FOUNDATIONONE™ Heme

Patient Name	Report Date	Tumor Type
Patient, Test	**25 August 2016**	**PEDIATRIC Bone osteosarcoma**

Date of Birth	12 December 2002	**Medical Facility**	ABC Oncology		
Sex	Male	**Ordering Physician**	Smith, John	**Specimen Received**	21 July 2016
FMI Case #	SMP37669	**Additional Recipient**	Not Given	**Specimen Site**	Blood
Medical Record #	12345678	**Medical Facility ID #**	200313	**Date of Collection**	08 December 2016
Specimen ID	Not Given	**Pathologist**	Public, John Q	**Specimen Type**	Block

ABOUT THE TEST:

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

PATIENT RESULTS[‖]

3 genomic findings

1 therapy associated with potential clinical benefit

0 therapies associated with lack of response

10 clinical trials

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

TUMOR TYPE: PEDIATRIC BONE OSTEOSARCOMA

Genomic Alterations Identified[†]

CCND3 amplification – equivocal[#]
CDK4 amplification
MYC amplification

[†] For a complete list of the genes assayed and performance specifications, please refer to the Appendix
[#] See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
CCND3 amplification - equivocal	None	Palbociclib	Yes, see clinical trials section
CDK4 amplification	None	Palbociclib	Yes, see clinical trials section
MYC amplification	None	None	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 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
● ***CCND3*** amplification - equivocal	**Gene and Alteration:** CCND3 encodes cyclin D3, a G1/S-specific cell cycle regulator. Cyclin D3 interacts with and regulates the cyclin-dependent kinases Cdk4 and Cdk6, resulting in the phosphorylation and inactivation of Rb and the progression of the cell cycle[1]. CCND1 amplification correlates with Cyclin D1 overexpression and may lead to excessive proliferation and oncogenic growth[2,3,4,5]. **Frequency and Prognosis:** One study reports frequent high-level amplification of CCND3 in aggressive osteosarcomas (5/6)[6]. Another study reports consistent overexpression of CCND3 in all 13 osteosarcoma patient samples analyzed; 2 of 4 of these samples also showed CCND3 gene amplification[7]. CCND3 overexpression was not correlated with increased cyclin D3 protein levels in this study[7]. Increased expression of Cyclin D3 has been reported in bone and soft tissue sarcomas compared with leiomyomas and normal tissue, suggesting a role for this protein in bone and soft tissue tumors[8]. **Potential Treatment Strategies:** Amplification or activation of CCND3 may predict sensitivity to CDK4/6 inhibitors[9,10,11], such as LEE011, abemaciclib, and the FDA-approved therapy palbociclib, all of which are under investigation in clinical trials (Infante et al., 2014; ASCO Abstract 2528, Shapiro et al., 2013; ASCO Abstract 2500)[12,13].
● ***CDK4*** amplification	**Gene and Alteration:** CDK4 encodes cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[14]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the retinoblastoma tumor suppressor protein (Rb)[3,15]. CDK4 amplification correlates with high CDK4 gene and protein expression[16]. **Frequency and Prognosis:** Amplification of CDK4 has been variously reported in 9-82% of osteosarcoma samples[17,18,19,20,21]. CDK4 amplification has been reported to be relatively rare in conventional high-grade osteosarcoma but frequent in low-grade osteosarcomas, including parosteal osteosarcomas and low-grade central osteosarcomas, suggesting that CDK4 expression may help facilitate subclassification in osteosarcoma[19,20,21]. Deregulation of the G1/S checkpoint genes, including CDK4, and expression of the cyclin D1/CDK4 complex have been associated with poor prognosis in osteosarcoma patients[22,23]. **Potential Treatment Strategies:** Amplification of CDK4 may predict sensitivity to CDK4/6 inhibitors, such as LEE011, abemaciclib, and the FDA-approved therapy palbociclib, all of which are under investigation in clinical trials (Infante et al., 2014; ASCO Abstract 2528, Shapiro et al., 2013; ASCO Abstract 2500)[12,13,24].
● ***MYC*** amplification	**Gene and Alteration:** MYC (c-MYC) encodes a transcription factor that regulates several genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[25]. MYC deregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[26]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[25,27,28]. **Frequency and Prognosis:** MYC amplification has been reported in 16% of osteosarcoma cases and has been significantly associated with poor prognosis[18]. In osteosarcoma, MYC amplification has been observed frequently with alterations of RB1[18]. c-Myc expression has been observed in up to 86% (48/56) of osteosarcomas, and has also been correlated with a poor prognosis[29].

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GENE ALTERATION	INTERPRETATION

Potential Treatment Strategies: There are no available therapies that directly target MYC. However, preclinical studies have suggested several synthetic lethal strategies to indirectly target MYC; these studies have shown that cells that overexpress MYC protein may be sensitive to CDK1, CDK2, or Aurora kinase B inhibitors, including those that are under investigation in clinical trials[30,31,32,33,34]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a partial response to an Aurora kinase inhibitor[35]. Furthermore, in numerous preclinical studies, inhibition of BET bromodomain-containing proteins, in particular BRD4, has been reported to downregulate MYC expression and MYC-dependent gene expression programs in a variety of hematopoietic and solid tumor cancer models and primary cells[36,37,38]. Phase 1 trials of the BET inhibitor OTX015 in patients with hematological malignancies reported clinical activity in patients with acute myeloid leukemia (AML) or lymphoma (Herait et al., 2015; TAT Abstract O7.3, Dombret et al., 2014; ASH Abstract 117, Thieblemont et al., 2014; ASH Abstract 4417). On the basis of preclinical (Sun et al., 2016; AACR Abstract 4634)[39,40] and limited clinical (Younes et al., 2015; ASH Abstract 257)[41] data, MYC alterations that lead to increased expression of MYC may predict sensitivity to combinatorial inhibition of HDAC and PI3K in diffuse large B-cell lymphoma (DLBCL); it is not clear whether this approach would be beneficial in other cancer types. MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[42,43]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[44,45].

THERAPIES

There are no therapies FDA-approved in this patient's tumor type that are specific to the reported genomic alterations.

ADDITIONAL THERAPIES – FDA-APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Palbociclib	**Approved Indications:** Palbociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination with letrozole as first-line therapy for postmenopausal women or in combination with fulvestrant following progression on endocrine therapy. **Gene Association:** Clinical studies in liposarcoma and mantle cell lymphoma as well as responses in patients with breast cancer or melanoma indicate that activation of cyclin D-CDK4/6 may predict sensitivity to therapies such as palbociclib (Infante et al., 2014; ASCO Abstract 2528)[13,46,47]. **Supporting Data:** Palbociclib has not been extensively studied in the context of osteosarcoma (PubMed, May 2016). Palbociclib has been studied primarily for the treatment of ER+ breast cancer[24,48,49]. Single-agent palbociclib has shown limited activity against solid tumors, with a Phase 1 study reporting no partial responses (PR) and a 16% (6/37) stable disease (SD) rate (>9 months)[12]. Phase 2 trials of palbociclib in patients with KRAS-mutant colorectal cancer or p16INK4a-deficient non-small cell lung cancer (NSCLC) also reported no responses, although SD was seen in 33% (5/15) and 50% (8/16) of patients, respectively (O'Hara et al., 2015; ASCO GI Abstract 626, Gopalan et al., 2014; ASCO Abstract 8077). A Phase 2 study of palbociclib for the treatment of advanced Rb-positive hepatocellular carcinoma reported disease control (responses or stable disease) for 9/21 (43%) patients, including one patient with a PR; the trial has met its primary endpoint (Littman et al., 2015; ASCO GI Abstract 277). For various tumor types, preclinical studies suggest that palbociclib may be useful in combination with other therapies targeting oncogenic drivers such as MEK, BRAF, PI3K, or IGF1R[50,51,52,53,54]. Multiple preclinical studies demonstrate that loss or inactivation of Rb predicts resistance to palbociclib[55,56,57,58].

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

CLINICAL TRIALS TO CONSIDER

IMPORTANT: While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not meant to be a complete list of available trials. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***CCND3*** amplification - equivocal	CCND3 amplification may predict sensitivity to CDK4/6 inhibitors.Due to the limited number of clinical trials available for pediatric patients, clinical trials recruiting adults only are listed below for informational purposes.Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "CDK4", "CDK6", "PD 0332991", "LEE011", "LY2835219", "palbociclib", "child", "osteosarcoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Targeted Agent and Profiling Utilization Registry (TAPUR) Study	Phase 2	CDK4, CDK6, Others	Michigan, North Carolina	NCT02693535
Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer	Phase 2	CDK4, CDK6	Pennsylvania	NCT01037790
Abemaciclib in Children With Newly Diagnosed Diffuse Intrinsic Pontine Glioma, and in Children With Recurrent and Refractory Solid Tumors Including Malignant Brain Tumors	Phase 1	CDK4, CDK6	Georgia	NCT02644460
A Phase I Study of the CDK4/6 Inhibitor PD-0332991, 5-Fluorouracil, and Oxaliplatin in Patients With Advanced Solid Tumor Malignancies	Phase 1	CDK4, CDK6	District of Columbia	NCT01522989
Modular Phase II Study to Link Targeted Therapy to Patients With Pathway Activated Tumors: Module 8 - LEE011 for Patients With CDK4/6 Pathway Activated Tumors	Phase 2	CDK4, CDK6	Texas	NCT02187783

CLINICAL TRIALS TO CONSIDER (cont.)

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
● ***CDK4*** amplification	Amplification of CDK4 may predict sensitivity to CDK4/6 inhibitors.Due to the limited number of clinical trials available for pediatric patients, clinical trials recruiting adults only are listed below for informational purposes.Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "CDK4", "CDK6", "PD 0332991", "LEE011", "LY2835219", "palbociclib", "child", "osteosarcoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I Study of the CDK4/6 Inhibitor PD-0332991, 5-Fluorouracil, and Oxaliplatin in Patients With Advanced Solid Tumor Malignancies	Phase 1	CDK4, CDK6	District of Columbia	NCT01522989
Modular Phase II Study to Link Targeted Therapy to Patients With Pathway Activated Tumors: Module 8 - LEE011 for Patients With CDK4/6 Pathway Activated Tumors	Phase 2	CDK4, CDK6	Texas	NCT02187783
PIPA: A Phase Ib Study to Assess the Safety, Tolerability and Efficacy of the PI3K Inhibitors, Taselisib (GDC-0032) or Pictilisib (GDC-0941), in Combination With PAlbociclib, With the Subsequent Addition of Fulvestrant in PIK3CA-mutant Breast Cancers	Phase 1	CDK4, CDK6, PI3K	London (United Kingdom)	NCT02389842
Abemaciclib in Children With Newly Diagnosed Diffuse Intrinsic Pontine Glioma, and in Children With Recurrent and Refractory Solid Tumors Including Malignant Brain Tumors	Phase 1	CDK4, CDK6	Georgia	NCT02644460
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
● ***MYC*** amplification	Several strategies are under investigation to address amplification or overexpression of MYC in human cancer. These strategies include inhibition of CDKs, especially CDK1 and CDK2; Aurora kinases, particularly Aurora kinase B; as well as BET inhibitors, reported to down-regulate MYC expression and MYC-dependent transcriptional programs in a variety of human cancer models.Due to the limited number of clinical trials recruiting pediatric patients, the list below may include trials that are only recruiting adult patients at this time.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 "MYC", "BET", "BRD4", "CDK1", "CDK2", "Aurora kinase B", "AZD1152", "AMG 900", "GSK1070916A", "BMS 777607", "chiauranib", "dinaciclib", "SCH727965", "BAY 1000394", "CS-2164", "CPI-0610", "I-BET762", "GSK525762", "GSK1324726A", "TEN-010", "RVX-208", "OTX015", "child", "osteosarcoma", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054329 in Subjects With Advanced Malignancies	Phase 1/Phase 2	BRD2, BRD3, BRD4	California, Colorado, Illinois, Indiana, Michigan, Missouri, Tennessee, Texas, Washington	NCT02431260
Phase 1 Trial of ABT-888 and SCH727965 in Patients With Advanced Solid Tumors	Phase 1	CDK1, CDK2, CDK5, CDK9, PARP	Massachusetts	NCT01434316
A Two Part, Phase 1, Multicenter, Open-label Study of TEN-010 Given Subcutaneously. Part A: A Dose-Escalation Study in Patients With Advanced Solid Tumors. Part B: An Expansion Cohort in Patients With Selected Malignancies.	Phase 1	BRD2, BRD3, BRD4, BRDT	Connecticut, Massachusetts, Michigan, Ohio	NCT01987362
A Phase I/IIa Trial With BMS-986158, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects With Selected Advanced Solid Tumors	Phase 1/Phase 2	BRD2, BRD3, BRD4, BRDT	California, Ontario (Canada), Victoria (Australia)	NCT02419417

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.

HDAC1
R77S

HDAC7
R166H

MYCN
S369N

NFE2L2
N262S

NUP98
E1303G

PIM1
amplification

RAD21
amplification

TLL2
L441F

Tumor Mutation Burden
TMB-Low; 0.73 Muts/Mb

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APPENDIX

GENES ASSAYED IN FOUNDATIONONE HEME

FoundationOne Heme is designed to include all genes known to be somatically altered in human hematologic malignancies, sarcomas, and pediatric cancers 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 utilizes DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA Gene List: Entire Coding Sequence for the Detection of Base Substitutions, Insertion/Deletions, and Copy Number Alterations

ABL1	*ACTB*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1*	*APC*	*APH1A*	*AR*	*ARAF*	*APFRP1*	*ARHGAP26*
ARID1A	*ARID2*	*ASMTL*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*	*B2M*	*BAP1*
BARD1	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*	*BCL7A*	*BCOR*	*BCORL1*	*BIRC3*	*BLM*	*BRAF*	*BRCA1*
BRCA2	*BRD4*	*BRIP1*	*BRSK1*	*BTG2*	*BTK*	*BTLA*	*C11orf30*	*CAD*	*CALR**	*CARD11*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CCT6B*	*CD22*	*CD274*	*CD36*	*CD58*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*
CIC	*CIITA*	*CKS1B*	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*	*CTCF*	*CTNNA1*	*CTNNB1*	*CUX1*
CXCR4	*DAXX*	*DDR2*	*DDX3X*	*DNM2*	*DNMT3A*	*DOT1L*	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*
EGFR	*ELP2*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*	*ERG*	*ESR1*	*ETS1*
ETV6	*EXOSC6*	*EZH2*	*FAF1*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*	*FANCG*	*FANCL*	*FAS*
FBXO11	*FBXO31*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FHIT*	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*	*FOXL2*	*FOXO1*	*FOXO3*	*FOXP1*	*FRS2*	*GADD45B*
GATA1	*GATA2*	*GATA3*	*GID4*	*GNA11*	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GSK3B*	*GTSE1*
HDAC1	*HDAC4*	*HDAC7*	*HGF*	*HIST1H1C*	*HIST1H1D*	*HIST1H1E*	*HIST1H2AC*	*HIST1H2AG*	*HIST1H2AL*	*HIST1H2AM*	*HIST1H2BC*	*HIST1H2BJ*
HIST1H2BK	*HIST1H2BO*	*HIST1H3B*	*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*	*IDH1*	*IDH2*	*IGF1R*	*IKBKE*	*IKZF1*
IKZF2	*IKZF3*	*IL7R*	*INHBA*	*INPP4B*	*INPP5D*	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KIT*	*KLHL6*	*KMT2A*
KMT2B	*KMT2C*	*KRAS*	*LEF1*	*LRP1B*	*LRRK2*	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*	*MAP2K2*	*MAP2K4*
MAP3K1	*MAP3K14*	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEF2C*	*MEN1*	*MET*
MIB1	*MITF*	*MKI67*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*	*MSH6*	*MTOR*	*MUTYH*	*MYC*	*MYCL*
MYCN	*MYD88*	*MYO18A*	*NCOR2*	*NCSTN*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*	*NOTCH1*	*NOTCH2*
NPM1	*NRAS*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*	*NUP98*	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*
PAX5	*PBRM1*	*PC*	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2*	*PDGFRA*	*PDGFRB*	*PDK1*	*PHF6*	*PIK3CA*
PIK3CG	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*	*POT1*	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*
PTPN11	*PTPN2*	*PTPN6*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*	*RARA*	*RASGEF1A*	*RB1*	*RELN*	*RET*
RHOA	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*RUNX1*	*S1PR2*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SERP2*	*SETBP1*
SETD2	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA1*	*SMARCA4*	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*	*SOCS1*	*SOCS2*
SOCS3	*SOX10*	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*	*STAG2*	*STAT3*	*STAT4*	*STAT5A*	*STAT5B*	*STAT6*
STK11	*SUFU*	*SUZ12*	*TAF1*	*TBL1XR1*	*TCF3*	*TCL1A*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*	*TMSB4XP8*	*TNFAIP3*
TNFRSF11A	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*	*TRAF2*	*TRAF3*	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*
TYK2	*U2AF1*	*U2AF2*	*VHL*	*WDR90*	*WHSC1*	*WISP3*	*WT1*	*XBP1*	*XPO1*	*YY1AP1*	*ZMYM3*	*ZNF217*
ZNF24	*ZNF703*	*ZRSR2*										

**Note: the assay was updated on 11/8/2016 to include the detection of alterations in CALR*

DNA Gene List: For the Detection of Select Rearrangements

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*	*EPOR*	*ETV1*	*ETV4*	*ETV5*	*ETV6*
EWSR1	*FGFR2*	*IGH*	*IGK*	*IGL*	*JAK1*	*JAK2*	*KMT2A*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*
RARA	*RET*	*ROS1*	*TMPRSS2*	*TRG*								

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RNA Gene List: For the Detection of Select Gene Fusions

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFF1*	*AFF4*	*ALK*	*ARHGAP26*	*ARHGEF12*	*ARID1A*	*ARNT*	*ASXL1*
ATF1	*ATG5*	*ATIC*	*BCL10*	*BCL11A*	*BCL11B*	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*
BCR	*BIRC3*	*BRAF*	*BTG1*	*CAMTA1*	*CARS*	*CBFA2T3*	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*
CD274	*CDK6*	*CDX2*	*CHIC2*	*CHN1*	*CIC*	*CIITA*	*CLP1*	*CLTC*	*CLTCL1*	*CNTRL*	*COL1A1*
CREB3L1	*CREB3L2*	*CREBBP*	*CRLF2*	*CSF1*	*CTNNB1*	*DDIT3*	*DDX10*	*DDX6*	*DEK*	*DUSP22*	*EGFR*
EIF4A2	*ELF4*	*ELL*	*ELN*	*EML4*	*EP300*	*EPOR*	*EPS15*	*ERBB2*	*ERG*	*ETS1*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*	*FCRL4*	*FEV*	*FGFR1*	*FGFR1OP*	*FGFR2*	*FGFR3*	*FLI1*
FNBP1	*FOXO1*	*FOXO3*	*FOXO4*	*FOXP1*	*FSTL3*	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*HERPUD1*
HEY1	*HIP1*	*HIST1H4I*	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*	*HOXA3*	*HOXA9*	*HOXC11*	*HOXC13*
HOXD11	*HOXD13*	*HSP90AA1*	*HSP90AB1*	*IGH*	*IGK*	*IGL*	*IKZF1*	*IL21R*	*IL3*	*IRF4*	*ITK*
JAK1	*JAK2*	*JAK3*	*JAZF1*	*KAT6A*	*KDSR*	*KIF5B*	*KMT2A*	*LASP1*	*LCP1*	*LMO1*	*LMO2*
LPP	*LYL1*	*MAF*	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MKL1*	*MLF1*	*MLLT1*	*MLLT10*	*MLLT3*
MLLT4	*MLLT6*	*MN1*	*MNX1*	*MSI2*	*MSN*	*MUC1*	*MYB*	*MYC*	*MYH11*	*MYH9*	*NACA*
NBEAP1	*NCOA2*	*NDRG1*	*NF1*	*NF2*	*NFKB2*	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NTRK1*
NTRK2	*NTRK3*	*NUMA1*	*NUP214*	*NUP98*	*NUTM2A*	*OMD*	*P2RY8*	*PAFAH1B2*	*PAX3*	*PAX5*	*PAX7*
PBX1	*PCM1*	*PCSK7*	*PDCD1LG2*	*PDE4DIP*	*PDGFB*	*PDGFRA*	*PDGFRB*	*PER1*	*PHF1*	*PICALM*	*PIM1*
PLAG1	*PML*	*POU2AF1*	*PPP1CB*	*PRDM1*	*PRDM16*	*PRRX1*	*PSIP1*	*PTCH1*	*PTK7*	*RABEP1*	*RAF1*
RALGDS	*RAP1GDS1*	*RARA*	*RBM15*	*RET*	*RHOH*	*RNF213*	*ROS1*	*RPL22*	*RPN1*	*RUNX1*	*RUNX1T1*
RUNX2	*SEC31A*	*SEPT5*	*SEPT6*	*SEPT9*	*SET*	*SH3GL1*	*SLC1A2*	*SNX29*	*SRSF3*	*SS18*	*SSX1*
SSX2	*SSX4*	*STAT6*	*STL*	*SYK*	*TAF15*	*TAL1*	*TAL2*	*TBL1XR1*	*TCF3*	*TCL1A*	*TEC*
TET1	*TFE3*	*TFG*	*TFPT*	*TFRC*	*TLX1*	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*	*TPM3*
TPM4	*TRIM24*	*TRIP11*	*TTL*	*TYK2*	*USP6*	*WHSC1*	*WHSC1L1*	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*
ZNF521											

Additional Assays : For the Detection of Select Cancer Biomarkers

Tumor Mutation Burden

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APPENDIX

FOUNDATIONONE HEME PERFORMANCE SPECIFICATIONS

SENSITIVITY	Base Substitutions at ≥5% Minor Allele Frequency	>99%
	Insertions/Deletions (1-40 base pairs) at ≥10% Minor Allele Frequency	98%
	Focal Copy Number Alterations (homozygous deletions or amplifications ≥8 copies)	>95%
	Known Gene Fusions	>95%
SPECIFICITY	Positive Predictive Value (PPV) for Base Substitutions, Insertions/Deletions, and Focal Copy Number Alterations	>99%
	Positive Predictive Value (PPV) for Known Gene Fusions	>95%
ACCURACY	Tumor Mutation Burden accuracy at ≥20% tumor nuclei	>90%
REPRODUCIBILITY	Concordance between replicates inter-batch	97%
	Concordance between replicates intra-batch	97%
	Tumor Mutation Burden precision	96%

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).

Tumor Mutation Burden (TMB) is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne and FoundationOne Heme tests and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne and FoundationOne Heme samples. TMB-High results are reported in all tumor types. In select tumor types, other TMB results may be reported (TMB-Intermediate, TMB-Low, TMB-Unknown) when relevant. TMB results are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (Muts/Mb); TMB-Intermediate corresponds to 6-19 Muts/Mb; TMB-Low corresponds to less than or equal to 5 Muts/Mb. Tumor Mutation Burden may be reported as "Unknown" if the sample is not of sufficient quality to confidently determine Tumor Mutation Burden.

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 or the receipt of only a pre-extracted DNA sample, precluding RNA sequencing. Any Tumor Mutation Burden (TMB) value (Muts/Mb) shown on a report with reduced sensitivity reflects an estimate of the lowest possible TMB.

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APPENDIX

ABOUT FOUNDATIONONE HEME™

FoundationOne Heme™: FoundationOne Heme (the 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: FoundationOne Heme 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 FoundationOne Heme 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 Heme 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 FoundationOne Heme data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that FoundationOne Heme 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 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.

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 Heme is performed using DNA and RNA 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 4, *TNFRSF11A* exon1, and *TP53* exon 1.

FoundationOne Heme complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Heme 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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