FOUNDATIONONE® HEME

PATIENT | TUMOR TYPE | REPORT DATE

COUNTRY CODE | ORDERED TEST #

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
- NAME
- DATE OF BIRTH
- SEX
- MEDICAL RECORD #

PHYSICIAN
- ORDERING PHYSICIAN
- MEDICAL FACILITY
- ADDITIONAL RECIPIENT
- MEDICAL FACILITY ID
- PATHOLOGIST

SPECIMEN
- SPECIMEN SITE
- SPECIMEN ID
- SPECIMEN TYPE
- DATE OF COLLECTION
- SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

FUS **FUS-DDIT3 fusion (Variant 10)**
EZH2 **Y646C**

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***FUS*** **FUS-DDIT3 fusion (Variant 10)** (p. 4)
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Trabectedin** (p. 6)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 2 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)**
FUS **-** FUS-DDIT3 fusion (Variant 10)	Trabectedin [1]	none
6 Trials see p. 8		
EZH2 **-** Y646C	none	none
1 Trial see p. 7		

[ ] *NCCN category*

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.

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, 25% of which were liposarcomas, only 0.8% (2/255) of samples were MSI-high (MSI-H)[7]. Smaller studies have reported MSI at any level in a subset of liposarcoma patients[8-9] or reported as absent in 21 cases analyzed[10]. Published data investigating the prognostic implications of MSI in liposarcoma are limited (PubMed, Mar 2024). Published data investigating the prognostic implications of MSI in solid tumors has largely been conducted in colon, endometrial, and gastrointestinal cancers due to the higher prevalence in these tumor types. For patients with Stage 2 CRC, deficient DNA MMR and MSI-High status are associated with better prognosis (NCCN Colon Cancer Guidelines, v1.2024, NCCN Rectal Cancer Guidelines, v1.2024)[11-14]; however, the prognostic impact for patients with more advanced cancer is less clear[11,15]. For patients with endometrial cancer, microsatellite status and the presence or absence of pathogenic alterations in POLE and TP53 molecularly defines subpopulations with specific prognostic implications (NCCN Uterine Neoplasms Guidelines, v2.2024)[16-22]. In gastric and gastroesophageal cancers, MSI-High has been associated with certain clinicopathological and molecular features as well as better prognosis[23-29], while MS-Stable and MSI-Low were correlated with increased benefit for patients treated with chemotherapy[29-30].

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[31]. 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[31-33]. 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[34-36]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[31,33,35-36].

BIOMARKER

Tumor Mutational Burden

RESULT
2 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[37-40], anti-PD-1 therapies[38-42], and combination nivolumab and ipilimumab[43-51]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[37-40,42,52-56]. 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[52]; similar findings were observed in the KEYNOTE 028 and 012 trials[42]. 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)[56]. 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[57]. 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[55]. 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[37] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[38].

FREQUENCY & PROGNOSIS

Liposarcoma harbors a median TMB of 1.7 Muts/Mb, and 0.2% of cases have high TMB (>20 Muts/Mb)[58]. Sarcomas in general harbor a median TMB of 2.5 Muts/Mb, with angiosarcoma (13.4%) and malignant peripheral nerve sheath tumor (8.2%) having the highest percentage of cases with high TMB (>20 Muts/Mb)[58]. Published data investigating the prognostic implications of tissue TMB in sarcoma are conflicting (PubMed, Jan 2025). High tissue TMB was associated with improved PFS and metastasis-free survival in a study of undifferentiated sarcomas[59], but with reduced survival in a study of patients with rhabdomyosarcoma[60].

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[61-62] and cigarette smoke in lung cancer[63-64], treatment with temozolomide-based chemotherapy in glioma[65-66], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19,67-70], and microsatellite instability[19,69-70]. 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[38-39,52].

GENE
FUS

ALTERATION
FUS-DDIT3 fusion (Variant 10)

REARRANGEMENT DETAILS
FUS(NM_004960)-DDIT3(NM_004083) fusion (F6; D2)

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address fusions or inactivation of the FUS gene. However, rhabdomyosarcomas harboring EWSR1- or FUS-TFCP2 fusion have been reported to have increased ALK expression[71-75] and a case study of a patient with intraosseous rhabdomyosarcoma with FUS-TFCP2 fusion reported a good response to sequential treatment with radiotherapy, crizotinib, alectinib, then lorlatinib, with the patient stable at 19 months[72]. FUS-DDIT3 fusion may predict sensitivity to the approved therapy trabectedin. Trabectedin has enabled significant responses for patients with myxoid liposarcoma harboring FUS-DDIT3 in retrospective[76-77] and case[78] studies, especially those with Variant 1 or Variant 2 fusions; however, 2 patients with FUS-DDIT3 Variant 3 experienced PD, and some patients harbored multiple types of the fusion[76-77]. In preclinical studies, myxoid liposarcoma cells showed sensitivity to trabectedin in xenografts harboring FUS-DDIT3 Variant 1, 2, or 3; reduced mRNA expression; and reduced promoter binding to target genes, although inhibition was less pronounced for cells harboring FUS-DDIT3 Variant 3[79-82]. However, due to the limited sample size of these studies, it is unclear whether response to trabectedin may be predicted by FUS-DDIT3 fusion type. The specific targets of the FUS-DDIT3 protein that can drive oncogenesis have not been fully identified. Initial preclinical studies utilizing a panel of myxoid liposarcomas containing DDIT3 fusions reported FGFR2 overexpression and in vitro sensitivity to FGFR2 inhibitors[83].

FREQUENCY & PROGNOSIS

FUS-DDIT3 fusions are frequent in myxoid liposarcoma, having been reported in 90-95% of samples; the remaining samples often contain an EWSR1-DDIT3 fusion[84-88]. FUS-DDIT3 fusions have also been reported in well-differentiated and pleomorphic liposarcomas[89] and have been reported to transform cultured cells and induce liposarcoma development in mice[90-91]. Median disease-free survival was significantly higher for patients with myxoid/round cell liposarcoma harboring FUS-DDIT3 fusion Variant 2 (75 months, n=13) than those harboring FUS-DDIT3 fusion Variant 1 (17 months, n=6); OS did not differ[87].

Published data investigating the prognostic implications of FUS alterations in soft tissue sarcoma are limited (PubMed, Sep 2024).

FINDING SUMMARY

Fused in sarcoma (FUS, also called TLS) encodes a protein component of the heterogeneous nuclear ribonucleoprotein complex, which is involved in pre-mRNA splicing and the export of fully processed mRNA to the cytoplasm. Several different FUS-DDIT3 fusion variants have been observed for patients with myxoid liposarcoma, with type 2 (FUS exons 1-5 fused to DDIT3 exon 2) fusion more frequently detected than type 1 (FUS exons 1-7 fused to DDIT3 exon 2) or type 3 (FUS exons 1-8 fused to DDIT3 exon 2) fusions, and other variants were more rare; no significant association between variant type and histological grade or survival outcome has been reported[87,89,92]. Non-type 3 variant fusions, such as observed here, have been associated with clinical response to trabectedin, as compared with type 3 fusions[76-77,81-82].

POTENTIAL DIAGNOSTIC IMPLICATIONS

FUS-DDIT3 fusions are hallmark alterations of myxoid liposarcoma (NCCN Soft Tissue Sarcoma Guidelines, v3.2024)[84-88].

GENE
EZH2

ALTERATION
Y646C

HGVS VARIANT
NM_004456.4:c.1937A>G (p.Y646C)

VARIANT CHROMOSOMAL POSITION
chr7:148508727

VARIANT ALLELE FREQUENCY (% VAF)
43.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical evidence indicates that activating EZH2 alterations may predict sensitivity to EZH2 inhibitors[93-101]. Multiple Phase 2 trials of the EZH2 inhibitor tazemetostat have associated activating EZH2 mutations with improved clinical outcomes for patients with diffuse large B-cell lymphoma or follicular lymphoma[94,97,102]. Additional EZH2 inhibitors have been tested in Phase 1 trials, including CPI-1205 for patients with B-cell lymphoma (1 CR and 5 SDs, n=32)[93], CPI-0209 for patients with solid tumors (2 PRs and 14 SDs, n=39)[103], and GSK2816126 for patients with lymphoma (1 PR, 6 SDs, and 10 PDs, n=20) or solid tumors (8 SDs and 11 PDs, n=21), although this study was terminated for lack of efficacy[104]. The dual EZH1/2 inhibitor valemetostat has shown promising clinical activity with a 53% response rate (1/15 CRs, 7/15 PRs) for patients with non-Hodgkin lymphoma and an 80% ORR for the subset of patients with T-cell lymphoma (1/5 CRs, 3/5 PRs)[105]. In preclinical studies, cells resistant to EZH2 inhibitors retain sensitivity to compounds that block EED, a core subunit of the PRC2 complex[106-109]. Other therapeutic approaches targeting EZH2 include DNA demethylation agents and histone deacetylation inhibitors[110-112]. In addition, preclinical studies in breast cancer cells have suggested that PI3K inhibition may reverse some of the effects of EZH2 overexpression[113].

FREQUENCY & PROGNOSIS

EZH2 alterations are rare in sarcomas, detected in fewer than 1% of cases in a large genomic study[114]. Published data investigating the prognostic implications of EZH2 alteration in liposarcoma are limited (PubMed, Nov 2023).

FINDING SUMMARY

EZH2 encodes a histone-lysine N-methyltransferase, which methylates lysine 9 and 27 on histone H3 and mediates transcriptional repression of target genes[115-118]. The role of EZH2 in cancer is complex, described as both an oncogene and a tumor suppressor in different contexts[119-123]. Mutation of EZH2 Y646 (corresponding to Y641 in another well-studied EZH2 transcript), as seen here, results in an increase in H3K27 trimethylation[124-128].

Trabectedin

Assay findings association

FUS
FUS-DDIT3 fusion (Variant 10)

AREAS OF THERAPEUTIC USE

Trabectedin is a small molecule that interferes with DNA repair pathways. It is FDA approved for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Significant responses to trabectedin have been reported for patients with myxoid liposarcoma and FUS-DDIT3 fusion in retrospective[76-77] and case[78] studies. Preclinical data have shown that trabectedin inhibits FUS-DDIT3 binding to promoter regions of several target genes[79-81] , reduces mRNA expression[80-81,129] , and suppresses xenograft growth of FUS-DDIT3-expressing myxoid liposarcoma cell lines[81-82] . Therefore, FUS-DDIT3 may predict response to trabectedin.

SUPPORTING DATA

A Phase 3 study for 518 patients with liposarcoma or leiomyosarcoma reported a significant improvement in PFS when treated with trabectedin rather than dacarbazine (4.2 vs. 1.5 months), with the greatest response in myxoid liposarcoma (5.6 vs. 1.5 months)[130]. Phase 2 trials for patients with translocation-related soft tissue sarcoma comparing trabectedin with best supportive care reported significantly improved median PFS (mPFS; 5.6 vs. 0.9 months, HR=0.07), median OS (mOS; not reached vs. 8.0 months, HR=0.42), and ORR (11% [4/37; all PRs] vs. 0% [0/36]) from trabectedin; for patients with myxoid or round cell liposarcoma, an mPFS of 7.4 months, an mOS of 18.1 months, and an ORR of 27% (6/22; all PRs) were reported[131]. Studies of trabectedin for patients with myxoid liposarcoma harboring FUS-DDIT3 have reported clinical responses, including CRs for 6.7% (4/60) of patients, PRs for 63% (38/60), and an mPFS of 14-17 months[76-77] . Combining trabectedin with radiation enabled an ORR of 36% (5/14; all PRs) for patients with myxoid liposarcoma in a Phase 1 trial[132], and for patients with soft tissue sarcoma, an ORR of 72% (18/25; 2 CRs, 16 PR) and an mPFS of 9.9 months in a Phase 1/2 trial[133].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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
EZH2

ALTERATION
Y646C

RATIONALE
EZH2 inhibitors may be relevant in the case of EZH2 activating mutations.

NCT05598151

PHASE 1

Dose Escalation and Expansion Study of HM97662 in Advanced or Metastatic Solid Tumors

TARGETS
EZH1, EZH2

LOCATIONS: Seoul (Korea, Republic of), Adelaide (Australia), Ballarat (Australia), Clayton (Australia), Frankston (Australia)

GENE
FUS

ALTERATION
FUS-DDIT3 fusion (Variant 10)

RATIONALE
FUS-DDIT3 fusion may predict sensitivity to trabectedin.

NCT05597917

PHASE 3

tTF-NGR Randomized Study - STS

TARGETS
FUS-DDIT3, CD61, CD13, CD51

LOCATIONS: Berlin (Germany), Dresden (Germany), Graz (Austria), Bad Saarow (Germany), Frankfurt am Main (Germany), Münich (Germany), Münster (Germany), Mainz (Germany), Heidelberg (Germany)

NCT04794127

PHASE 2

Study on Trabectedin in Combination With Pioglitazone in Patients Myxoid Liposarcomas With Stable Disease After T Alone.

TARGETS
FUS-DDIT3

LOCATIONS: Milano (Italy)

NCT02275286

PHASE 1/2

Phase I-II Trial, Multicenter, Open, Exploring Trabectedin Plus Radiotherapy in Soft Tissue Sarcoma Patients

TARGETS
FUS-DDIT3

LOCATIONS: Milan (Italy), Candiolo (Italy), Lyon (France), Bordeaux (France), Barcelona (Spain), Palma de Mallorca (Spain), Zaragoza (Spain), Madrid (Spain), Sevilla (Spain), San Cristobal de la Laguna (Spain)

NCT05131386

PHASE 2

Multicohort Trial of Trabectedin and Low-dose Radiation Therapy in Advanced/Metastatic Sarcomas

TARGETS
FUS-DDIT3

LOCATIONS: Barcelona (Spain), Madrid (Spain), Tenerife (Spain)

NCT03138161

PHASE 1/2

Trabectedin, Ipilimumab and Nivolumab as First Line Treatment for Advanced Soft Tissue Sarcoma

TARGETS
FUS-DDIT3, PD-1, CTLA-4

LOCATIONS: California

NCT03886311

PHASE 2

Talimogene Laherparepvec, Nivolumab and Trabectedin for Sarcoma

TARGETS
FUS-DDIT3, PD-1

LOCATIONS: California

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.

CILK1 (ICK)
NM_016513.4: c.1106_1117del (p.P369_L372del)
chr6:52878494-52878506
41.2% VAF

CUX1
NM_001202544.1: c.1525C>G (p.L509V)
chr7:101921229
51.5% VAF

KMT2A (MLL)
NM_005933.3: c.4369A>G (p.K1457E)
chr11:118359365
47.9% VAF

LRP1B
NM_018557.2: c.393G>A (p.M131I)
chr2:142012161
48.4% VAF

MAP3K6
NM_004672.3: c.3373_3375del (p.K1125del)
chr1:27683229-27683232
49.7% VAF

MKI67
NM_002417.4: c.4807G>A (p.E1603K)
chr10:129905297
94.3% VAF

MYO18A
NM_078471.3: c.5780A>G (p.K1927R)
chr17:27413528
47.6% VAF

NCOR2
NM_006312.4: c.1520_1531dup (p.Q507_Q510dup)
chr12:124887058
48.2% VAF

NUP93
NM_014669.3: c.1749T>G (p.I583M)
chr16:56868657
91.5% VAF

PTEN
NM_000314.4: c.206A>T (p.N69I)
chr10:89685311
89.3% VAF

SETD2
NM_014159.6: c.4193T>C (p.I1398T)
chr3:47161933
52.9% VAF

WDR90
NM_145294.4: c.3994C>T (p.R1332C)
chr16:712020
50.5% VAF

APPENDIX Genes Assayed in FoundationOne®Heme

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. Foundation Medicine GmbH is accredited by DAkkS according to DIN EN ISO 15189:2014. The accreditation only applies to the scope of accreditation listed in certificate D-ML-21105-01-00.

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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.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

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
ctDNA	Circulating tumor DNA
DCR	Disease control rate
DFS	Disease-free survival
DOR	Duration of response
EFS	Event-free survival
ER	Estrogen receptor
HR +/-	Hormone-receptor positive/negative
ITD	Internal tandem duplication
MR	Molecular response
MMR	Mismatch repair
Muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
mOS	Median overall survival
PD	Progressive disease
PFS	Progression-free survival
mPFS	Median progression-free survival
PR	Partial response
PSA	Prostate-specific antigen
R/R	Relapsed or refractory
SD	Stable disease
TKI	Tyrosine kinase inhibitor
CRC	Colorectal cancer
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
NSCLC	Non-small cell lung cancer
RCC	Renal cell carcinoma
SCC	Squamous cell carcinoma

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) 8.6.1
MR Reporting Config Version 70
Analysis Pipeline Version v3.39.0
Computational Biology Suite Version 6.34.0

The median exon coverage for this sample is 2,229x

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