PATIENT	TUMOR TYPE	REPORT DATE
Chen, Li Heng	Uterus endometrial stromal sarcoma	09 May 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1618386-01

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 Uterus endometrial stromal sarcoma
NAME Chen, Li Heng
DATE OF BIRTH 23 July 1967
SEX Female
MEDICAL RECORD # 43273263

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 Soft Tissue
SPECIMEN ID S112-16705A (PF23041)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 18 April 2023
SPECIMEN RECEIVED 27 April 2023

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.

CDK4 amplification
MDM2 amplification
BCOR BCOR-ZC3H7B fusion
FRS2 amplification
STAT6 PCBP2-STAT6 fusion

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: *BCOR* BCOR-ZC3H7B fusion (p. 4)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 6)

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)
***CDK4 -** amplification*	none	none
10 Trials see p. 6		
***MDM2 -** amplification*	none	none
6 Trials see p. 9		

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.

BCOR - BCOR-ZC3H7B fusion .... p. 4
FRS2 - amplification .... p. 4
STAT6 - PCBP2-STAT6 fusion .... p. 5

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 Lena Stuart, M.D. | 09 May 2023
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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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FOUNDATIONONE®HEME

PATIENT
Chen, Li Heng

TUMOR TYPE
Uterus endometrial stromal sarcoma

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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]. 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)[5].

FREQUENCY & PROGNOSIS

Several studies of endometrial stromal sarcoma (ESS) have reported an absence of MSI[6-8]. 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)[9]. 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[10]. 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[11-16]. Published data investigating the prognostic implications of MSI in uterine or endometrial sarcoma are limited (PubMed, Sep 2022).

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 mismatch repair (MMR) in the tumor[17]. 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[17-19]. 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[20-22]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[17,19,21-22].

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[23-25], anti-PD-1 therapies[23-26], and combination nivolumab and ipilimumab[27-32]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[23-26,33-37]. 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[33]; similar findings were observed in the KEYNOTE 028 and 012 trials[26]. 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)[37]. 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[38]. 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[36]. 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[39] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[24].

FREQUENCY & PROGNOSIS

Endometrial stromal sarcoma (ESS) harbors a median TMB of 1.7 mutations per megabase (muts/ Mb), and 1.2% of cases have high TMB (>20 muts/ Mb)[40]. Published data investigating the prognostic implications of tissue TMB in sarcoma are conflicting (PubMed, Feb 2023). High tissue TMB was associated with improved PFS and metastasis-free survival in a study of undifferentiated sarcomas[41], but with reduced survival in a study of patients with rhabdomyosarcoma[42].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution 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[43-44] and cigarette smoke in lung cancer[45-46], treatment with temozolomide-based chemotherapy in glioma[47-48], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[49-53], and microsatellite instability (MSI)[49,52-53]. 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[24-25,33].

FOUNDATIONONE®HEME

PATIENT
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GENOMIC FINDINGS

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GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[54-57]. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib[58], palbociclib[54,59], and ribociclib[60].

FREQUENCY & PROGNOSIS
One study identified amplification of the chromosomal region including CDK4 in 26% (5/19) of uterine adenosarcoma cases[61]. Another study reported copy number gain of CDK4, with associated overexpression of CDK4 protein in 6/16 Mullerian adenosarcoma cases[62]. Published data investigating the prognostic implications of CDK4 alterations in uterine sarcomas are limited (PubMed, Mar 2023).

FINDING SUMMARY
CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[63]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[64-65]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[54,66-72].

GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[73]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[74-75]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[76-77]. A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of 5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[78]. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[79-80]; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[81]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[82]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[83-84].

FREQUENCY & PROGNOSIS
One study of uterine adenosarcomas found MDM2 amplification in 28% (5/18) of samples analyzed[85]. A genomic sub-analysis of uterine adenosarcomas reported focal amplification of 12q14.1-15, harboring the MDM2 and CDK4 loci, in 26% (5/19) of cases; amplification was only observed in the mesenchymal component of the adenosarcoma samples[61,86]. Published data investigating the prognostic implications of MDM2 amplification in uterine sarcoma are limited (PubMed, Mar 2023). No significant association of MDM2 expression with survival was observed in one immunohistochemical analysis for 49 patients with uterine leiomyosarcoma[87]; the impact of MDM2 expression or amplification in other uterine sarcoma subtypes has not been assessed (PubMed, Mar 2023).

FINDING SUMMARY
MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[88-90]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[91-92]. Overexpression or amplification of MDM2 is frequent in cancer[93]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[94] and 2/3 patients with MDM2 or MDM4 amplification[95] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[96]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[96].

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GENOMIC FINDINGS

ORDERED TEST # ORD-1618386-01

GENE
BCOR

ALTERATION
BCOR-ZC3H7B fusion

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no targeted therapies available to address BCOR alterations.

FREQUENCY & PROGNOSIS

In sarcomas, the ZC3H7B-BCOR fusion has been identified in ossifying fibromyxoid tumors (OFMTs)[97-98], high-grade endometrial stromal sarcoma[99-105], and undifferentiated small blue round cell sarcomas (SBRCT)[106]. Published data investigating the prognostic implications of non-

BCOR-CCNB3 alterations in solid tumors are generally limited (PubMed, Sep 2022). ZC3H7B-BCOR fusion-positive endometrial stromal sarcoma has been characterized as an independent group of high-grade endometrial stromal sarcoma that often shows unique morphological features such as microcyst containing myxoid material, cytoplasmic signet ring cell appearance, and haemangiopericytoma-like vascular pattern[102-104]. ZC3H7B-BCOR fusion-positive cases often exhibit aggressive disease courses and unfavorable outcomes[102-103].

FINDING SUMMARY

BCOR encodes a transcriptional corepressor that interacts with BCL6 but not with related POZ domain-containing proteins[107]. BCOR activity is required for normal development; de novo germline mutations in BCOR have been linked to syndromic microphthalmia-2 and

oculofaciocardiodental syndrome[108]. Multiple BCOR-involving fusions with various partners including CCNB3, ZC3H7B, EP300, CREBBP, RARA, and MAML3 have been described in cancer[97-102,106,109-119]. The ZC3H7B-BCOR fusion observed here is similar to the t(X;22)(p11;q13) translocations reported in ossifying fibromyxoid tumors and high-grade endometrial stromal sarcoma, which usually have an aggressive disease course[97-106].

POTENTIAL DIAGNOSTIC IMPLICATIONS

BCOR fusions are characteristic of sarcomas such as small round cell tumors, high-grade endometrial stromal sarcomas, clear cell sarcomas of the kidney, and ossifying fibromyxoid tumors (NCCN Soft Tissue Sarcoma Guidelines, v2.2022, NCCN Uterine Neoplasms Guidelines, v1.2023)[109,112-116,120-122].

GENE
FRS2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no approved therapies that target alterations in FRS2. Amplification of FRS2 can lead to activation of the FGFR and MAPK-ERK pathways, and preliminary studies in liposarcoma cell lines have shown that cells with this alteration

are sensitive to FGFR inhibitors[71,123].

FREQUENCY & PROGNOSIS

FRS2 amplification is particularly prevalent in liposarcoma, where amplification of the 12q13-15 region of chromosome 12 is considered to be a hallmark genetic alteration, although the effects of amplification of CDK4 and MDM2, also located in this region, have been studied in more detail than FRS2 in this context[124-125]. Amplification of FRS2 has been observed in 93%-100% of dedifferentiated liposarcoma, 32% of undifferentiated high-grade pleomorphic sarcoma, and 100% of well-differentiated liposarcoma[71,126]. Amplification of the 12p15 chromosomal region containing FRS2, but

not CDK4 or MDM2, was found in 12.5% of high-grade serous ovarian carcinomas, and knockdown of FRS2 in these cells resulted in apoptosis, indicating that cells with 12p15 amplification require FRS2[123].

FINDING SUMMARY

FRS2 encodes the fibroblast growth factor receptor (FGFR) substrate 2, an adaptor protein involved in FGFR signaling, which may also mediate signaling through EGFR, NTRK, and VEGF receptors[127-130]. FRS2 amplification was found to correlate with overexpression in high-grade serous ovarian tumors, and FRS2 overexpression promoted tumorigenesis in a preclinical study[123].

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GENOMIC FINDINGS

GENE
STAT6

ALTERATION
PCBP2-STAT6 fusion

POTENTIAL TREATMENT STRATEGIES
— **Targeted Therapies** —

There are no therapies available to directly target somatic alterations in STAT6, although phosphorylation and activation of STAT6 is known to be decreased by inhibitors of JAK2, such as ruxolitinib[131].

FREQUENCY & PROGNOSIS

The frequency of STAT6 rearrangements in uterus/endometrial sarcoma has not been evaluated (PubMed, May 2023). Published data investigating the prognostic implications of STAT6 alterations in uterus/endometrial sarcoma are limited (PubMed, May 2023).

FINDING SUMMARY

STAT6 encodes a member of the STAT family of transcription factors; these proteins are phosphorylated in response to cytokine receptor signaling and act to transduce those signals to the cell nucleus where they activate transcription of a variety of genes. The STAT family of transcription factors are activated in response to signaling from the JAK kinases, and this signaling pathway is well known to be dysregulated in the context of hematological malignancies[132-133]. One or more STAT6 rearrangements observed here have not been characterized, and their effect on protein function is unknown; however, they have been reported in the context of cancer, which may indicate biological relevance.

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CLINICAL TRIALS

ORDERED TEST # ORD-1618386-01

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
CDK4

RATIONALE
CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

ALTERATION
amplification

NCT04282031
PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT03239015
PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04557449
PHASE 1

Study to Test the Safety and Tolerability of PF-07220060 in Participants With Advance Solid Tumors

TARGETS
CDK4, Aromatase, ER

LOCATIONS: Wuhan (China), Zhengzhou (China), Xi'an (China), Beijing (China), Nove Zamky (Slovakia), Bratislava (Slovakia), Praha 2 (Czechia), Edinburgh (United Kingdom), Manchester (United Kingdom), London (United Kingdom)

NCT04801966
PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

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CLINICAL TRIALS

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific
Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
CDK4, CDK6, FLT3, VEGFRs, CSF1R,
KIT, RET, mTOR, ERBB2, MEK, BRAF,
PARP, PD-1, CTLA-4, PD-L1, TRKB, ALK,
TRKC, ROS1, TRKA, FGFRs

LOCATIONS: Hawaii, Washington, Oregon, California

NCT05262400

PHASE 1/2

A Study to Learn About the Study Medicine (Called PF-07220060 in Combination With PF-07104091)
In Participants With Breast Cancer and Solid Tumors

TARGETS
CDK2, Aromatase, CDK4, ER

LOCATIONS: Prague (Czechia), Washington, California, Michigan, Massachusetts, Texas, Merida (Mexico)

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)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL,
TRKA, MET, TRKC, DDR2, KIT, EGFR,
PD-1, CTLA-4, PARP, CDK4, CDK6,
FLT3, CSF1R, RET, mTOR, ERBB2, MEK,
BRAF, SMO

LOCATIONS: Vancouver (Canada), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada),
Toronto (Canada), Kingston (Canada), London (Canada)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4,
CDK6, PI3K, mTOR

LOCATIONS: Washington, Oregon, Idaho, Montana

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CLINICAL TRIALS

ORDERED TEST #   ORD-1618386-01

NCT04040205

PHASE 2

Abemaciclib for Treatment of Advanced Bone and Soft Tissue Sarcoma Identified as Having CDK
Pathway Alteration

TARGETS
CDK4, CDK6

LOCATIONS: California, Iowa, Wisconsin, Missouri, Florida

Electronically signed by Lena Stuart, M.D. | 09 May 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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CLINICAL TRIALS

GENE
MDM2

ALTERATION
amplification

RATIONALE
Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or amplification of MDM2 may increase sensitivity to these agents, but more data are required.

NCT04589845 — PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha, RAFs, NRAS

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Xi'an (China)

NCT04785196 — PHASE 1/2

APG-115 in Combination With PD-1 Inhibitor in Patients With Advanced Liposarcoma or Advanced Solid Tumors

TARGETS
PD-1, MDM2

LOCATIONS: Shanghai (China), Guangzhou (China)

NCT03449381 — PHASE 1

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TARGETS
MDM2

LOCATIONS: Tokyo, Chuo-ku (Japan), Stockholm (Sweden), Warsaw (Poland), Poznan (Poland), Berlin (Germany), Göttingen (Germany), Köln (Germany), Tübingen (Germany), Leuven (Belgium), Bruxelles (Belgium)

NCT05012397 — PHASE 2

Milademetan in Advanced/Metastatic Solid Tumors

TARGETS
MDM2

LOCATIONS: Washington, California, South Dakota, Missouri, New York, Ohio, Massachusetts, Tennessee, Texas

NCT03611868 — PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Brisbane (Australia), South Brisbane (Australia), Bedford Park (Australia), Heidelberg (Australia), California, Arizona, Missouri, Arkansas, Ohio, Pennsylvania

FOUNDATIONONE®HEME

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CLINICAL TRIALS

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NCT05180695

PHASE 1/2

HDM201 and Pazopanib in Patients With P53 Wild-type Advanced/Metastatic Soft Tissue Sarcomas

TARGETS
FGFR3, KIT, FGFR1, VEGFRs, FGFR2,
MDM2

LOCATIONS: Lyon (France)

FOUNDATIONONE®HEME

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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 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.

BCOR
NM_017745.5: c.1708G>A
(p.A570T)
chrX:39932891

EMSY (C11ORF30)
NM_020193.3: c.3429G>T
(p.K1143N)
chr11:76256996

ERG
amplification

KDM2B
amplification,
rearrangement and
rearrangement

KDM4C
NM_015061.3: c.2720T>G
(p.F907C)
chr9:7128175

MDM2
rearrangement

MSH2
NM_000251.1: c.505A>G
(p.I169V)
chr2:47637371

NCOR2
NM_006312.4: c.1520_1531del
(p.Q507_Q510del)
chr12:124887058-124887070

NUP93
NM_014669.3: c.1897A>C
(p.K633Q)
chr16:56870627

PTPN6
NM_080549.3: c.1565A>C
(p.K522T)
chr12:7069386

SPEN
NM_015001.2: c.6875C>T
(p.S2292L)
chr1:16259610

TMPRSS2
rearrangement and
rearrangement

TSC2
NM_000548.3: c.3806C>A
(p.S1269Y)
chr16:2131791

ZRSR2
NM_005089.3: c.1317C>G
(p.S439R)
chrX:15841233

FOUNDATIONONE®**HEME**

PATIENT
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TUMOR TYPE
Uterus endometrial stromal sarcoma

REPORT DATE
09 May 2023

ORDERED TEST # ORD-1618386-01

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

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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)

FOUNDATIONONE®HEME

PATIENT
Chen, Li Heng

TUMOR TYPE
Uterus endometrial stromal
sarcoma

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APPENDIX   Performance Specifications

The median exon coverage for this sample is 771x

ACCURACY

Sensitivity: Base Substitutions	At ≥5% Minor Allele Frequency	>99.0%
Sensitivity: Insertions/Deletions (1-40bp)	At ≥10% Minor Allele Frequency	98.0%
Sensitivity: Focal Copy Number Alterations (Homozygous Deletions or Amplifications)	At ≥8 copies	>95.0%
Sensitivity: Microsatellite Instability-High (MSI-H) status	Positive Predictive Agreement (PPA)	100.0% (87.54%-100.00%)*
Sensitivity: Microsatellite Stable (MSS) status	Positive Predictive Agreement (PPA)	89.66% (81.50%, 94.46%)*
Sensitivity: Known Gene Fusions	>95.0%	
Specificity: Base Substitutions, Insertions/Deletions, and Focal Copy Number Alterations	Positive Predictive Value (PPV)	>99.0%
Specificity: Known Gene Fusions	Positive Predictive Value (PPV)	>95.0%
Specificity: Microsatellite Instability-High (MSI-H) status	Negative Predictive Agreement (NPA)	97.44% (91.12%-99.29%)*
Specificity: Microsatellite Stable (MSS) status	Negative Predictive Agreement (NPA)	94.44% (86.57%, 97.82%)*
Accuracy: Tumor Mutation Burden	At ≥20% tumor nuclei	>90.0%
Reproducibility (average concordance between replicates)	97.0% inter-batch precision 97.0% intra-batch precision 95.0% microsatellite status precision 96.0% tumor mutation burden precision	

*95% Confidence Interval

Assay specifications were determined for typical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne®Heme, please refer to the article He, J. et al. Integrated genomic DNA/RNA profiling of hematologic malignancies in the clinical setting, Blood (2016 Jun. 16).

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 (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.

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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 is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. 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 was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme 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. FoundationOne Heme 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.

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

FOUNDATIONONE®HEME

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APPENDIX | About FoundationOne®Heme

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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.

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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.

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.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only.

Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. 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.

MR Suite Version (RG) 7.8.0

FOUNDATIONONE®HEME

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APPENDIX References

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