FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
		Lung adenocarcinoma

Date of Birth		**Medical Facility**		**Specimen Received**	
Sex		**Ordering Physician**		**Specimen Site**	Lymph Node
FMI Case #	SRF201603	**Additional Recipient**		**Date of Collection**	
Medical Record #		**Medical Facility ID #**		**Specimen Type**	
Specimen ID		**Pathologist**			

ABOUT THE TEST:

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

PATIENT RESULTS

8 genomic alterations

3 therapies associated with potential clinical benefit

2 therapies associated with lack of response

5 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†

EGFR G598V, L858R, T790M
EP300 Q145*
KEAP1 R362Q
RB1 S829*
SMAD4 Q256*
TP53 splice site 672G>A

Additional Disease-relevant Genes with No Reportable Alterations Identified†

KRAS
ALK
BRAF
MET
RET
ERBB2
ROS1

† 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
EGFR G598V, L858R, T790M	(-) Erlotinib ‡ (-) Gefitinib ‡ Osimertinib	Cetuximab Panitumumab	Yes, see clinical trials section
EP300 Q145*	None	None	None
KEAP1 R362Q	None	None	None
RB1 S829*	None	None	None

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Electronically Signed by Julia A. Elvin, M.D., Ph.D. | Jeffrey S. Ross, M.D., Medical Director | CLIA Number: 22D2027531 | 05 July 2016
Foundation Medicine, Inc., 150 2nd Street, 1st Floor, Cambridge, MA 02141 | 1.888.988.3639

Genomic Alterations Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
SMAD4 Q256*	None	None	None
TP53 splice site 672G>A	None	None	None

‡ (-) Patient may be resistant to therapy

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
● ***EGFR*** G598V, L858R, T790M	**Gene and Alteration:** EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[1]. EGFR L858R is a mutation within the kinase domain and has been shown to activate kinase activity and confer sensitivity to EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib[2,3,4]. The EGFR T790M resistance mutation suggests that this tumor may be resistant to the first-generation EGFR inhibitors gefitinib and erlotinib[5] and may be less responsive to the second-generation EGFR inhibitor afatinib[6]. The amplification of EGFR with the T790M mutation has also been linked to resistance to the irreversible EGFR inhibitor dacomitinib[7]. EGFR mutations that have been characterized in biochemical assays to be activating, as also observed here, are predicted to confer sensitivity to EGFR-targeted therapies[8,9,9,10,11,12,13,14,15,16,17,18,19,20,21,22]. **Frequency and Prognosis:** EGFR alterations have been reported in 13-35% of lung adenocarcinomas[23,24]. EGFR amplification has been documented in up to 62% of non-small cell lung cancer (NSCLC), and has been correlated with EGFR protein expression as measured by immunohistochemistry, although this correlation is not consistent for low-level gene amplification[25,26,27,28]. EGFR protein expression or overexpression has been reported in up to 70% of NSCLC tumors[29]. EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[30] or resected Stage 1 NSCLC[31].

GENE ALTERATION	INTERPRETATION

Potential Treatment Strategies: EGFR activating mutations or amplification may predict sensitivity to EGFR inhibitors, including osimertinib, afatinib, erlotinib, gefitinib, cetuximab, panitumumab, and lapatinib[32,33,34,35,36]. However, strong clinical evidence indicates that the EGFR T790M mutation confers resistance to gefitinib and erlotinib[5], and preclinical studies indicate that cells expressing EGFR T790M are resistant to lapatinib[37,38]. T790M has also been reported in 48% (20/42) of patients with acquired afatinib resistance[6], suggesting patients with T790M may be less responsive to this therapy[6,39,40]; however, disease control rates of more than 50% have been reported for patients with erlotinib- or gefitinib-resistant NSCLC treated with afatinib[41], including T790M-positive patients[42]. A combination of afatinib and cetuximab has shown clinical efficacy for T790M-positive NSCLC[43,44], although careful dosing may be required[44,45]. Third-generation EGFR inhibitors, such as osimertinib and rociletinib, selectively target mutated forms of EGFR including EGFR T790M; osimertinib is FDA approved to treat patients with EGFR T790M-positive advanced NSCLC who have progressed on EGFR inhibitor therapy[32]. Osimertinib and rociletinib, respectively, achieved objective response rates (ORR) of 61% and 59% in T790M-positive cases and 21% and 29% in T790M-negative cases[32,46]. Resistance to EGFR inhibition may arise by reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may retard the development of acquired resistance to third-generation EGFR inhibitors[47,48,49]. Necitumumab is an anti-EGFR antibody that is FDA approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin. Addition of necitumumab increased overall and progression-free survival in patients with squamous NSCLC relative to chemotherapy alone; however, it exhibited a poor tolerability profile in non-squamous NSCLC, and EGFR expression has not been demonstrated to be predictive of clinical benefit in NSCLC[50,51]. Preclinical studies have reported that EGFR-mutant cells are sensitive to HSP90 inhibitors[52,53,54,55]. Clinical studies of HSP90 inhibitors, alone and in combination with EGFR inhibitors, have reported response rates ranging from 0% to 18% in patients with NSCLC harboring EGFR mutations (Garon et al., 2012; ASCO Abstract 7543)[56,57,58,59], although combination treatment was deemed too toxic[59]. The reovirus Reolysin, which targets cells that harbor activated RAS signaling due to alterations in RAS genes or upstream activators such as EGFR[60,61,62], is also in clinical trials in some tumor types. A trial of Reolysin in combination with paclitaxel and carboplatin in patients with NSCLC harboring activating KRAS or EGFR alterations reported significantly improved response and survival rates compared to assumed historical data for paclitaxel and carboplatin alone[63].

● ***EP300***
Q145*

Gene and Alteration: EP300 encodes p300, a multifunctional regulatory protein with transcriptional coactivation and acetyltransferase activities. P300 is structurally similar to CREBBP and has been implicated in the control of a diverse array of cellular processes, including interferon-mediated transcriptional response to viral infection[64], astrocyte differentiation[65], and DNA repair[66]. P300 cooperates with MDM2 to regulate turnover of the tumor suppressor p53[67].

Frequency and Prognosis: Gene fusions conjoining EP300 with MLL have been identified in acute myeloid leukemia (AML) with t(11; 22)(q23; q13) chromosomal rearrangements[68], and infrequent somatic mutations of EP300 have been documented in several cancer types, including B-cell lymphoma[69], colorectal cancer[70], bladder cancer[71], esophageal squamous cell carcinoma[72], and cervical squamous cell carcinoma[73]. High tumor tissue expression of p300 has been linked with unfavorable outcomes in breast[74,75], colorectal[76], prostate[77], laryngeal[78], nasopharyngeal[79], non-small cell lung[80], small cell lung[81], hepatocellular[82], and esophageal squamous cell[83] carcinomas. A study of 327 patients with melanoma found a correlation between high expression of BRAF and cytoplasmic p300 and disease progression[84].

GENE ALTERATION	INTERPRETATION
	Potential Treatment Strategies: There are no targeted therapies available to address genomic alterations in EP300, but the use of histone deacetylase inhibitors is being investigated in clinical trials recruiting patients with either lymphoma or urothelial carcinoma harboring EP300 alterations.
● ***KEAP1*** R362Q	**Gene and Alteration:** KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate-specificity for a CUL3-dependent ubiquitin ligase[85]. This regulation is affected through suppression of NRF2, a transcription factor encoded by NFE2L2[86,87,88]. Inactivation of KEAP1 is hypothesized to promote tumor survival through constitutive activation of cytoprotective proteins normally regulated as part of the oxidative stress response. This hypothesis is strengthened by the observation that many tumors lacking KEAP1 mutations instead exhibit NFE2L2 mutations which prevent NRF2 recognition, and therefore polyubiquitination, by KEAP1/CUL3 E3 ligase[89]. KEAP1 mutations may be hypomorphic with respect to activating NRF2 but have been associated with DPP3 overexpression, which can result in a more complete activation of NRF2[88]. **Frequency and Prognosis:** Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[90]. NRF2 activation has been associated with poor prognosis in patients with head and neck squamous cell carcinoma (HNSCC)[91]. **Potential Treatment Strategies:** There are no targeted therapies available to address inactivating mutations of KEAP1; however, loss of KEAP1 function may stabilize NRF2 and a number of compounds that inhibit NRF2 are being evaluated preclinically[92]. Additionally, KEAP1 mutation has been identified as a potential biomarker for sensitivity to combined AKT- and TXNRD1-inhibition in lung cancer[93].
● ***RB1*** S829*	**Gene and Alteration:** RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[94,95]. RB1 alterations that disrupt or remove the pocket domain (aa 373-771) and/or the C-terminal domain (aa 773-928), such as observed here, are predicted to be inactivating[96,97,98,99,100,101,102]. Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases diagnosed worldwide per year[103]. Germline mutations in RB1 account for approximately 40% of RB tumors[104] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[105,106]. In the appropriate clinical context, germline testing of RB1 is recommended. **Frequency and Prognosis:** In the TCGA dataset, RB1 mutation was observed in 4% of lung adenocarcinoma cases and RB1 homozygous deletion was observed in 3% of cases[107]. Functional Rb inactivation, by mutation, dysregulated phosphorylation, aberrant promoter methylation of other tumor suppressor genes, or homozygous deletion, is found in most non-small cell lung cancer (NSCLC) cases[108]. A study reported that Rb expression was correlated with poor prognosis in patients with Stage 1 or 2 non-squamous NSCLC[109]. **Potential Treatment Strategies:** Preclinical studies are investigating possible therapies to address Rb inactivation, exploring avenues such as Aurora kinase inhibitors, BCL2 family inhibitors, and NOTCH pathway activation[110,111,112]. Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in preclinical studies and in patients with bladder or breast cancer[95,113]. Rb loss or inactivation predicts resistance to CDK4/6 inhibitors, such as palbociclib, abemaciclib, or ribociclib, which act upstream of Rb[114,115,116,117,118].

GENE ALTERATION	INTERPRETATION
● ***SMAD4*** Q256*	**Gene and Alteration:** SMAD4 encodes a transcription factor downstream of TGF-beta[119]. SMAD4, also known as DPC4 or MADH4, was first identified in a screen for tumor suppressors in pancreatic cancer[120]. SMAD4 alterations that result in loss or disruption of the MH1 domain (amino acids 18-142), MH2 domain (amino acids 323-552), or SAD domain (amino acids 275-320), such as observed here, are predicted to be inactivating[121,122,123,124,125,126,127,128,129,130,131,132,133,134]. Germline mutations of SMAD4 are commonly seen in juvenile polyposis syndrome, which is associated with an increased risk of gastrointestinal cancers[135]. **Frequency and Prognosis:** In the Lung Adenocarcinoma TCGA dataset, SMAD4 mutations and deletion have been found in 3% and 2% of cases, respectively[107]. Loss or mutation of proteins in the TGF-beta pathway, which includes SMAD4, is believed to play a role in lung cancers, and restoration of this pathway has been shown to reduce tumorigenicity[136,137,138]. Numerous studies in a variety of cancers have associated decreased SMAD4 expression or loss of SMAD4 protein with poor prognosis, poor patient survival, and/or tumor metastasis[139,140,141,142,143,144,145]. **Potential Treatment Strategies:** There are no therapies available to address SMAD4 loss or mutation in cancer. Some studies suggest that pancreatic tumors with low SMAD4 protein expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[146,147].
● ***TP53*** splice site 672G>A	**Gene and Alteration:** Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[148]. Mutations affecting the DNA binding domain (aa 100-292), the tetramerization domain (aa 325-356), or the C-terminal regulatory domain (aa 356-393), such as observed here, are thought to disrupt the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[149,150,151,152]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[153,154,155,156,157,158]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[159] to 1:20,000[158], and in the appropriate clinical context, germline testing of TP53 is recommended. **Frequency and Prognosis:** TP53 is one of the most commonly mutated genes in lung cancer, and mutations in this gene have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[107,160,161,162,163] and specifically in 45% of lung adenocarcinoma samples[164,165]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[166]. **Potential Treatment Strategies:** There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor AZD1775[167,168,169,170], therapies that reactivate mutant p53 such as APR-246[171], or p53 gene therapy and immunotherapeutics such as SGT-53[172,173,174,175] and ALT-801 (Hajdenberg et al., 2012; ASCO Abstract e15010). Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer (Oza et al., 2015; ASCO Abstract 5506). Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel (Leijen et al., 2015; ASCO Abstract 2507). In a Phase 1 clinical trial, 8 of 11 evaluable patients receiving SGT-53 as a single agent exhibited stable disease[176]. Clinical trials of SGT-53 in combination with chemotherapy are underway. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[177]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53 (Kumar et al., 2012; AACR Abstract 2874). Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

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GENE ALTERATION	INTERPRETATION

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THERAPIES

FDA-APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Osimertinib	**Approved Indications:** Osimertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI) that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved to treat patients with metastatic EGFR T790M-positive non-small cell lung cancer (NSCLC) and disease progression on or after EGFR TKI therapy. **Gene Association:** EGFR TKI-sensitizing mutations and/or the EGFR T790M mutation may predict sensitivity to osimertinib[32,178]. T790M-positive patients showed higher response rates than T790M-negative cases in a Phase 1 study for patients with acquired EGFR TKI resistance (61% vs. 21%)[32]. **Supporting Data:** Osimertinib has been studied primarily for the treatment of EGFR-mutant NSCLC. Phase 2 studies of osimertinib demonstrated objective response rates (ORR) of 57-61% and disease control rates (DCR) of 90-92% for patients with T790M-positive advanced NSCLC who had progressed on prior EGFR TKI therapy; most objective responses (96%) were ongoing at the median 4-month follow-up (Yang et. al., 2015; WCLC Abstract 943, Mitsudomi et al., 2015; WCLC Abstract 1406). In the Phase 1 expansion cohort with the approved dose of osimertinib (80 mg), the ORR was 54% (32/59), the median duration of response was 12.4 months, and the median progression-free survival (PFS) was 13.5 months for patients with T790M-positive NSCLC (Janne et al., 2015; DOI: 10.1093/annonc/mdv128.05). This trial reported an ORR of 21% and median PFS of 2.8 months for T790M-negative cases with acquired EGFR TKI resistance[32]. Treatment-naïve patients with EGFR-mutant NSCLC achieved an ORR of 60% (18/30) and a DCR of 93% (28/30) (Ramalingnam et al., 2015; ASCO Abstract 8000). A Phase 1b study combined osimertinib with the investigational immunotherapy durvalumab, MEK inhibitor selumetinib, or MET inhibitor savolitinib, and observed partial responses (PR) for each of the combinations (9/14 PR with durvalumab, 9/23 PR with selumetinib, 6/11 PR with savolitinib) (Ramalingam et al., 2015; ASCO Abstract 2509). Osimertinib is being compared with erlotinib or gefitinib as first-line treatment for EGFR-mutant NSCLC (NCT02296125).

THERAPIES ASSOCIATED WITH LACK OF RESPONSE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Erlotinib	**Approved Indications:** Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved for the treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer. **Gene Association:** EGFR activating mutations or amplification may predict sensitivity to erlotinib. However, the EGFR T790M mutation has been associated with resistance to erlotinib, leading to the suggestion that these drugs will not be effective a tumor that contains the T790M mutation, particularly in patients who have already received erlotinib or gefitinib[5]. **Supporting Data:** The approval of erlotinib in NSCLC is based on a Phase 3 randomized trial demonstrating prolonged overall survival for unselected patients with NSCLC treated with erlotinib compared to standard chemotherapy[179]. Furthermore, several randomized Phase 3 trials have shown a significant improvement in response and progression-free survival for this class of medications compared with combination chemotherapy in patients with known EGFR mutations. This includes the EURTAC trial of erlotinib vs. platinum-based chemotherapy[33].

Gefitinib	**Approved Indications:** Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. **Gene Association:** EGFR activating mutations or amplification may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and progression-free survival for patients with EGFR-mutated NSCLC treated with gefitinib, compared to chemotherapy[180,181,182,183,184,185]. However, the EGFR T790M mutation has been associated with resistance to gefitinib, leading to the suggestion that these drugs will not be effective in a tumor that contains the T790M mutation, particularly in patients who have already received erlotinib or gefitinib[5]. **Supporting Data:** Gefitinib achieved an objective response rate of 69.8% and an overall survival of 19.2 months as first-line treatment of Caucasian patients with NSCLC and EGFR sensitizing mutations, which were mostly EGFR exon 19 deletions and EGFR L858R[34]. In the retrospective analysis of a Phase 3 study in Asia, gefitinib increased progression-free survival in a subgroup of patients with EGFR mutation-positive NSCLC as compared with carboplatin/paclitaxel doublet chemotherapy (hazard ratio for progression 0.48)[183,186].

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Cetuximab	**Approved Indications:** Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS wild-type metastatic colorectal cancer (CRC). **Gene Association:** EGFR activating mutations or amplification may confer sensitivity to EGFR inhibitory antibodies such as cetuximab. **Supporting Data:** In previously untreated patients with non-small cell lung cancer (NSCLC), the FLEX study demonstrated that in NSCLC tumors with high expression of EGFR, treatment with cetuximab plus chemotherapy resulted in longer overall survival compared to chemotherapy alone[36]. There was no clear association between cetuximab response and EGFR mutations in the FLEX trial[36]. In a Phase 2 study of 31 patients with Stage 3 NSCLC, addition of cetuximab to radiotherapy and chemotherapy produced an overall response rate of 67%; EGFR gene copy number was not predictive of efficacy outcome[187]. A Phase 3 study of 938 patients with progressive NSCLC after platinum-based therapy concluded that, in unselected patients, the addition of cetuximab to chemotherapy was not recommended in this second-line setting[188]. Cetuximab is also being studied as part of a therapeutic regimen for patients with EGFR mutations who develop secondary resistance to erlotinib or gefitinib. A Phase 1b study combining afatinib and the anti-EGFR antibody cetuximab in patients with advanced EGFR-mutant lung cancer with acquired resistance to erlotinib/gefitinib observed an overall objective response rate of 29%, and comparable response rates in both T790M-positive and T790M-negative tumors (32% vs. 25%)[43]. A Phase 1 study of combination erlotinib and cetuximab treatment in patients with NSCLC, including those with squamous tumors, inhibitor-resistant EGFR mutations, and wild-type EGFR, as well as those who had progressed on prior erlotinib treatment, reported partial responses in two of 20 patients and stable disease lasting at least 6 months in three of 20 patients[189]; however, in this study a patient identified with an exon 19 deletion and T790M progressed rapidly on cetuximab and erlotinib, consistent with predictions based on computational analysis of T790M[190].
Panitumumab	**Approved Indications:** Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of KRAS wild-type metastatic colorectal cancer (CRC).

Gene Association: EGFR activating mutations or amplification may confer sensitivity to EGFR inhibitory antibodies such as panitumumab.

Supporting Data: In a Phase 2 trial of advanced non-small cell lung cancer (NSCLC), the addition of panitumumab to paclitaxel/carboplatin did not result in improved clinical benefit[191], and subsequent studies investigating the addition of panitumumab to pemetrexed/cisplatin reported no benefit for patients with wild-type KRAS lung adenocarcinoma[192]. The combination of afatinib and panitumumab has been explored for 2 patients with EGFR T790M NSCLC, with 1 partial response reported[45].

Genomic alterations detected may be associated with activity of certain 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
● ***EGFR*** G598V, L858R, T790M	Activating mutations in EGFR have been shown to confer sensitivity to EGFR inhibitors. However, the presence of the T790M resistance mutation suggests that some inhibitors will be ineffective. Other agents, including third generation EGFR inhibitors and HSP90 inhibitors, may be relevant. 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 "EGFR", "cetuximab", "panitumumab", "osimertinib", "BIBW 2992", "CO-1686", "AZD9291", "PF-00299804", "HSP90", "reolysin", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase 1/2 Open-Label Study Of PF-06747775 (Epidermal Growth Factor Receptor T790M Inhibitor) In Patients With Advanced Epidermal Growth Factor Receptor (EGFR) Mutant (Del 19 Or L858R +/- T790M) Advanced Non-Small Cell Lung Cancer	Phase 1/Phase 2	EGFR	California, Connecticut, Pennsylvania, Washington, Seoul (Korea, Republic of)	NCT02349633
A Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Combination With Ascending Doses of Novel Therapeutics in Patients With EGFRm+ Advanced NSCLC Who Have Progressed Following Therapy With an EGFR TKI	Phase 1	EGFR, PD-L1, MEK	Georgia, Massachusetts, New York, Tennessee, Chuo-ku (Japan), Goyang-si (Korea, Republic of), Habikino-shi (Japan), Hirakata-shi (Japan), Kashiwa-shi (Japan), Nagoya-shi (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Tainan (Taiwan), Taipei (Taiwan)	NCT02143466
A Phase I/II, Multicenter, Open-label Study of EGFRmut-TKI EGF816, Administered Orally in Adult Patients With EGFRmut Solid Malignancies	Phase 1/Phase 2	EGFR	Massachusetts, New York, Catalunya (Spain), Fukuoka (Japan), Koeln (Germany), Korea (Korea, Republic of), Madrid (Spain), Ontario (Canada), Singapore (Singapore), Taiwan ROC (Taiwan)	NCT02108964
A Phase 1B Study of AZD9291 in Combination With Navitoclax in EGFR-Mutant Non-small Cell Lung Cancer Following Resistance to Initial EGFR Kinase Inhibitor	Phase 1	EGFR, BCL2	Colorado, Massachusetts	NCT02520778
Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients With	Phase 3	EGFR	(Argentina), (Australia), (Austria), (Belgium), (Brazil), (Canada), (China), (Denmark),	NCT02474355

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Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy With an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)			(Ireland), (Italy), (Korea, Republic of), (Mexico), (Saudi Arabia), (Spain), (Sweden), (Switzerland), (Taiwan), (United Arab Emirates), (United Kingdom)	

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.

C11orf30	***EGFR***	***GABRA6***	***JUN***	***MDM4***	***NPM1***
R205M	P266Q	G191V	L61F	A398V	K250E
NTRK2	***PRKDC***				
S167Y	L1707Q				

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.

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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

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