FOUNDATIONONE™ Heme

Patient Name	Report Date	Tumor Type
Shrivastava, Tvarita	**24 June 2016**	**PEDIATRIC Soft tissue rhabdomyosarcoma (NOS)**

Date of Birth	05 April 2008	**Medical Facility**	Max Healthcare	**Specimen Received**	13 June 2016
Sex	Female	**Ordering Physician**	Verma, Amit	**Specimen Site**	Pleura
FMI Case #	TRF154823	**Additional Recipient**	Not Given	**Date of Collection**	06 April 2016
Medical Record #	SKMS.0000144534	**Medical Facility ID #**	201107	**Specimen Type**	Block
Specimen ID	S-6763 16A	**Pathologist**	Not Provided		

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[II]

1 genomic alteration

0 therapies associated with potential clinical benefit

0 therapies associated with lack of response

1 clinical trial

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

TUMOR TYPE: PEDIATRIC SOFT TISSUE RHABDOMYOSARCOMA (NOS)

Genomic Alteration Identified[†]

TP53 R249S

[†] 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
TP53 R249S	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
● ***TP53*** R249S	**Gene and Alteration:** Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[1]. 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[2,3,4,5]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[6,7,8,9,10,11]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[12] to 1:20,000[11], and in the appropriate clinical context, germline testing of TP53 is recommended. **Frequency and Prognosis:** TP53 mutations have been reported in 13% of rhabdomyosarcomas (COSMIC, Jun 2016). In a study of rhabdomyosarcomas that screened TP53 exons 5-9, TP53 mutation was reported in 22.2% (10/45) of cases[13]. However, another study reported lower incidence of TP53 mutations in a large collection of rhabdomyosarcoma samples (1/75, 1.3%); exons 4-9 were screened for TP53 mutations in this study[14]. A study examining 75 cases of rhabdomyosarcoma reported p53 overexpression in 31% (22 of 72) of the samples[13]. **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[15,16,17,18], therapies that reactivate mutant p53 such as APR-246[19], or p53 gene therapy and immunotherapeutics such as SGT-53[20,21,22,23] 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[24]. 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[25]. 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

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

There are no therapies FDA-approved in other tumor types that are specific to the reported genomic alterations.

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
● ***TP53*** R249S	Tumors with TP53 loss of function alterations may be sensitive to WEE1 inhibitors, or p53 gene therapy and immunotherapeutics. 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 "p53", "AZD1775", "MK1775", "WEE1", "APR-246", "kevetrin", "ALT-801", "SGT-53", "p53MVA", "rhabdomyosarcoma", "child", and/or "solid tumor". 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.

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Phase I Study of SGT-53, a TfRscFv-Liposome-p53 Complex, in Children With Refractory or Recurrent Solid Tumors	Phase 1	TP53	Texas	NCT02354547

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APPENDIX

VARIANTS OF UNKNOWN SIGNIFICANCE

Note: One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations make their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BARD1	***ESR1***	***GPR124***	***HDAC7***	***HIST1H1D***	***MAP3K1***
P358_S364del	A13T	R700W	P409L	E43K	K64Q
MLL	***PCLO***	***PRKDC***	***SPEN***	***ZRSR2***	
E1860D,S2319T	N3983S	S11fs*24	G3464A	S434_R435insRDRS	

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 405 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*	*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*											

DNA Gene List: For the Detection 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											

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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%
REPRODUCIBILITY	Concordance between replicates inter-batch	97%
	Concordance between replicates intra-batch	97%

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 or the receipt of only a pre-extracted DNA sample, precluding RNA sequencing.

APPENDIX

REFERENCES

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

2 Kato S, Han SY, Liu W, et al. (2003) Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc Natl Acad Sci USA 100(14):8424-9.

3 Joerger AC, Fersht AR (2008) Structural biology of the tumor suppressor p53. Annu Rev Biochem 77:557-82.

4 Kamada R, Nomura T, Anderson CW, et al. (2011) Cancer-associated p53 tetramerization domain mutants: quantitative analysis reveals a low threshold for tumor suppressor inactivation. J Biol Chem 286(1):252-8.

5 Kim H, Kim K, Choi J, et al. (2012) p53 requires an intact C-terminal domain for DNA binding and transactivation. J Mol Biol 415(5):843-54.

6 Bougeard G, Renaux-Petel M, Flaman JM, et al. (2015) Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol 33(21):2345-52.

7 Sorrell AD, Espenschied CR, Culver JO, et al. (2013) Tumor protein p53 (TP53) testing and Li-Fraumeni syndrome : current status of clinical applications and future directions. Mol Diagn Ther 17(1):31-47.

8 Nichols KE, Malkin D, Garber JE, et al. (2001) Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 10(2):83-7.

9 Taubert H, Meye A, Würl P (1998) Soft tissue sarcomas and p53 mutations. Mol Med 4(6):365-72.

10 Kleihues P, Schäuble B, zur Hausen A, et al. (1997) Tumors associated with p53 germline mutations: a synopsis of 91 families. Am J Pathol 150(1):1-13.

11 Gonzalez KD, Noltner KA, Buzin CH, et al. (2009) Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol 27(8):1250-6.

12 Lalloo F, Varley J, Ellis D, et al. (2003) Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 361(9363):1101-2.

13 Takahashi Y, Oda Y, Kawaguchi K, et al. (2004) Altered expression and molecular abnormalities of cell-cycle-regulatory proteins in rhabdomyosarcoma. Mod Pathol 17(6):660-9.

14 Ognjanovic S, Martel G, Manivel C, et al. (2012) Low Prevalence of TP53 Mutations and MDM2 Amplifications in Pediatric Rhabdomyosarcoma. Sarcoma 2012:492086.

15 Hirai H, Arai T, Okada M, et al. (2010) MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer Biol Ther 9(7):514-22.

16 Bridges KA, Hirai H, Buser CA, et al. (2011) MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells. Clin Cancer Res 17(17):5638-48.

17 Rajeshkumar NV, De Oliveira E, Ottenhof N, et al. (2011) MK-1775, a potent Wee1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. Clin Cancer Res 17(9):2799-806.

18 Osman AA, Monroe MM, Ortega Alves MV, et al. (2015) Wee-1 kinase inhibition overcomes cisplatin resistance associated with high-risk TP53 mutations in head and neck cancer through mitotic arrest followed by senescence. Mol Cancer Ther 14(2):608-19.

19 Lehmann S, Bykov VJ, Ali D, et al. (2012) Targeting p53 in vivo: a first-in-human study with p53-targeting compound APR-246 in refractory hematologic malignancies and prostate cancer. J Clin Oncol 30(29):3633-9.

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APPENDIX

REFERENCES

20 Xu L, Huang CC, Huang W, et al. (2002) Systemic tumor-targeted gene delivery by anti-transferrin receptor scFv-immunoliposomes. Mol Cancer Ther 1(5):337-46.

21 Xu L, Tang WH, Huang CC, et al. (2001) Systemic p53 gene therapy of cancer with immunolipoplexes targeted by anti-transferrin receptor scFv. Mol Med 7(10):723-34.

22 Camp ER, Wang C, Little EC, et al. (2013) Transferrin receptor targeting nanomedicine delivering wild-type p53 gene sensitizes pancreatic cancer to gemcitabine therapy. Cancer Gene Ther 20(4):222-8.

23 Kim SS, Rait A, Kim E, et al. (2015) A tumor-targeting p53 nanodelivery system limits chemoresistance to temozolomide prolonging survival in a mouse model of glioblastoma multiforme. Nanomedicine 11(2):301-11.

24 Senzer N, Nemunaitis J, Nemunaitis D, et al. (2013) Phase I study of a systemically delivered p53 nanoparticle in advanced solid tumors. Mol Ther 21(5):1096-103.

25 Ma CX, Cai S, Li S, et al. (2012) Targeting Chk1 in p53-deficient triple-negative breast cancer is therapeutically beneficial in human-in-mouse tumor models. J Clin Invest 122(4):1541-52.

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

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