FOUNDATIONONE®HEME

PATIENT
Chang, Shun-Hung

TUMOR TYPE
Soft tissue Ewing sarcoma
COUNTRY CODE
TW

REPORT DATE
23 Jan 2024
ORDERED TEST #
ORD-1789887-02

ABOUT THE TEST FoundationOne® Heme is a comprehensive genomic profiling test designed to identify genomic alterations within hundreds of cancer-related genes in hematologic malignancies and sarcomas.

PATIENT
DISEASE Soft tissue Ewing sarcoma
NAME Chang, Shun-Hung
DATE OF BIRTH 13 May 1991
SEX Male
MEDICAL RECORD # 49827556

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lung
SPECIMEN ID S112-58288E (PF23190)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 17 November 2023
SPECIMEN RECEIVED 29 December 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 7 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

EWSR1 EWSR1-ERG fusion
TP53 S241_C242del

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***EWSR1*** **EWSR1-ERG fusion** (p. 3)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 5)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 7 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
EWSR1 **-** EWSR1-ERG fusion	none	none
10 Trials see p. 5		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

TP53 - S241_C242del ..... p. 4

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.

Electronically signed by Douglas A. Mata, MD, MPH | 23 January 2024
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Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4-5]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[6].

FREQUENCY & PROGNOSIS

In a computational analysis of paired tumor and normal sarcomas in the TCGA dataset, of which 25% were liposarcomas, only 0.8% (2/255) of samples were MSI-high (MSI-H)[7]. However, reports of MSI in sarcomas in the literature are conflicting and varied due to substantial heterogeneity, lack of consensus on the markers and methods used for MSI assessment, and small sample size in most studies[8]. In these smaller studies of soft tissue sarcoma, reports of MSI at any level have been rare, with the highest incidences between 11% (2/18) to 25% (10/40) of cases[9-14]. In Ewing sarcoma, MSI at any level has been reported in 6% (1/18) to 48% (11/23) of cases[15-17] or reported as absent[12,18], and high MSI has been observed in 2% (1/55) to 17% (4/23) of cases[16-17]. Studies of small patient cohorts have not shown a significant correlation between MSI status and survival in Ewing sarcoma[16-17].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA MMR in the tumor[19]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[19-21]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[22-24]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19,21,23-24].

BIOMARKER

Tumor Mutational Burden

RESULT
7 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[25-28], anti-PD-1 therapies[26-30], and combination nivolumab and ipilimumab[31-39]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[25-28,30,40-44]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[40]; similar findings were observed in the KEYNOTE 028 and 012 trials[30]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[44]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[45]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[43]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[25] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[27].

FREQUENCY & PROGNOSIS

Ewing sarcoma harbors a median TMB of 1.7 Muts/Mb, and 0.5% of cases have high TMB (>20 Muts/Mb)[46]. Published data investigating the prognostic implications of TMB levels in Ewing sarcoma are generally limited (PubMed, Jul 2023). In one study, TMB greater than 11 muts/Mb (as measured in tissue samples) was associated with inferior outcomes for patients with Ewing sarcoma, although these patients also harbored alterations associated with poor prognosis, such as STAG2 and TP53 mutations[47].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[48-49] and cigarette smoke in lung cancer[50-51], treatment with temozolomide-based chemotherapy in glioma[52-53], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[54-58], and microsatellite instability[54,57-58]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[27-28,40].

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GENE
EWSR1

ALTERATION
EWSR1-ERG fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapies targeting IGF1R may be relevant for a patient with an EWSR1-ERG fusion. Phase 2 studies of anti-IGF1R antibodies reported response rates of 6-14%[59-61], including a response to the IGF1R inhibitor figitumumab for 17% (1/6) of patients with Ewing sarcoma harboring EWSR1-ERG fusions[60]. However, the presence of EWSR1 fusions alone does not predict response to IGF1R-targeted therapies[62]. In preclinical xenograft models, combinations of IGF1R inhibitors with mTOR inhibitors were reported to have better efficacy than IGF1R single-agent therapy[63-64]. In a Phase 1 study of the IGF1R inhibitor cixutumumab in combination with the mTOR inhibitor temsirolimus for 17 patients with Ewing sarcoma, 1 patient had a CR and 4 patients had PRs[65]. Several preclinical studies have shown that EWSR1-FLI1 sensitizes cells to PARP inhibitors[66-69], and 1 study reported that EWSR1-ERG-driven cell lines were similarly sensitive to PARP inhibitors[67]. However, in a Phase 2 trial in Ewing sarcoma, 0% (0/12) of patients responded to single-agent olaparib[70]. A Phase 1/2 study of olaparib in combination with irinotecan for pediatric patients with advanced sarcoma with either EWSR1-FLI1 (n=22) or EWSR1-ERG fusion (n=4) reported 1 CR, 1 PR, and 7 SDs, 3 of which were prolonged[71]. The combination of PARP inhibitors with either temozolomide or irinotecan was more effective than single-agent olaparib against EWSR1-FLI1 cells in preclinical studies[67-69].

FREQUENCY & PROGNOSIS

Fusions involving EWSR1 are hallmark driver mutations in some types of sarcoma, including Ewing sarcoma and clear cell sarcoma[72-74]. EWSR1-ERG fusions have been reported to occur in ~10% of Ewing sarcoma cases[74-77]. Fusions of ERG, as well as other transcription factors in the ETS family, such as the TMPRSS2-ERG fusion, have also been reported in ~50% of patients with prostate cancer[78]. In one study of Ewing sarcoma, the percentage of patients with metastatic disease at diagnosis was higher for patients with EWSR1/FUS-ERG fusions (44%) compared with EWSR1-FLI1 fusions (30%), but OS did not differ between the two fusion groups[79]. Translocations and deletions of ERG are also seen in some acute myeloid leukemias, and ERG overexpression has been associated with poor prognosis[80-81]. Patients with EWSR1-ERG and EWSR1-FLI1 fusions exhibit significant similarities in their pathological and clinical characteristics, as well as progression-free and overall survival[75,82].

FINDING SUMMARY

EWSR1 (Ewing sarcoma breakpoint region 1) encodes the EWS protein, an RNA binding protein of largely unknown function that has been postulated to play a role in the regulation of hematopoietic stem cells[83]. Rearrangements that result in fusions between the EWSR1 transcriptional activation domain and the DNA binding domains of other transcription factors have been shown to be oncogenic[77,84]. Rearrangements leading to fusion between the N-terminus of EWSR1 that mediates transcriptional activation and the C-terminal ETS domain of ERG that binds DNA, such as observed here, are expected to be oncogenic, as proteins with similar domain composition are able to transform cultured cells and drive tumor formation in mouse xenograft models[84-85].

POTENTIAL DIAGNOSTIC IMPLICATIONS

EWSR1 fusions with partners such as FLI1, ERG, FEV, ETV1, E1AF, ZSG, POU5F1, and others are hallmark driver alterations of Ewing sarcoma and other mesenchymal tumors, including chondrosarcomas, round cell tumors, and myoepithelial tumors (NCCN Soft Tissue Sarcoma Guidelines, v2.2023)[73-77,86-88].

GENE
TP53

ALTERATION
S241_C242del

HGVS VARIANT
NM_000546.4:c.720_725del (p.S241_C242del)

VARIANT CHROMOSOMAL POSITION
chr17:7577555-7577561

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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 adavosertib[89-92] or p53 gene therapy such as SGT53[93-98]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[99]. Phase 2 studies of adavosertib in combination with chemotherapy reported ORRs of 32% (30/94) and 41% (12/29) for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[100-101]. For patients with platinum-sensitive TP53-mutated ovarian cancer, the combination of adavosertib with paclitaxel and carboplatin significantly increased PFS compared with paclitaxel and carboplatin alone (9.9 vs. 8.0 months)[102]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[103]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[104]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[105]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[98]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[106]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[107].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 10-20% of Ewing sarcoma tumors in the literature, although disruption of the p53 pathway is thought to be more frequent[108]. TP53 mutations have been observed in 42% of uterine and 19% of soft tissue sarcoma samples analyzed in the MSK Sarcoma dataset[109]. One small genomic characterization study observed TP53 mutations in 78% (14/18) of bladder sarcoma samples analyzed[110]. TP53 mutation in Ewing sarcoma has been associated with aggressive tumors and poor response to chemotherapy[111-112].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[113]. Alterations such as seen here may disrupt TP53 function or expression[114-118].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[119-121], including sarcomas[122-123]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[124] to 1:20,000[123]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[125]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[126-131]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[126-127]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[132]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[130,133-134]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. 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 a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
EWSR1

ALTERATION
EWSR1-ERG fusion

RATIONALE
Preclinical evidence suggests that cancers with EWSR1-ERG fusion may be sensitive to PARP and IGF1R inhibitors.

NCT04434482

PHASE 1/2

IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Wuhan (China), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of), Cheongju-si (Korea, Republic of), Beijing (China), Jilin (China)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT05824455

PHASE 1/2

A Clinical Study of IMP4297 Capsule (JS109) Combined With Irinotecan in the Treatment of Advanced Malignant Solid Tumors

TARGETS
PARP

LOCATIONS: Guangzhou (China)

NCT05894018

PHASE 2

Brachytherapy (Iodine-125 Seeds) and Fluzoparib Combination Therapy for Advanced Unresectable Soft Tissue Sarcoma

TARGETS
PARP

LOCATIONS: Guangzhou (China)

NCT05952128

PHASE 2

Phase Ib/II Study of Fluzoparib in Combination With Dalpiciclib in Patients With Locally Advanced or Metastatic Sarcoma

TARGETS
PARP, CDK6, CDK4

LOCATIONS: Guangzhou (China)

NCT05938374

PHASE 2

Preoperative Moderately Fractionated IMRT for Locally Extremity or Trunk Sarcoma

TARGETS
PARP

LOCATIONS: Beijing (China)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03784014

PHASE 3

MOLECULAR PROFILING OF ADVANCED SOFT-TISSUE SARCOMAS

TARGETS
ABL, KIT, ROS1, ALK, MET, ERBB2, EGFR, BRAF, MEK, PARP, PD-L1, CDK4, CDK6

LOCATIONS: Strasbourg (France), Dijon (France), Paris (France), Villejuif (France), Lyon (France), Clermont-Ferrand (France), Marseille (France), Saint-Herblain (France), Bordeaux (France)

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: California, Colorado, Illinois, Pennsylvania, Kentucky, Virginia, Texas

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

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 makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future. Please note that some VUS rearrangements between targeted genes and unknown fusion partners or intergenic regions detected by RNA sequencing may not be reported.

ADGRA2 (GPR124)
NM_032777.9: c.3587G>A
(p.C1196Y)
chr8:37699443

CDK12
NM_016507.2: c.4402T>C
(p.Y1468H)
chr17:37687498

ERBB2
NM_004448.2: c.3672C>A
(p.D1224E)
chr17:37884201

EWSR1
rearrangement

HDAC4
NM_006037.3: c.2900G>A
(p.R967Q)
chr2:239988506

KMT2C (MLL3)
NM_170606.2: c.2702T>C
(p.L901P)
chr7:151932969

MKI67
NM_002417.4:
c.7994_8710dup
(p.R2665_R2903dup)
chr10:129901393

MRE11 (MRE11A)
NM_005590.3: c.263C>G
(p.P88R)
chr11:94219141

NTRK1
NM_002529.3: c.824A>C
(p.E275A)
chr1:156841521

NUP98
NM_016320.4: c.3453T>A
(p.N1151K)
chr11:3723752

PCLO
NM_014510.2: c.1861T>A
(p.C621S)
chr7:82784096

RICTOR
NM_152756.3: c.2729G>A
(p.R910H)
chr5:38953624

STAT5A
NM_003152.3: c.916C>T
(p.P306S)
chr17:40452815

FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies and sarcomas 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.

HEMATOLOGICAL MALIGNANCY DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACTB*	*ADGRA2 (GPR124)*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	
APC	*APH1A*	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*		*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*	*CAD*	*CALR**	*CARD11*	*CBFB*	*CBL*
CCN6 (WISP3)	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CCT6B*	*CD22*	*CD274 (PD-L1)*	*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	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*
ERBB4	*ERG*	*ESR1*	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*	*FAF1*	*FANCA*
FANCC	*FANCD2*	*FANCE*	*FANCF*	*FANCG*	*FANCL*	*FAS (TNFRSF6)*	*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 (C17orf39)	*GNA11*	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GRIN2A*	*GSK3B*	*GTSE1*
HDAC1	*HDAC4*	*HDAC7*	*HGF*	*H1-2 (HIST1H1C)*		*H1-3 (HIST1H1D)*		
H1-4 (HIST1H1E)		*H2AC6 (HIST1H2AC)*		*H2AC11 (HIST1H2AG)*		*H2AC16 (HIST1H2AL)*		
H2AC17 (HIST1H2AM)		*H2BC4 (HIST1H2BC)*		*H2BC11 (HIST1H2BJ)*		*H2BC12 (HIST1H2BK)*		
H2BC17 (HIST1H2BO)		*H3C2 (HIST1H3B)*		*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*
IDH1	*IDH2*	*IGF1R*	*IKBKE*	*IKZF1*	*IKZF2*	*IKZF3*	*IL7R*	*INHBA*
INPP4B	*INPP5D (SHIP)*	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*
KEAP1	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*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*	*MRE11 (MRE11A)*
MSH2	*MSH3*	*MSH6*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
MYO18A	*NCOR2*	*NCSTN*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*
NOTCH1	*NOTCH2*	*NPM1*	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NT5C2*	*NTRK1*	*NTRK2*
NTRK3	*NUP93*	*NUP98*	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*	*PAX5*
PBRM1	*PC*	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*		*PDGFRA*
PDGFRB	*PDK1*	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*
PTPN2	*PTPN6 (SHP-1)*	*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 (E2A)*	*TCL1A (TCL1)*	*TENT5C (FAM46C)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*
TMSB4XP8 (TMSL3)		*TNFAIP3*	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*
TRAF2	*TRAF3*	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*

U2AF2	*VHL*	*WDR90*	*WT1*	*XBP1*	*XPO1*	*YY1AP1*	*ZMYM3*	*ZNF217*
ZNF24 (ZSCAN3)	*ZNF703*	*ZRSR2*						

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

HEMATOLOGICAL MALIGNANCY 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 (MLL)*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*	*RARA*
RET	*ROS1*	*TMPRSS2*	*TRG*					

HEMATOLOGICAL MALIGNANCY RNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS*

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFDN (MLLT4 or AF6)*		*AFF1*	*AFF4*	*ALK*
ARHGAP26 (GRAF)		*ARHGEF12*	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*
BCL10	*BCL11A*	*BCL11B*	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*
BCR	*BIRC3*	*BRAF*	*BTG1*	*CAMTA1*	*CARS1 (CARS)*	*CBFA2T3*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CD274 (PD-L1)*	*CDK6*	*CDX2*	*CEP43 (FGFR1OP)*	*CHIC2*	*CHN1*
CIC	*CIITA*	*CLP1*	*CLTC*	*CLTCL1*	*CNTRL (CEP110)*	*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*	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*
FOXO4	*FOXP1*	*FSTL3*	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*H4C9 (HIST1H4I)*
HERPUD1	*HEY1*	*HIP1*	*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 (MYST3)*	*KDSR*	*KIF5B*	*KMT2A (MLL)*	*LASP1*	*LCP1*	*LMO1*	*LMO2*
LPP	*LYL1*	*MAF*	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MLF1*	*MLLT1 (ENL)*
MLLT10 (AF10)	*MLLT3*	*MLLT6*	*MN1*	*MNX1*	*MRTFA (MKL1)*	*MSI2*	*MSN*	*MUC1*
MYB	*MYC*	*MYH11*	*MYH9*	*NACA*	*NBEAP1 (BCL8)*	*NCOA2*	*NDRG1*	*NF1*
NF2	*NFKB2*	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NSD2 (WHSC1 or MMSET)*	
NSD3 (WHSC1L1)	*NTRK1*	*NTRK2*	*NTRK3*	*NUMA1*	*NUP214*	*NUP98*	*NUTM2A*	*OMD*
P2RY8	*PAFAH1B2*	*PAX3*	*PAX5*	*PAX7*	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2 (PD-L2)*
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*
RNF217-AS1 (STL)		*ROS1*	*RPL22*	*RPN1*	*RUNX1*	*RUNX1T1 (ETO)*	*RUNX2*	*SEC31A*
SEPTIN5 (SEPT5)	*SEPTIN6 (SEPT6)*	*SEPTIN9 (SEPT9)*	*SET*	*SH3GL1*	*SLC1A2*	*SNX29 (RUNDC2A)*		*SRSF3*
SS18	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*SYK*	*TAF15*	*TAL1*	*TAL2*
TBL1XR1	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TEC*	*TET1*	*TFE3*	*TFG*	*TFPT*	*TFRC*
TLX1	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*	*TPM3*	*TPM4*	*TRIM24*
TRIP11	*TTL*	*TYK2*	*USP6*	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*	*ZNF521*

*Note: some VUS rearrangements between targeted genes and unknown fusion partners or intergenic regions detected by RNA sequencing may not be reported.

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

ABOUT FOUNDATIONONE HEME

FoundationOne Heme is a comprehensive genomic profiling test for hematologic malignancies and sarcomas. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials and quantitative markers that may support immunotherapy clinical trial enrollment.

FoundationOne Heme was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research.

INTENDED USE

FoundationOne Heme is a next generation sequencing-based *in vitro* diagnostic device for hematologic malignancies and sarcomas. The test is intended for the detection of substitutions, insertion and deletion alterations (indels), copy number alterations (CNAs), and select rearrangements from the complete coding DNA sequences of 406 genes, as well as selected introns of 31 genes using DNA isolated from peripheral blood, bone marrow aspirate (BMA), and formalinfixed paraffin embedded (FFPE) tumor tissue specimens. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across 265 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas. FoundationOne Heme is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with hematologic malignancies and sarcomas.

PERFORMANCE SPECIFICATIONS

Please refer to technical information for performance specification details: https://www.foundationmedicine.qarad.eifu.online/foundationmedicine/en/foundationmedicine.

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.

Diagnostic Significance

FoundationOne Heme identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the 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.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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 Heme.

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 fulfills the requirements of the European Directive 98/79 EC for *in vitro* diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium.

CE

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

MICROSATELLITE STATUS

In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the FoundationOne Heme assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

TUMOR MUTATIONAL BURDEN

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne Heme test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne Heme samples and is reported as the number of mutations per megabase (Muts/Mb). Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 7.15.0
MR Reporting Config Version Config 49
Analysis Pipeline Version v3.29.0
Computational Biology Suite Version 6.29.0

The median exon coverage for this sample is 727x

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