FOUNDATIONONE®HEME

PATIENT

TUMOR TYPE
Soft tissue liposarcoma
COUNTRY CODE
PE

REPORT DATE
28 Feb 2022
ORDERED TEST #
ORD-1289410-02

**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 liposarcoma
**DATE OF BIRTH** 10 January 1941
**SEX** Male
**MEDICAL RECORD #** Not given

PHYSICIAN
**MEDICAL FACILITY** Arias Stella
**ADDITIONAL RECIPIENT** None
**MEDICAL FACILITY ID** 317319
**PATHOLOGIST** Not Provided

SPECIMEN
**SPECIMEN SITE** Retroperitoneum
**SPECIMEN ID** 21-18594 9 (Q21-14642.9)
**SPECIMEN TYPE** Block
**DATE OF COLLECTION** 15 October 2021
**SPECIMEN RECEIVED** 21 January 2022

## 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
***CBL*** C384Y - subclonal†
***FRS2*** amplification
***HMGA2*** HMGA2-TSFM fusion

† See About the Test in appendix for details.

## Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***CDK4* amplification** (p. 4), ***MDM2* amplification** (p. 5)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: Abemaciclib (p. 8)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***CBL* C384Y** (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 | Abemaciclib |
| **10 Trials** see p. 9 | | |
| ***MDM2* -** amplification | none | none |
| **5 Trials** see p. 11 | | |

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

*Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.*

***CBL* -** C384Y - subclonal ..... p. 6



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## 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.*



**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.



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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

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)[6]. Smaller studies have reported MSI at any level in a subset of liposarcoma patients[7-8] or reported as absent in 21 cases analyzed[9]. The prognostic significance of MSI in liposarcoma is unknown (PubMed, Jun 2021).

## 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[10]. 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[10-12]. 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[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

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[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[16-19,26]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[16]. 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[27] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[17]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[19,26]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

## FREQUENCY & PROGNOSIS

Liposarcoma harbors a median TMB of 1.7 mutations per megabase (muts/Mb), and 0.2% of cases have high TMB (>20 muts/Mb)[28]. Sarcomas in general harbor a median TMB of 2.5 muts/Mb, with angiosarcoma (13.4%) and malignant peripheral nerve sheath tumor (MPNST) (8.2%) having the highest percentage of cases with high TMB (>20 muts/Mb)[28]. Published data investigating the prognostic implications of TMB in sarcoma are limited (PubMed, Feb 2022). High TMB was associated with improved PFS and metastasis-free survival in a study of undifferentiated sarcomas[29] and with reduced survival in a study of patients with rhabdomyosarcoma[30].

## 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[31-32] and cigarette smoke in lung cancer[33-34], treatment with temozolomide-based chemotherapy in glioma[35-36], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[37-41], and microsatellite instability (MSI)[37,40-41]. 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[17-18,26].



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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[42-45]. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib[46], palbociclib[42,47], and ribociclib[48].

### FREQUENCY & PROGNOSIS

In a genomic analysis of sarcomas, amplification of CDK4 was found in 24% of cases, including 88% of dedifferentiated liposarcoma (DDLPS) cases, but was not observed in any of the 21 myxoid/round-cell liposarcoma cases or the 24 pleomorphic liposarcoma cases[49]. Amplification of the chromosome subregion 12q13-15, with concomitant copy number gains of the CDK4 and MDM2 genes, is a hallmark genetic alteration in well-differentiated liposarcoma (WDLPS) and DDLPS, reported in up to 100% of cases[42,50-51]. Amplification of CDK4 has been correlated with increased CDK4 protein expression in liposarcoma, undifferentiated high-grade pleomorphic sarcoma, leiomyosarcoma, and rhabdomyosarcoma[50-53]. CDK4 amplification predicts poor progression-free and disease-specific survival in patients with WDLPS or DDLPS as well as recurrence of WDLPS after surgical resection[54-56].

### FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[57]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[58-59]. 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[42,50-53,60-62].

### POTENTIAL DIAGNOSTIC IMPLICATIONS

Amplification of 12q13–q15, including CDK4 and MDM2, is characteristic of well-differentiated liposarcoma (WDLPS) and dedifferentiated (DDLPS) liposarcoma (NCCN Soft Tissue Sarcoma Guidelines, v3.2021)[49-50,63-64], and low-grade osteosarcomas, including parosteal osteosarcomas and low-grade central osteosarcomas as opposed to conventional high-grade osteosarcoma (NCCN Soft Tissue Sarcoma Guidelines, v3.2021)[62,65-68].



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GENE
# *MDM2*

ALTERATION
amplification

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[69]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[70-71]. 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[72-73] . 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 of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[74]. 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[75-76] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[77]. 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[78]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[79-80] .

## FREQUENCY & PROGNOSIS

Amplification of MDM2 has reported in 27-33% of sarcomas overall and in up to 90% of liposarcomas[49,63-64]. Amplification of the chromosome subregion 12q13–q15, with concomitant copy number gains of the CDK4 and MDM2 genes, is a hallmark genetic alteration in well-differentiated liposarcomas (WDLPS) and dedifferentiated (DDLPS) liposarcomas[50]. Patients with a diagnosis of WDLPS or DDLPS and the accompanying 12q13-15 amplification have a high chance of recurrence and a poor chance of survival if surgical resection is incomplete[55].

## FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[81-83]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[84-85]. Overexpression or amplification of MDM2 is frequent in cancer[86]. 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[87] and 2/3 patients with MDM2 or MDM4 amplification[88] 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)[89]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[89].

## POTENTIAL DIAGNOSTIC IMPLICATIONS

Amplification of 12q13–q15, including CDK4 and MDM2, is characteristic of well-differentiated liposarcoma (WDLPS) and dedifferentiated (DDLPS) liposarcoma (NCCN Soft Tissue Sarcoma Guidelines, v3.2021)[49-50,63-64], and low-grade osteosarcomas, including parosteal osteosarcomas and low-grade central osteosarcomas as opposed to conventional high-grade osteosarcoma (NCCN Soft Tissue Sarcoma Guidelines, v3.2021)[62,65-68].



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GENE
## *CBL*

**ALTERATION**
C384Y - subclonal

**TRANSCRIPT ID**
NM_005188

**CODING SEQUENCE EFFECT**
1151G>A

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

CBL inactivation may lead to the hyperactivation of various receptor tyrosine kinases (RTKs), including MET[90], PDGFRA[91], KIT[92], VEGFR2[93], and the TAM (TYRO3, AXL, MER) RTKs[94]. These RTKs are targets of the multikinase inhibitor sitravatinib[95], which has shown activity in CBL-mutated advanced solid tumors[96]. Among 8 patients with CBL inactivating alterations in a Phase 1b trial, sitravatinib produced 2 PRs (25% ORR), with 1 NSCLC and 1 melanoma responding for over 4 months, and 4 SD outcomes, with 3 prolonged SDs seen in a patient with NSCLC, a patient with esophageal cancer, and a patient with a pancreatic neuroendocrine tumor[96]. CBL has been shown to downregulate EGFR[97-101] and FLT3[102-104]. Preclinical models of myeloid malignancies have demonstrated that CBL inactivation confers sensitivity to the FLT3-targeting therapies sunitinib[102], midostaurin[104], and quizartinib[105], as well as to dasatinib[106], although clinical evidence for this approach in solid tumors is lacking.

### FREQUENCY & PROGNOSIS

CBL alterations have been reported in 1% of liposarcoma cases (COSMIC, Oct 2021)[107]. Published data investigating the prognostic implications of CBL alterations in liposarcoma are limited (PubMed, Oct 2021).

### FINDING SUMMARY

CBL encodes an E3 ubiquitin protein ligase that is involved in cell signaling and ubiquitination, targeting proteins such as EGFR, FGFR1, FGFR2, PDGFR-alpha, PDGFR-beta, FLT3, and SRC for degradation by the proteasome[108-112]. CBL alterations that result in loss or disruption of the tyrosine kinase binding domain, RING finger domain, and/or tail domain, as observed here, are predicted to be inactivating and to promote tumorigenesis[113-130].

### 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[131-136]. 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[131-132]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[137]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[135,138-139]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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[51,140].

### 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[141-142]. 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[51,143]. 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[140].

### 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[144-147]. FRS2 amplification was found to correlate with overexpression in high-grade serous ovarian tumors, and FRS2 overexpression promoted tumorigenesis in a preclinical study[140].



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GENE
## *HMGA2*

**ALTERATION**
HMGA2-TSFM fusion

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no targeted therapies available to address fusions involving the HMGA2 gene. However, HMGA2 expression has been reported to be the driver of embryonic rhabdomyosarcoma (ERMS) via up-regulation of NRAS expression[148], suggesting that MEK inhibitors that are predicted to inhibit NRAS-dependent signaling may be beneficial for patients with HMGA2 activation or overexpression. However, it is unknown whether this approach would be beneficial here.

### FREQUENCY & PROGNOSIS

HMGA2 rearrangements have been most frequently identified in benign neoplasms such as lipomas, uterine leiomyomas, angiomyxomas, as well as in malignant tumors such as well-differentiated liposarcomas and inflammatory myofibroblastic tumors[149-154]. Amplifications of HMGA2 have also been described in a variety of tumors[148,151,155-156], including in up to 25% of sarcomas, including uterine leiomyomas, leiomyosarcomas, embryonic rhabdomyosarcomas (ERMS), and lipomas[152,157-159].

### FINDING SUMMARY

HMGA2 encodes a protein that may act as a transcriptional regulator[150]. Rearrangements involving HMGA2 typically result in a separation of the three DNA-binding domains, encoded by exons 1-3 (or sometimes two DNA-binding domains encoded by exons 1-2), from the modulatory acidic tail encoded by exons 4-5 as well as the 3' UTR that has been reported to inhibit HMGA2 expression[151-154,160]. Both truncations of HMGA2 at exon 3 and HMGA2 (exon 1-3)-involving fusions have been reported to transform cultured cells[161]. HMGA2-RAD51B fusions have been reported to be produced in t(12;14) uterine leiomyomas and reported to lead to HMGA2 overexpression[162-163].



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# Abemaciclib

*Assay findings association*

**CDK4**
amplification

## AREAS OF THERAPEUTIC USE

Abemaciclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat adults with hormone-receptor-positive (HR+), HER2-negative (HER2-) breast cancer as monotherapy as well as in combination with tamoxifen or an aromatase inhibitor, including anastrozole, letrozole, and exemestane. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

Targeting CDK4 amplification with abemaciclib may be an effective strategy to treat advanced liposarcoma based on a positive Phase 2 study[46].

## SUPPORTING DATA

A Phase 2 trial of abemaciclib for patients with metastatic or recurrent dedifferentiated liposarcoma met the primary endpoint with a 12-week PFS rate of 76% (22/29) and reported a median PFS of 30 weeks and an ORR of 3% (1/29), with 3 additional patients experiencing tumor size reduction by >10%; all evaluable patients had CDK4 and MDM2 amplification and intact RB1[46]. Studies with other CDK4/6 inhibitors also observed clinical benefit for a subset of patients with CDK4-amplified liposarcoma[42,45,47,164] .

**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.

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## CLINICAL TRIALS

**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*

**ALTERATION**
amplification

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

### 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**
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, CDK4, CDK6, FLT3, CSF1R, KIT, RET, mTOR, EGFR, ERBB2, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

**LOCATIONS:** Florida, Georgia, South Carolina, Texas, Alabama, North Carolina

### NCT03994796

**PHASE 2**

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

**LOCATIONS:** Florida, Louisiana, Texas, Mississippi, Georgia

### 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)

### NCT03310879

**PHASE 2**

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

**TARGETS**
CDK4, CDK6

**LOCATIONS:** Massachusetts

## 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:** London (Canada), Toronto (Canada), Kingston (Canada), Ottawa (Canada), Montreal (Canada), Regina (Canada), Saskatoon (Canada), Edmonton (Canada), Vancouver (Canada)

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

## NCT04557449

**PHASE 1**

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

**TARGETS**
CDK4, Aromatase, ER

**LOCATIONS:** Texas, Tennessee, Connecticut, Massachusetts, Michigan

## NCT03114527

**PHASE 2**

Phase II Trial of Ribociclib and Everolimus in Advanced Dedifferentiated Liposarcoma (DDL) and Leiomyosarcoma (LMS)

**TARGETS**
mTOR, CDK6, CDK4

**LOCATIONS:** Pennsylvania

## NCT04438824

**PHASE 2**

Palbociclib and INCMGA00012 in People With Advanced Liposarcoma

**TARGETS**
CDK4, CDK6, PD-1

**LOCATIONS:** New Jersey, New York

## NCT03065062

**PHASE 1**

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

**TARGETS**
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

**LOCATIONS:** Massachusetts

**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.

## NCT04979442

**PHASE 3**

Treatment of Milademetan Versus Trabectedin in Patient With Dedifferentiated Liposarcoma

**TARGETS**
FUS-DDIT3

**LOCATIONS:** Florida, Texas, Pennsylvania, Missouri, New York, Ohio, Massachusetts, Michigan, Toronto (Canada)

## 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

**LOCATIONS:** Sao Paulo (Brazil), San Juan (Puerto Rico), Florida, Alabama, Texas, Georgia, South Carolina

## 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:** Florida, Texas, Tennessee, Virginia, Arkansas, District of Columbia, Pennsylvania, Missouri

## 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:** Florida, Tennessee, New York, Connecticut, Ottawa (Canada), Barcelona (Spain), Leuven (Belgium), Tübingen (Germany), Berlin (Germany), Tokyo, Chuo-ku (Japan)

## NCT03725436

**PHASE 1**

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

**TARGETS**
MDM2, MDM4

**LOCATIONS:** Texas

**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.

***APC***
S881F

***CARD11***
L706F

***CUX1***
Q1245R

***ECT2L***
amplification

***ESR1***
amplification

***FOXO3***
amplification

***GATA3***
amplification

***GSK3B***
amplification

***INPP5D***
L1061P

***KMT2A (MLL)***
A53V

***MAP3K7***
amplification

***NOTCH1***
D740H

***PRDM1***
amplification

***SGK1***
amplification

***SPEN***
S2306del

***TNFAIP3***
amplification

***TSC1***
K587R

***WISP3***
amplification



Electronically signed by Chelsea Marcus, M.D. | 28 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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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* | *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* | *C11orf30 (EMSY)* | *CAD* |
| *CALR** | *CARD11* | *CBFB* | *CBL* | *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* | *EP300* | *EPHA3* | *EPHA5* | *EPHA7* | *EPHB1* | *ERBB2* |
| *ERBB3* | *ERBB4* | *ERG* | *ESR1* | *ETS1* | *ETV6* | *EXOSC6* | *EZH2* |
| *FAF1* | *FAM46C* | *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* | *GPR124* | *GRIN2A* | *GSK3B* |
| *GTSE1* | *HDAC1* | *HDAC4* | *HDAC7* | *HGF* | *HIST1H1C* | *HIST1H1D* | *HIST1H1E* |
| *HIST1H2AC* | *HIST1H2AG* | *HIST1H2AL* | *HIST1H2AM* | *HIST1H2BC* | *HIST1H2BJ* | *HIST1H2BK* | *HIST1H2BO* |
| *HIST1H3B* | *HNF1A* | *HRAS* | *HSP90AA1* | *ICK* | *ID3* | *IDH1* | *IDH2* |
| *IGF1R* | *IKBKE* | *IKZF1* | *IKZF2* | *IKZF3* | *IL7R* | *INHBA* | *INPP4B* |
| *INPP5D (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* | *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* | *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)* | *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* | *WHSC1 (MMSET or NSD2)* | *WISP3* | *WT1* | *XBP1* | *XPO1* |
| *YY1AP1* | *ZMYM3* | *ZNF217* | *ZNF24 (ZSCAN3)* | *ZNF703* | *ZRSR2* | | |



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*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* | *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* | *CARS* | *CBFA2T3* | *CBFB* | *CBL* | *CCND1* | *CCND2* |
| *CCND3* | *CD274 (PD-L1)* | *CDK6* | *CDX2* | *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* |
| *FGFR1OP* | *FGFR2* | *FGFR3* | *FLI1* | *FNBP1* | *FOXO1* | *FOXO3* | *FOXO4* | *FOXP1* |
| *FSTL3* | *FUS* | *GAS7* | *GLI1* | *GMPS* | *GPHN* | *HERPUD1* | *HEY1* | *HIP1* |
| *HIST1H4I* | *HLF* | *HMGA1* | *HMGA2* | *HOXA11* | *HOXA13* | *HOXA3* | *HOXA9* | *HOXC11* |
| *HOXC13* | *HOXD11* | *HOXD13* | *HSP90AA1* | *HSP90AB1* | *IGH* | *IGK* | *IGL* | *IKZF1* |
| *IL21R* | *IL3* | *IRF4* | *ITK* | *JAK1* | *JAK2* | *JAK3* | *JAZF1* | *KAT6A (MYST3)* |
| *KDSR* | *KIF5B* | *KMT2A (MLL)* | *LASP1* | *LCP1* | *LMO1* | *LMO2* | *LPP* | *LYL1* |
| *MAF* | *MAFB* | *MALT1* | *MDS2* | *MECOM* | *MKL1* | *MLF1* | *MLLT1 (ENL)* | *MLLT10 (AF10)* |
| *MLLT3* | *MLLT4 (AF6)* | *MLLT6* | *MN1* | *MNX1* | *MSI2* | *MSN* | *MUC1* | *MYB* |
| *MYC* | *MYH11* | *MYH9* | *NACA* | *NBEAP1 (BCL8)* | *NCOA2* | *NDRG1* | *NF1* | *NF2* |
| *NFKB2* | *NIN* | *NOTCH1* | *NPM1* | *NR4A3* | *NSD1* | *NTRK1* | *NTRK2* | *NTRK3* |
| *NUMA1* | *NUP214* | *NUP98* | *NUTM2A* | *OMD* | *P2RY8* | *PAFAH1B2* | *PAX3* | *PAX5* |
| *PAX7* | *PBX1* | *PCM1* | *PCSK7* | *PDCD1LG2 (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* | *ROS1* | *RPL22* | *RPN1* | *RUNX1* |
| *RUNX1T1 (ETO)* | *RUNX2* | *SEC31A* | *SEPT5* | *SEPT6* | *SEPT9* | *SET* | *SH3GL1* | *SLC1A2* |
| *SNX29 (RUNDC2A)* | *SRSF3* | *SS18* | *SSX1* | *SSX2* | *SSX4* | *STAT6* | *STL* | *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* | *WHSC1 (MMSET or NSD2)* | |
| *WHSC1L1* | *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)



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The median exon coverage for this sample is 853x

| 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<br>97.0% intra-batch precision<br>95.0% microsatellite status precision<br>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 fractional-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. 2022. 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.



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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 |

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