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 #	SRF201601	**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[II]

3 genomic alterations

5 therapies associated with potential clinical benefit

0 therapies associated with lack of response

8 clinical trials

[II] Reduced sensitivity due to sample quality – See Appendix: Performance Specifications for details.

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified[†]

ERBB2 amplification
CDK12 deletion exon 2
TP53 deletion exons 2-9

Additional Disease-relevant Genes with No Reportable Alterations Identified[†]

EGFR
KRAS
ALK
BRAF
MET
RET
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
ERBB2 amplification	Afatinib	Ado-trastuzumab emtansine Lapatinib Pertuzumab Trastuzumab	Yes, see clinical trials section
CDK12 deletion exon 2	None	None	Yes, see clinical trials section
TP53 deletion exons 2-9	None	None	None

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Electronically Signed by James Suh, M.D. | Jeffrey S. Ross, M.D., Medical Director | CLIA Number: 22D2027531 | 01 July 2016

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.

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GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
● ***ERBB2*** amplification	**Gene and Alteration:** ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[1]. **Frequency and Prognosis:** In the TCGA datasets, ERBB2 amplification or mutation was observed in 6% of lung adenocarcinoma cases[2]. HER2 overexpression has been documented in 11-32% of non-small cell lung cancers (NSCLC), and is higher in lung adenocarcinomas (38%) than in squamous cell (16%) and large cell (17.9%) tumors[3,4]. A tendency toward shorter survival has been observed in patients with NSCLC harboring ERBB2 amplification and strong HER2 protein expression[5]. **Potential Treatment Strategies:** Based on extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[6,7,8,9,10,11], pertuzumab in combination with trastuzumab[8,12,13], and ado-trastuzumab emtansine (T-DM1)[14], as well as dual EGFR/HER2 kinase inhibitors such as lapatinib[15,16,17,18], afatinib[11,19,20,21,22], neratinib[23,24], and dacomitinib[25]. In patients with breast cancer, concurrent PIK3CA or PTEN alterations that activate the PI3K pathway have been associated with resistance to therapies that target HER2, including trastuzumab and lapatinib[26,27,28,29,30]. However, other studies have reported conflicting results, with one study suggesting that neither PIK3CA nor PTEN alteration is associated with trastuzumab resistance[31], and another study reporting a correlation between PIK3CA mutation and increased clinical response to the combination of letrozole and lapatinib[32]. Clinical trials of agents aimed at preventing or overcoming resistance to anti-HER2 therapies are under way, including agents targeting the PI3K-AKT pathway or HSP90[33,34].
● ***CDK12*** deletion exon 2	**Gene and Alteration:** CDK12 encodes a cyclin-dependent kinase that interacts with cyclin K to regulate the phosphorylation of RNA polymerase II and the expression of genes involved in maintaining genomic stability, including BRCA1 and ATR[35]. Cells lacking CDK12 incur spontaneous DNA damage and exhibit heightened sensitivity to DNA-damaging agents[36,37,38,39]. CDK12 also reportedly interacts with cyclin L1 to regulate alternative splicing[40]. **Frequency and Prognosis:** Homozygous mutations in CDK12 have been identified in approximately 3% of ovarian carcinomas, supporting a role for CDK12 as a tumor suppressor in this tumor type[41,42]. CDK12 rearrangements resulting in truncation have also been reported in 13% of HER2-positive breast cancers[37], and CDK12-ERBB2 fusions leading to truncation of CDK12 have been identified in gastric cancers[43]. **Potential Treatment Strategies:** PARP inhibitors have been shown to be an effective treatment for ovarian, breast, pancreatic, and prostate tumors with BRCA1/2 alterations, indicating that this approach may be relevant for tumors with defects in homologous recombination[44,45,46,47,48]. Preclinical studies suggest that CDK12 truncations and inactivating mutations that affect the kinase domain (amino acids 719-1051) impair homologous recombination, and sensitize cells to PARP inhibitors[36,37,38,39]. However, the functional effect of mutations that do not disrupt the kinase domain is unknown. CDK12 amplification has also been reported in several cancer types (cBioPortal, 2016), but it is unlikely that PARP inhibitors would be relevant in tumors with CDK12 amplification.

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GENE ALTERATION	INTERPRETATION
● ***TP53*** deletion exons 2-9	**Gene and Alteration:** Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[49]. 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[50,51,52,53]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[54,55,56,57,58,59]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[60] to 1:20,000[59], 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)[2,61,62,63,64] and specifically in 45% of lung adenocarcinoma samples[65,66]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[67]. **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[68,69,70,71], therapies that reactivate mutant p53 such as APR-246[72], or p53 gene therapy and immunotherapeutics such as SGT-53[73,74,75,76] 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[77]. 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[78]. 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.

THERAPIES

FDA-APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Afatinib	**Approved Indications:** Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the treatment of metastatic non-small cell lung cancer (NSCLC) in patients with EGFR exon 19 deletions or exon 21 (L858R) missense mutations. **Gene Association:** ERBB2 amplification or activating mutations may indicate sensitivity to afatinib. **Supporting Data:** Phase 3 clinical trials have demonstrated that treatment with afatinib, compared to chemotherapy, leads to significantly increased progression-free survival for patients with EGFR-mutant NSCLC[79,80], and increased overall survival (OS) for patients with EGFR exon 19 alterations specifically[81]. A Phase 3 trial comparing afatinib with erlotinib as second-line therapies for advanced lung squamous cell carcinoma reported significantly higher OS (7.9 months vs. 6.8 months) and disease control rate (DCR) (51% vs. 40%) for patients treated with afatinib[82]. Phase 2/3 studies of afatinib treatment for patients with erlotinib- or gefitinib-resistant NSCLC have generally reported partial responses (PRs) of only 7-9%[22,83,84,85,86,87], and DCRs of more than 50%[22]; in particular, disease control was achieved for 2/2 patients with EGFR-amplified NSCLC[22] and 9/14 patients with T790M-positive NSCLC[87]. The T790M mutation has been implicated in reduced response to afatinib[86,88,89], with a secondary T790M mutation reported in 48% (20/42) of patients with afatinib-resistant lung adenocarcinoma[88]. The combination of afatinib with cetuximab resulted in a higher response rate (29%) for patients with erlotinib- or gefitinib-resistant disease[90], including T790M-positive cases[90,91], although adverse reactions may be a concern with this combination[92]. Upon progression on afatinib, further benefit has been reported from combination treatment with afatinib and paclitaxel[93].

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Ado-trastuzumab emtansine	**Approved Indications:** Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, inhibiting HER2 signaling[94,95]; it also releases the cytotoxic therapy DM1 into cells, leading to cell death[95,96]. T-DM1 is FDA approved for the treatment of HER2-positive (HER2+), metastatic breast cancer. **Gene Association:** ERBB2 amplification may predict sensitivity to T-DM1.

	Supporting Data: A patient with non-small cell lung cancer, disease progression on two prior lines of chemotherapy, and an activating ERBB2 alteration (exon 20 insertion) experienced a rapid and durable response to T-DM1[97,98]. The vast majority of data on the therapeutic use of T-DM1 has been collected in the context of breast cancer, although clinical trials investigating T-DM1 are underway in several tumor types, primarily in HER2+ cancers. A Phase 3 trial in 602 patients with HER2+ breast cancer reported that those who received T-DM1 showed an improved progression-free survival (PFS) and a lower rate of adverse events than patients who received the physician's choice of therapy[99]. A second Phase 3 trial in 991 patients with HER2+ breast cancer reported that T-DM1 brought about significantly longer overall survival (OS) and PFS, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab plus a taxane[14,100]. Two separate Phase 2 trials reported robust activity for single-agent T-DM1 as a treatment for HER2+ metastatic breast cancer in patients previously treated with standard HER2-directed therapies or HER2-directed therapies plus chemotherapy, with objective response rates of 34.5% and 25.9%, respectively, and PFS of 6.9 months and 4.9 months, respectively[101,102].
Lapatinib	**Approved Indications:** Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer. **Gene Association:** ERBB2 amplification may predict sensitivity to lapatinib. **Supporting Data:** In preclinical assays, lapatinib reduced cell proliferation in vitro and reduced the number and size of tumors in mouse xenograft models of EGFR- and ERBB2-amplified non-small cell lung cancer (NSCLC) cells[103]. A Phase 1 study of single-agent lapatinib included 9 unselected patients with lung cancer and reported 1 case of prolonged stable disease[104]. In a Phase 2 trial in patients with advanced or metastatic NSCLC, lapatinib monotherapy did not result in significant tumor reduction, but further investigation of lapatinib in combination with other therapies may be warranted[105].
Pertuzumab	**Approved Indications:** Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is FDA approved in combination with trastuzumab and docetaxel to treat a subset of patients with HER2-positive (HER2+) breast cancer[12]. **Gene Association:** ERBB2 amplification or activating mutations may predict sensitivity to pertuzumab. **Supporting Data:** In a Phase 1 study of pertuzumab in advanced cancer, 2/19 patients reported partial responses and 6/19 patients reported stable disease after two cycles, including one patient with lung cancer[106]. In another Phase 1 study in Japanese patients with solid tumors, no responses were observed and stable disease was reported in 1 of 7 patients with NSCLC[107]. In a Phase 2 study of pertuzumab in NSCLC, no responses were observed and the progression-free survival was 6.1 weeks[108]. Phase 1 and 2 trials of pertuzumab in combination with erlotinib in NSCLC have reported a response rate of 20% (3/15, 2 of the responders had mutant EGFR)[109]; a reduction in circulating tumor cells was noted and correlated with reduction in tumor size[110]. In a Phase 2 study of pertuzumab plus erlotinib in relapsed patients with NSCLC, PET-CT imaging showed that the primary endpoint of response rate (RR) was met in 19.5% of all patients (n = 41) and in 8.7% of patients with wild-type EGFR NSCLC (n = 23); however, 68.3% (28/41) of patients showed treatment-related grade 3 (or higher) adverse events[111].
Trastuzumab	**Approved Indications:** Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved for the treatment of breast cancers or metastatic gastric or gastroesophageal adenocarcinomas that overexpress HER2. **Gene Association:** ERBB2 amplification or activating mutations may confer sensitivity to trastuzumab.

Supporting Data: A Phase 2 clinical trial of docetaxel with trastuzumab in non-small cell lung cancer (NSCLC) reported partial responses in 8% of patients; response did not correlate with HER2 status as assessed by immunohistochemistry[112]. Another Phase 2 study of 169 patients with NSCLC reported an objective response rate of 23% (7/30 patients) in the patients treated with a combination therapy of docetaxel and trastuzumab, and 32% (11/34) in patients treated with paclitaxel and trastuzumab[113]. HER2 expression did not impact the results of this study[113]. A patient with lung adenocarcinoma that was HER-positive by FISH and harbored an ERBB2 G776L mutation experienced a partial response on trastuzumab and paclitaxel[9]. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported in 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy[11].

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
● ***ERBB2*** amplification	ERBB2 amplification or activating mutations may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of chemotherapy or other targeted therapies, such as HSP90 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "ERBB2", "HER2", "trastuzumab", "lapatinib", "pertuzumab", "ado-trastuzumab emtansine", "afatinib", "HSP90", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase I Active Immunotherapy Trial With a Combination of Two Chimeric (Trastuzumab-like and Pertuzumab-like)Human Epidermal Growth Factor Receptor 2 (HER-2) B Cell Peptide Vaccine Emulsified in ISA 720 and Nor-MDP Adjuvant in Patients With Advanced Solid Tumors	Phase 1	ERBB2	Ohio	NCT01376505
Phase I Trial Evaluating Safety and Tolerability of the Irreversible Epidermal Growth Factor Receptor Inhibitor Afatinib (BIBW 2992) in Combination With the SRC Kinase Inhibitor Dasatinib for Patients With Non-small Cell Lung Cancer (NSCLC)	Phase 1	SRC, BCR-ABL, EPHA, KIT, PDGFRs, LYN, EGFR, ERBB2, ERBB4	Florida	NCT01999985
My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents	Phase 2	EGFR, ERBB2, BRAF, SMO	Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Virginia, Washington	NCT02091141
Targeted Agent and Profiling Utilization Registry (TAPUR) Study	Phase 2	CDK4, CDK6, Others	Michigan, North Carolina	NCT02693535

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***CDK12*** deletion exon 2	Preclinical data suggests that tumors with CDK12 mutation or loss may be sensitive to PARP 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 "CDK12", "PARP", "olaparib", "rucaparib", "BMN 673", "ABT-888", "veliparib", "E7449", "niraparib", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase 1 Trial of ABT-888 and SCH727965 in Patients With Advanced Solid Tumors	Phase 1	PARP, CDK1, CDK2, CDK5, CDK9	Massachusetts	NCT01434316
An Early Phase 1 Study of ABT-888 in Combination With Carboplatin and Paclitaxel in Patients With Hepatic or Renal Dysfunction and Solid Tumors	Phase 1	PARP	California, Maryland, Massachusetts, Michigan, New Jersey, New York, Pennsylvania, Texas, Wisconsin	NCT01366144
A Phase I Multi-centre Trial of the Combination of Olaparib (PARP Inhibitor) and AZD5363 (AKT Inhibitor) in Patients With Advanced Solid Tumours	Phase 1	PARP, AKT	Newcastle upon Tyne (United Kingdom), Surrey (United Kingdom)	NCT02338622
A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD6738 in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies.	Phase 1	PARP, PD-L1, ATR	California, New York, London (United Kingdom), Manchester (United Kingdom), Seoul (Korea, Republic of), Sutton (United Kingdom), Villejuif (France)	NCT02264678

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.

CDK12	***PALB2***	***TNFAIP3***
amplification	T397S	T647P

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.

[II] Reduced Sensitivity: Although we can definitively confirm the presence of the genomic alterations detailed in this report, the data obtained may have been insufficient for comprehensive detection of genomic alterations. Reduced sensitivity may be due to poor sample quality or, in rare cases, to patient transplant history.

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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