion in Breast Cancer Cell Lines. J Cancer 5(7):537-47.

[78] Volckaert T, De Langhe S (2014) Lung epithelial stem cells and their niches: Fgf10 takes center stage. Fibrogenesis Tissue Repair 7:8.

[79] Entesarian M, Matsson H, Klar J, et al. (2005) Mutations in the gene encoding fibroblast growth factor 10 are associated with aplasia of lacrimal and salivary glands. Nat Genet 37(2):125-7.

[80] Gao J, Aksoy BA, Dogrusoz U, et al. (2013) Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 6(269):pl1.

[81] Zack TI, Schumacher SE, Carter SL, et al. (2013) Pan-cancer patterns of somatic copy number alteration. Nat Genet 45(10):1134-1140.

[82] Javle M, Rashid A, Churi C, et al. (2014) Molecular characterization of gallbladder cancer using somatic mutation profiling. Hum Pathol 45(4):701-8.

[83] Ooi A, Oyama T, Nakamura R, et al. (2015) Semi-comprehensive analysis of gene amplification in gastric cancers using multiplex ligation-dependent probe amplification and fluorescence in situ hybridization. Mod Pathol ePub Mar 2015.

[84] Chattopadhyay I, Singh A, Phukan R, et al. (2010) Genome-wide analysis of chromosomal alterations in patients with esophageal squamous cell carcinoma exposed to tobacco and betel quid from high-risk area in India. Mutat Res 696(2):130-8.

[85] Cha JD, Kim HJ, Cha IH (2011) Genetic alterations in oral squamous cell carcinoma progression detected by combining array-based comparative genomic hybridization and multiplex ligation-dependent probe amplification. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 111(5):594-607.

[86] Theodorou V, Boer M, Weigelt B, et al. (2004) Fgf10 is an oncogene activated by MMTV insertional mutagenesis in mouse mammary tumors and overexpressed in a subset of human breast carcinomas. Oncogene 23(36):6047-55.

[87] Memarzadeh S, Xin L, Mulholland DJ, et al. (2007) Enhanced paracrine FGF10 expression promotes formation of multifocal prostate adenocarcinoma and an increase in epithelial androgen receptor. Cancer Cell 12(6):572-85.

[88] Nomura S, Yoshitomi H, Takano S, et al. (2008) FGF10/FGFR2 signal induces cell migration and invasion in pancreatic cancer. Br J Cancer 99(2):305-13.

[89] Nakao Y, Mitsuyasu T, Kawano S, et al. (2013) Fibroblast growth factors 7 and 10 are involved in ameloblastoma proliferation via the mitogen-activated protein kinase pathway. Int J Oncol 43(5):1377-84.

[90] Shaw AT, Kim DW, Mehra R, et al. (2014) Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 370(13):1189-97.

[91] Shaw AT, Kim DW, Nakagawa K, et al. (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368(25):2385-94.

[92] Vaishnavi A, Capelletti M, Le AT, et al. (2013) Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat Med 19(11):1469-72.

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APPENDIX

REFERENCES

[93] Frampton GM, Ali SM, Rosenzweig M, et al. (2015) Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov ePub May 2015.

[94] Paik PK, Drilon A, Yu H, et al. (2015) Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov ePub May 2015.

[95] Jenkins RW, Oxnard GR, Elkin S, et al. (2015) Response to Crizotinib in a Patient With Lung Adenocarcinoma Harboring a MET Splice Site Mutation. Clin Lung Cancer ePub Feb 2015.

[96] Waqar SN, Morgensztern D, Sehn J (2015) MET Mutation Associated with Responsiveness to Crizotinib. J Thorac Oncol 10(5):e29-31.

[97] Mendenhall MA, Goldman JW (2015) MET-Mutated NSCLC with Major Response to Crizotinib. J Thorac Oncol 10(5):e33-4.

[98] Ou SH, Kwak EL, Siwak-Tapp C, et al. (2011) Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 6(5):942-6.

[99] Leonard JP, LaCasce AS, Smith MR, et al. (2012) Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma. Blood 119(20):4597-607.

[100] Turner NC, Ro J, André F, et al. (2015) Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med ePub Jun 2015.

[101] DeMichele A, Clark A, Tan KS, et al. (2014) CDK 4/6 Inhibitor Palbociclib (PD0332991) in Rb+ Advanced Breast Cancer: Phase II Activity, Safety and Predictive Biomarker Assessment. Clin Cancer Res ePub Dec 2014.

[102] Kwong LN, Costello JC, Liu H, et al. (2012) Oncogenic NRAS signaling differentially regulates survival and proliferation in melanoma. Nat Med 18(10):1503-10.

[103] Huillard E, Hashizume R, Phillips JJ, et al. (2012) Cooperative interactions of BRAFV600E kinase and CDKN2A locus deficiency in pediatric malignant astrocytoma as a basis for rational therapy. Proc Natl Acad Sci USA 109(22):8710-5.

[104] Vora SR, Juric D, Kim N, et al. (2014) CDK 4/6 Inhibitors Sensitize PIK3CA Mutant Breast Cancer to PI3K Inhibitors. Cancer Cell 26(1):136-49.

[105] Miller ML, Molinelli EJ, Nair JS, et al. (2013) Drug synergy screen and network modeling in dedifferentiated liposarcoma identifies CDK4 and IGF1R as synergistic drug targets. Sci Signal 6(294):ra85.

[106] Heilmann AM, Perera RM, Ecker V, et al. (2014) CDK4/6 and IGF1 Receptor Inhibitors Synergize to Suppress the Growth of p16INK4A-Deficient Pancreatic Cancers. Cancer Res 74(14):3947-58.

[107] Fry DW, Harvey PJ, Keller PR, et al. (2004) Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther 3(11):1427-38.

[108] Dean JL, Thangavel C, McClendon AK, et al. (2010) Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure. Oncogene 29(28):4018-32.

[109] Dean JL, McClendon AK, Hickey TE, et al. (2012) Therapeutic response to CDK4/6 inhibition in breast cancer defined by ex vivo analyses of human tumors. Cell Cycle 11(14):2756-61.

[110] Garnett MJ, Edelman EJ, Heidorn SJ, et al. (2012) Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 483(7391):570-5.

APPENDIX

ABOUT FOUNDATIONONE™

FoundationOne™: FoundationOne was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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 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 identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test 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 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 for identifying a copy number amplification is five (5) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne 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 analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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.

Alterations and Drugs Not Presented in Ranked Order: In this Report, neither any biomarker alteration, nor any drug associated with potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

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.

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. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne is performed using DNA derived from tumor, and as such germline events may not be reported. The following targets typically have low coverage resulting in a reduction in sensitivity: *SDHD* exon 6 and *TP53* exon 1.

FoundationOne complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Assay has been registered for CE mark by our EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

For more comprehensive information please log on to the Interactive Cancer Explorer™
To set up your Interactive Cancer Explorer account, contact your sales representative or call (888) 988-3639.