FOUNDATIONONE™

Patient Name	Report Date	Diagnosis
Agenor, Gethro	**29 March 2013**	**Stomach GIST**

Date of Birth	20 October 1954	**Client**	Boston Medical Center	**Specimen Received**	18 March 2013
Gender	Male	**Ordering Physician**	Eton, Omar	**Specimen Site**	Not Provided
FMI Case #	TRF009601	**Additional Recipient**	Carmen Sarita Peyes	**Date of Collection**	15 March 2013
Medical Record #	2794528	**FMI Client #**	200411	**Specimen Type**	Block
Specimen ID	S13-2531 A4	**Pathologist**	Not Provided		

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

2 genomic alterations

8 therapies associated with potential clinical benefit

0 therapies associated with lack of response

4 clinical trials

TUMOR TYPE: STOMACH GIST

Genomic Alterations Identified†

KIT Q556_V560del
CRKL amplification

Additional Disease-relevant Genes with No Reportable Alterations Detected
PDGFRA

†For a complete list of the genes assayed, 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
KIT Q556_V560del	Imatinib Sunitinib	Dasatinib Everolimus Nilotinib Pazopanib Sorafenib Temsirolimus	Yes, see clinical trials section
CRKL amplification	None	Dasatinib	Yes, see clinical trials section

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
KIT Q556_V560del	The KIT gene encodes the tyrosine kinase receptor Kit (also known as c-Kit or CD117), which is expressed on the cell surface of a variety of cell types, including hematopoietic stem cells and melanocytes. Binding of the Kit ligand SCF leads to Kit dimerization and activation of the PI3K/Akt and Ras/MAPK signaling pathways that regulate cellular proliferation and survival (Linnekin, 1999; 10582339). KIT Q556_V560del results in a deletion of amino acids 556-560, which are encoded by exon 11 and are located within the Kit cytoplasmic juxtamembrane domain, a "hotspot" region for KIT alterations (COSMIC, Mar 2013). Several mutations within this region have been reported to be activating (Hirota et al., 1998; 9438854, Chan et al., 2003; 12697809, Allander et al., 2001; 11751374, Rubin et al., 2001; 11719439, Tarn et al., 2005; 15897563). Therefore, this deletion is expected to lead to Kit activation. KIT mutations have been observed in up to 80% of GISTs, and almost all tumors studied exhibit overexpression of the Kit oncogene (COSMIC, Mar 2013) (Hirota et al., 1998; 9438854, Corless et al., 2011; 22089421). The kinase inhibitors imatinib and sunitinib are approved to treat GIST, and the kinase inhibitors sorafenib, dasatinib, nilotinib, and pazopanib, which are approved in other indications, are in clinical trials for patients with GIST. Preclinical studies have also demonstrated that activation of Kit leads to activation of downstream pathways including MAPK, PI3K/Akt, STAT, and mTOR (Duensing et al., 2004; 15007386, Rossi et al., 2006; 16908864, Sápi et al., 2011; 21326036, Ríos-Moreno et al., 2011; 21868553). Patients with GISTs harboring exon 11 mutations have been found to be most responsive to imatinib, compared to patients with KIT mutations at other locations, but have also been reported to be at higher risk for the development of secondary mutations (Cameron et al., 2010; 19294538, Pelz et al., 2011; 21237497, Wardelmann et al., 2006; 16551858, Joensuu, 2006; 17018739). The combination of first line kinase inhibitors with new therapies such as switch kinase inhibitors, or MEK, PI3K, mTOR, and Hsp90 inhibitors, may be a useful strategy to target kinase inhibitor resistant GIST.
CRKL amplification	CRKL encodes a protein that has been shown to mediate growth, motility, and adhesion in solid tumor cells (Yanagi et al., 2012; 22244889). In the Sarcoma Genome Project dataset, putative amplification of CRKL has been found in only 1.4% (3/207) of all of the soft tissue sarcoma cases analyzed and has not been found in the subset of 22 gastrointestinal stromal tumor (GIST) cases (The cBio Cancer Genomics Portal, http://www.cbioportal.org, Mar 2013). CRKL amplification has not been a significant subject of study in GISTs in the general scientific literature (PubMed, Mar 2013). Studies in NSCLC and gastric cancer cells have linked CRKL amplification and overexpression with increased cell proliferation via upregulation of the cell cycle and with tumorigenesis (Wang et al., 2012; 22753141, Natsume et al., 2012; 22591714, Cheung et al., 2011; 22586683). In NSCLC, CRKL overexpression was shown to correlate with advanced stage, metastasis, and reduced overall survival (Wang et al., 2012; 22753141). At the present time there are no approved therapies that directly target CRKL. However, preclinical studies in NSCLC and gastric cancer cells have suggested CRKL as a therapeutic target (Natsume et al., 2012; 22591714, Cheung et al., 2011; 22586683). Preclinical studies reported that gastric cancer cell lines with CRKL amplification were sensitive to the Src/Bcr-Abl kinase inhibitor BMS354825 (dasatinib), which was suggested to be due to inhibition of CRKL phosphorylation (Natsume et al., 2012; 22591714). Dasatinib has been approved for use in CML and ALL and is currently under clinical investigation in solid tumors. In NSCLC with EGFR mutation, CRKL amplification has been shown to be a mechanism of acquired resistance to Egfr tyrosine kinase inhibitors (Suda et al., 2012; 22736441, Cheung et al., 2011; 22586683).

THERAPIES

FDA APPROVED THERAPIES IN PATIENT'S TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Imatinib	Imatinib is a small molecule tyrosine kinase inhibitor that targets the Bcr-Abl fusion protein, PDGFR, and Kit. Imatinib has been FDA-approved for treatment for Kit-positive GIST, for Ph+ CML and ALL, for MDS/MPS, for aggressive systematic mastocytosis without a D816V KIT mutation, for hypereosinophilic syndrome and/or chronic eosinophilic leukemia, and for dermatofibrosarcoma protuberans. Activating mutations in KIT may confer sensitivity to tyrosine kinase inhibitors such as imatinib.
Sunitinib	Sunitinib is a small molecule tyrosine kinase inhibitor that targets Pdgfr-alpha, Pdgfr-beta, Vegfr1/2/3, Kit, Flt3, Csf-1R, and Ret. Sunitinib has been FDA-approved for the treatment of GIST after progression on imatinib, for advanced renal cell carcinoma, and advanced or metastatic pancreatic neuroendocrine tumors. Activating mutations in KIT may confer sensitivity to tyrosine kinase inhibitors such as sunitinib.

ADDITIONAL THERAPIES – FDA APPROVED IN OTHER TUMOR TYPES

THERAPY	RATIONALE
Dasatinib	Dasatinib is a kinase inhibitor that targets the Bcr-Abl fusion protein, Src family kinase receptors, Kit, EPHA2, and Pdgfr-beta. Dasatinib has been FDA-approved for the treatment of Ph+ CML in chronic phase, Ph+ CML in myeloid or lymphoid blast phase with resistance to prior therapy including imatinib, and Ph+ ALL with resistance to prior therapy. Activating mutations in KIT may confer sensitivity to tyrosine kinase inhibitors such as dasatinib. Amplification of CRKL has been associated with response to dasatinib in gastric cancer cell lines (Natsume et al., 2012; 22591714), and may predict sensitivity to dasatinib in other tumor types. Dasatinib is currently in clinical trials in multiple tumor types. Preclinical studies of a mouse model of GIST showed that combined treatment with imatinib and dasatinib resulted in the arrest of tumor cell growth and an increase in cell death, and also a decrease in Kit and Akt phosphorylation (Rossi et al., 2010; 20736294).
Everolimus	Everolimus is an orally available mTOR inhibitor that has been approved for use in renal cell carcinoma, pancreatic neuroendocrine tumors, subependymal giant cell astrocytoma associated with TSC, and hormone receptor positive, HER2 negative advanced breast cancer. Activating mutations in KIT have been shown to result in activation of the mTOR pathway in a subset of tumors (Duensing et al., 2004; 15007386, Rossi et al., 2006; 16908864). Therefore, tumors with KIT activating mutations may be sensitive to treatment with everolimus. A Phase 2 trial of everolimus and imatinib reported some response to the drug combination, but due to increasing treatment options for imantinib-resistant GIST, the second stage of the trial was not continued (Hohenberger et al., 2010; ASCO Absract 10048). Another Phase 2 trial of everolimus in combination with imatinib also reported some activity in imatinib-resistant GIST patients; in patients with disease progression after imatinib only, 36% exhibited stable disease (SD), and in patients with disease progression after imatinib and sunitinib or another tyrosine kinase inhibitor, 2% exhibited partial response and 43% had SD. In addition, the predetermined efficacy criteria of 4-month progression-free survival were achieved, indicating that this combination warrants further investigation as a third-line therapy in GIST patients after failure of imatinib and sunitinib (Schöffski et al., 2010; 20507881).
Nilotinib	Nilotinib is a kinase inhibitor that targets the Bcr-Abl fusion protein by binding to the Abl kinase domain, and also Pdgfr, Kit, Csf-1R, and DDRIa. Nilotinib has been FDA-approved for the treatment of Ph+ CML in chronic phase, and Ph+ CML in chronic or accelerated blast phase with resistance to prior therapy including imatinib. Activating mutations in KIT may confer sensitivity to tyrosine kinase inhibitors such as nilotinib. Nilotinib is currently under clinical investigation in multiple tumor types. A Phase 2 clinical trial showed that nilotinib was well tolerated and suggested that it may be particularly useful in treating a subset of GIST with KIT exon 17 mutations (Cauchi et al., 2012; 22119758).

Pazopanib	Pazopanib is a tyrosine kinase inhibitor that targets Vegfr1/2/3, Pdgfr-alpha, Fgfr1/3, Kit, Itk, Lck, and c-Fms. Pazopanib has been FDA-approved for the treatment of advanced renal cell carcinoma and soft tissue sarcomas that have progressed after prior chemotherapy. Activating mutations in KIT may confer sensitivity to tyrosine kinase inhibitors such as pazopanib. Pazopanib is currently in clinical trials in multiple tumor types. Pazopanib is under investigation in clinical trials as a second line treatment for patients with GIST who have progressed after prior treatment with imatinib and sunitinib (reviewed in Demetri 2011; 21419931).
Sorafenib	Sorafenib is a kinase inhibitor that targets the intracellular kinases Braf (WT and mutant) and Craf, and the cell surface kinases Kit, Flt3, Ret, Vegfr1/2/3, Pdgfr-alpha, and Pdgfr-beta. Sorafenib is FDA-approved for the treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma. Activating mutations in KIT may confer sensitivity to tyrosine kinase inhibitors such as sorafenib. Sorafenib is currently in clinical trials in multiple tumor types. A Phase 2 clinical trial reported that sorafenib treatment of GIST patients, who had progressed after prior treatment with both imatinib and sunitinib, resulted in a disease control rate of 36%, with 13% of patients achieving a partial response, and 52% achieving stable disease at 24 weeks (Park et al., 2012; 22270258).
Temsirolimus	Temsirolimus is an intravenous mTOR inhibitor that has been approved for use in advanced renal cell carcinoma. Activating mutations in KIT have been shown to result in activation of the mTOR pathway in a subset of tumors (Duensing et al., 2004; 15007386, Rossi et al., 2006; 16908864). Therefore, tumors with KIT activating mutations may be sensitive to treatment with temsirolimus. Temsirolimus is being studied in clinical trials in multiple tumor types.

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 continuously 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
KIT Q556_V560del	KIT activating mutations may predict sensitivity to small molecule tyrosine kinase inhibitors. Also, because Kit activation leads to activation of the PI3K/Akt and mTOR pathways, PI3K and mTOR pathway inhibitors may be relevant in a tumor with Kit activation. Hsp90 inhibitors are also being studied in Phase 2 clinical trials for patients whose tumors are resistant to imatinib and sunitinib. A search of the trial website clinicaltrials.gov, using terms such "KIT", "PI3K", "mTOR", "HSP90", "imatinib", "GIST", and/or "solid tumor", retrieves more than 10 trials that may be relevant for this patient's tumor. Examples of these trials are shown below.

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Prospective, Multicenter, Randomized, Open-label, Active-controlled, 2-parallel Group, Phase III Study to Compare Efficacy and Safety of Masitinib at 7.5 mg/kg/Day to Imatinib at 400 or 600 mg in Treatment of Patients With Gastro-intestinal Stromal Tumour in First Line Medical Treatment	Phase 3	BCR-ABL, KIT, PDGFR	Florida, Georgia, Michigan, New York, Ohio, South Carolina, Wisconsin, Abbeville (France), Avignon (France), Beirut (Lebanon), Besançon (France), Bordeaux (France), Brest (France), Créteil (France), Dijon (France), Dreux (France), Evreux (France), Gap (France), La Roche sur Yon (France), La Rochelle (France), Libourne (France), Lille (France), Lyon (France), Marseille (France), Metn (Lebanon), Montpellier (France), Nantes (France), Orléans (France), Paris (France), Reims (France), Rouen (France), Saida (Lebanon), Saint Brieuc (France), Saint-Cloud (France), St Priez-en-Jarez (France)	NCT00812240
A Multi-arm Dose-finding Phase Ib Multicenter Study of Imatinib in Combination With the Oral Phosphatidyl-inositol 3-kinase (PI3-K) Inhibitor BKM120 in Patients With Gastrointestinal Stromal Tumor (GIST) Who Failed Prior Therapy With Imatinib and Sunitinib	Phase 1	BCR-ABL, c-kit (CD117), PDGFR, PI3K	Massachusetts, New York, Washington, Alberta (Canada), MI (Italy), Barcelona (Spain), Berlin (Germany), Leiden (Netherlands), Leuven (Belgium), London (United Kingdom), Lyon Cedex (France), Manchester (United Kingdom), Muenchen (Germany), Villejuif Cedex (France)	NCT01468688

CLINICAL TRIALS TO CONSIDER (CONT.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
CRKL amplification	Amplification of CRKL has been associated with response to the Src/Bcr-Abl kinase inhibitor BMS354825 (dasatinib) in gastric cancer cell lines, and may predict sensitivity to dasatinib in other tumor types. A search of the trial website clinicaltrials.gov, using terms such as "dasatinib", "GIST", and/or "solid tumor", retrieves fewer than 10 trials that may be relevant for this patient's tumor. Examples of these trials are shown below.

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase I Pharmacokinetic Study of Dasatinib (BMS-354825) (NSC-732517; IND-73969) in Patients With Advanced Malignancies and Varying Levels of Liver Dysfunction	Phase 1	BCR-ABL, c-kit (CD117), EphA2, PDGFR, SRC	California, Michigan, Texas, Washington	NCT00608361
A Phase I Study of Dasatinib in Combination With Bevacizumab in Advanced Solid Tumors	Phase 1	BCR-ABL, c-kit (CD117), EphA2, PDGFR, SRC, VEGF	Maryland	NCT01445509

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 236 genes as well as 47 introns of 19 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

ABL1	AKT1	AKT2	AKT3	ALK	APC	AR	ARAF	ARFRP1	ARID1A	ARID2	ASXL1	ATM
ATR	ATRX	AURKA	AURKB	AXL	BAP1	BARD1	BCL2	BCL2L2	BCL6	BCOR	BCORL1	BLM
BRAF	BRCA1	BRCA2	BTK	CARD11	CBFB	CBL	CCND1	CCND2	CCND3	CCNE1	CD79A	CD79B
CDC73	CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2
CIC	CREBBP	CRKL	CRLF2	CSF1R	CTCF	CTNNA1	CTNNB1	DAXX	DDR2	DNMT3A	DOT1L	EGFR
EMSY (C11orf30)	EP300	EPHA3	EPHA5	EPHB1	ERBB2	ERBB3	ERBB4	ERG	ESR1	EZH2	FAM123B (WTX)	FAM46C
FANCA	FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FBXW7	FGF10	FGF14	FGF19	FGF23	FGF3
FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FLT1	FLT3	FLT4	FOXL2	GATA1	GATA2	GATA3
GID4 (C17orf39)	GNA11	GNA13	GNAQ	GNAS	GPR124	GRIN2A	GSK3B	HGF	HRAS	HSP90AA1	IDH1	IDH2
IGF1R	IKBKE	IKZF1	IL7R	INHBA	IRF4	IRS2	JAK1	JAK2	JAK3	JUN	KAT6A (MYST3)	KDM5A
KDM5C	KDM6A	KDR	KEAP1	KIT	KLHL6	KRAS	LRP1B	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MCL1
MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLL	MLL2	MPL	MRE11A	MSH2
MSH6	MTOR	MUTYH	MYC	MYCL1	MYCN	MYD88	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1
NOTCH2	NPM1	NRAS	NTRK1	NTRK2	NTRK3	NUP93	PAK3	PALB2	PAX5	PBRM1	PDGFRA	PDGFRB
PDK1	PIK3CA	PIK3CG	PIK3R1	PIK3R2	PPP2R1A	PRDM1	PRKAR1A	PRKDC	PTCH1	PTEN	PTPN11	RAF1
RARA	RB1	RET	RICTOR	RNF43	ROS1	RPTOR	RUNX1	SETD2	SF3B1	SMAD2	SMAD4	SMARCA4
SMARCB1	SMO	SOCS1	SOX10	SOX2	SPEN	SPOP	SRC	STAG2	STAT3	STAT4	STK11	SUFU
TET2	TGFBR2	TNFAIP3	TNFRSF14	TOP1	TP53	TSC1	TSC2	TSHR	VHL	WISP3	WT1	XPO1
ZNF217	ZNF703											

Select Rearrangements

ALK	BCL2	BCR	BRAF	EGFR	ETV1	ETV4	ETV5	ETV6	EWSR1	MLL	MYC	NTRK1
PDGFRA	RAF1	RARA	RET	ROS1	TMPRSS2							

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APPENDIX

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APPENDIX

ABOUT THE TEST

Foundation Medicine Test: FoundationOne (Test) was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). The Test 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. The Test 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/Lack of Significance of Reported Biomarkers: Foundation Medicine's Test identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Test identifies biomarkers that lack detectable evidence of cancer- associated alterations. These alterations (and, in some cases, lack of alterations) are reported to a patient's treating physician in this report (Report).

The Report incorporates analyses of peer-reviewed studies and other publicly available information provided to Foundation Medicine by N-of-One, Inc. (N-of-One); 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. Additional information from N-of-One is available on its website at www.n-of-one.com

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 the Test.

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.