FOUNDATIONONE®HEME

PATIENT

TUMOR TYPE
Unknown primary leiomyosarcoma

COUNTRY CODE
PE

REPORT DATE
12 Jul 2021

ORDERED TEST #
ORD-1123405-02

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 Unknown primary leiomyosarcoma

DATE OF BIRTH 10 July 1946
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID Q18-7962-3
SPECIMEN TYPE Block
DATE OF COLLECTION 22 November 2018
SPECIMEN RECEIVED 18 June 2021

Sensitivity for the detection of alterations and genomic signatures is reduced due to sample quality.

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 9 Muts/Mb

Genomic Findings

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

NF1 R2258*
C17orf39 amplification - equivocal†
CCND3 amplification - equivocal†
CDKN2A/B CDKN2A loss, CDKN2B loss
ESR1 T311M

† See About the Test in appendix for details.

2 Therapies with Clinical Benefit
0 Therapies with Lack of Response
10 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 9 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
NF1 **-** R2258*	none	Selumetinib
10 Trials *see p. 7*		Trametinib

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS 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.

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

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[6]. In a computational analysis of paired tumor and normal sarcomas in the TCGA dataset, 40% of which were leiomyosarcomas, only 0.8% (2/255) of samples were MSI-high (MSI-H)[7]. Smaller studies have reported MSI at any level in a subset of leiomyosarcoma patients[8-13], including MSI-H in two of seven cases[13-14]. The prognostic significance of MSI in leiomyosarcoma is unknown (PubMed, Jan 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[15]. 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[15-17]. 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[18-20]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15,17,19-20].

BIOMARKER

Tumor Mutational Burden

RESULT
9 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[21-23], anti-PD-1 therapies[21-24], and combination nivolumab and ipilimumab[25-30]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[21-24,31]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[21]. 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[32] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[22]. 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[24,31]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Leiomyosarcoma harbors a median TMB of 2.5 mutations per megabase (muts/Mb), and <1% of cases have high TMB (>20 muts/Mb)[33]. Sarcomas in general also 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)[33]. The association of mutational burden and prognosis of specific sarcoma subtypes has not been extensively investigated in the literature (PubMed, Feb 2021). One study associated high TMB with improved progression-free and metastasis-free survival for tumor samples from patients with undifferentiated sarcomas[34].

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[35-36] and cigarette smoke in lung cancer[37-38], treatment with temozolomide-based chemotherapy in glioma[39-40], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[41-45], and microsatellite instability (MSI)[41,44-45]. 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[22-23,31].

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
NF1

ALTERATION
R2258*

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
6772C>T

POTENTIAL TREATMENT STRATEGIES
On the basis of clinical evidence in neurofibromatosis type 1[46-47] and neurofibromatosis-associated glioma or glioblastoma[48-49], as well as extensive preclinical evidence in several tumor types[50-55], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including the approved agents everolimus and temsirolimus, based on limited clinical data[56-58] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[59-60]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[61]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[62], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[63].

FREQUENCY & PROGNOSIS
In the sarcoma MSKCC dataset, mutation or putative homozygous deletion of NF1 has been found in 2% and 1% of cases, respectively[64]. NF1 mutations were reported in 8.8% (5/57) of fibrosarcomas, 5.3% (4/76) of fibrous histiocytomas, and 4.3% (1/23) of epithelioid sarcomas, but were not detected in any of the 68 synovial sarcomas, 35 desmoplastic small round cell tumors, 13 clear cell sarcomas, or 2 granular cell tumors analyzed in COSMIC (Oct 2020)[65]. However, NF1 mutations were reported in 10.5% of myxofibrosarcomas and 8% of pleomorphic liposarcomas[64]. NF1 has been reported to be one of the genes more frequently found with alterations in sarcomas[66]. There are rare reports of leiomyosarcoma arising in patients with neurofibromatosis with the assumption of NF1 mutation[67-68]. The appearance of soft tissue sarcoma in patients with neurofibromatosis is associated with a poor prognosis[69].

FINDING SUMMARY
NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[70]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[71]. Alterations such as seen here may disrupt NF1 function or expression[71-80].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the NF1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with neurofibromatosis type 1 (ClinVar, Mar 2021)[81]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[82-84]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[85-86], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
C17orf39

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address alterations in C17orf39.

FREQUENCY & PROGNOSIS
C17orf39 lies in a region of human chromosome 17p11 that is frequently amplified in osteosarcoma[87-88], and observed to be amplified occasionally in other tumor types including gliomas, bladder, esophageal, stomach, prostate and uterine carcinomas (cBioPortal, 2021)[89-91]. C17orf39 loss has also been reported, with the highest rates in tumors of the pancreas, prostate, bladder, liver, lung, and ovary (cBioPortal, 2021)[90-91].

FINDING SUMMARY
C17orf39, also known as GID4, encodes a regulatory subunit of the Mediator complex, the human homolog of the yeast Gid E3 ubiquitin ligase complex[92]. The yeast Gid complex plays a key role in regulation of carbohydrate metabolism[93].

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
CCND3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
Amplification or activation of CCND3 may predict sensitivity to CDK4/6 inhibitors[94-96], such as abemaciclib, palbociclib, and ribociclib[97-102]. As supported by strong preclinical studies, tumors with CCND3 activation depend on CDK4/6[94-96].

FREQUENCY & PROGNOSIS
CCND3 amplification has not been reported not in any of the 27 leiomyosarcoma samples in one dataset[64,90-91]. CCND3 expression was reported to be rare in leiomyosarcoma in one study (found in 0/6 samples), although it was found in a leiomyosarcoma cell line[103]. Another study reported nuclear expression of cyclin D3 in 22% (5/23) of leiomyosarcoma samples[104]. Published data investigating the prognostic implications of CCND3 alterations in sarcomas are limited (PubMed, Jan 2021).

FINDING SUMMARY
CCND3 encodes cyclin D3, a G1/S-specific cell cycle regulator. Cyclin D3 interacts with and regulates the cyclin-dependent kinases CDK4 and CDK6, resulting in the phosphorylation and inactivation of Rb and the progression of the cell cycle[105]. CCND3 amplification has been associated with increased cyclin D3 expression[106].

GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES
Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[107-110]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[111-112], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[99-100,102,113-116]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[117-118], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[97-100,114,119].

FREQUENCY & PROGNOSIS
In the Sarcoma Genome Project dataset, none of the 27 leiomyosarcomas were reported to harbor putative homozygous deletion of either CDKN2A or CDKN2B[64]. However, the loss of CDKN2A and CDKN2B and/or the reduction of p15INK4b and p16INK4a protein levels has been reported in multiple types of sarcomas[120-124]. Promoter hypermethylation of CDKN2A has been reported in 39-53% of leiomyosarcoma samples analyzed, and decreased expression of p16INK4a has been reported in 32% of samples[124-125]. In one study, expression of p16INK4a was absent in 88% of leiomyomas, 79% of smooth muscle tumors of unknown malignant potential, and 43% of leiomyosarcomas[126]. A study of seven leiomyosarcomas of the head and neck did not detect p16INK4a expression in 43% of samples[127]. Loss of p16INK4a, p15INK4b, and/or p14ARF has been associated with poor prognosis in several soft tissue sarcomas, including leiomyosarcoma[121,124,128].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[129-130]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[131-132]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[133-134]. One or more alterations observed here are predicted to result in p16INK4a loss of function[135-156]. One or more alterations seen here are predicted to result in p14ARF loss of function[139,156-159]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[160].

POTENTIAL GERMLINE IMPLICATIONS
Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[161]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[162-163]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[164-166]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[167-169]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
ESR1

ALTERATION
T311M

TRANSCRIPT ID
NM_000125

CODING SEQUENCE EFFECT
932C>T

POTENTIAL TREATMENT STRATEGIES
Therapies that directly target ER-alpha, such as selective ER modulators (SERMs) and the selective ER degrader (SERD) fulvestrant, as well as aromatase inhibitors (AIs) that inhibit estrogen production, are approved to treat ER-positive (ER+) and/or hormone receptor-positive (HR+) breast cancer (NCCN Guidelines v6.2020). AI treatment has also been reported to provide clinical benefit in a subset of HR+ gynecologic malignancies[170-174]. Combinations of fulvestrant and CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib, have also demonstrated efficacy for patients with ESR1-mutated breast cancer[175]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS
In the COSMIC dataset, ESR1 mutations or rearrangements have not been reported in any of the 109 leiomyosarcoma samples analyzed (COSMIC, Mar 2021)[65]. Patients with ER-positive uterine leiomyosarcoma have been reported to respond favorably to the use of aromatase inhibitors, with clinical benefit or improved progression free survival reported in some patients[176-178]. Although estrogen receptor expression is reported in approximately 50% of uterine leiomyosarcoma tumors[177-180], reports vary on the correlation between expression and prognosis, with some studies finding no association[179] and others reporting some correlation with improved progression-free survival for patients in which the disease is confined to the uterine body[180]. A study assessing ESR1 amplification in several tumor types found that ESR1 gene copy number was associated with ER-alpha protein expression in breast (p=0.036), but not in the other tumors[181].

FINDING SUMMARY
ESR1 encodes estrogen receptor alpha (ER-alpha), one of the major estrogen receptor isoforms in humans. Along with co-activator proteins, the ER complex promotes transcription of genes involved in cell cycle progression and survival[182]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Selumetinib

Assay findings association

NF1
R2258*

AREAS OF THERAPEUTIC USE
Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical evidence[46,49] and strong preclinical evidence[51-55] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA
A Phase 2 study of selumetinib with or without temsirolimus in sarcomas that have progressed on up to 2 lines of therapy reported no difference in PFS between the monotherapy and combination (median 1.9 vs 2.1 months, respectively; p=0.77, HR: 0.92), although improved PFS was observed for the combination in the subset of leiomyosarcoma patients (median 1.8 vs 3.7 months; P=0.01, HR: 4.1)[183].

Trametinib

Assay findings association

NF1
R2258*

AREAS OF THERAPEUTIC USE
Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical evidence[46,49] and strong preclinical evidence[51-55] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA
A Phase 1b/2 trial examining a combination of trametinib and pazopanib in patients with soft tissue sarcoma reported 2 partial responses (embryonal rhabdomyosarcoma and spindle cell sarcoma), 12 instances of stable disease and 11 instances of progressive disease with a median progression-free survival (PFS) of 2.27 months and a 4-month PFS of 21.1%; none of the patients with Ewing sarcoma (0/4), leiomyosarcoma (0/6) or liposarcoma (0/4) achieved a response[184]. A Phase 2 study of another MEK inhibitor, selumetinib, reported limited activity in 34 patients with soft tissue sarcoma treated with single-agent selumetinib, with partial response seen in 2 patients and stable disease in 9 patients; combination of selumetinib with the mTOR inhibitor temsirolimus improved progression-free survival in patients with leiomyosarcoma[183]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[62], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[63].

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.

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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
NF1

ALTERATION
R2258*

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Florida, Georgia, Texas, North Carolina, Tennessee, Virginia, Oklahoma, Maryland, Pennsylvania, Ohio

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Randwick (Australia), Blacktown (Australia), Melbourne (Australia), Nedlands (Australia)

NCT02584647

PHASE 1/2

PLX3397 Plus Sirolimus in Unresectable Sarcoma and Malignant Peripheral Nerve Sheath Tumors

TARGETS
mTOR, CSF1R, FLT3, KIT

LOCATIONS: Missouri, New York

NCT03114527

PHASE 2

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

TARGETS
mTOR, CDK6, CDK4

LOCATIONS: Pennsylvania

NCT03660930

PHASE 1/2

Nanoparticle Albumin-Bound Rapamycin and Pazopanib Hydrochloride in Patients With Nonadipocytic Soft Tissue Sarcomas

TARGETS
mTOR, FGFR1, FGFR2, FGFR3, KIT, VEGFRs

LOCATIONS: Washington

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)

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

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

NCT03778996

PHASE 2

SM-88 as Maintenance Therapy for Advanced Ewing's Sarcoma Patients and as Salvage Therapy for Sarcoma Patients

TARGETS
mTOR

LOCATIONS: California

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

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.

BCL2L2
A7D

BCOR
A1681T

BRD4
E1326D

CD36
R337K

CDK12
K976E

CUX1
V1028I

DNM2
H776Q

FLCN
amplification

GPR124
A1152V

HIST1H1E
P14L

KDR
Y209C

MAP3K1
L78P

RAD50
M208V

ROS1
L1204V

TCF3
L130Q

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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*		

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

*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*			

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

The median exon coverage for this sample is 920x

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 status	At ≥20% tumor nuclei	97.0%
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 status	Positive Predictive Value (PPV)	>95.0%
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	

Assay specifications were determined for pical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at 114 homopolymer repeat loci in or near the targeted gene regions of the FoundationOne Heme test. For MSI results, confirmatory testing using a validated orthogonal method should be considered.

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.

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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 more than 250 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 Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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. 2021. 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,

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Cipalstraat 3, 2440 Geel, Belgium.

CE

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

MR Suite Version 4.2.0

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Monument MJ, et al. ISRN Oncol (2012) pmid: 23401795
7. Bonneville R, et al. JCO Precis Oncol (2017) pmid: 29850653
8. Suwa K, et al. J Orthop Sci (1999) pmid: 10370164
9. Verelst SJ, et al. Hum. Pathol. (2004) pmid: 15668899
10. Urso E, et al. Mol. Biol. Rep. (2012) pmid: 22782591
11. Amant F, et al. Int. J. Gynecol. Cancer () pmid: 11437928
12. Quade BJ, et al. Am. J. Pathol. (1999) pmid: 10079273
13. Risinger JI, et al. Cancer Res. (1995) pmid: 7585651
14. Nilbert M, et al. Fam. Cancer (2009) pmid: 19130300
15. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
16. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
17. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
18. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
19. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
20. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
21. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
22. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
23. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
24. Cristescu R, et al. Science (2018) pmid: 30309915
25. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
26. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
27. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
28. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
29. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
30. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
31. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
32. Legrand et al., 2018; ASCO Abstract 12000
33. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
34. Steele CD, et al. Cancer Cell (2019) pmid: 30889380
35. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
36. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
37. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
38. Rizvi NA, et al. Science (2015) pmid: 25765070
39. Johnson BE, et al. Science (2014) pmid: 24336570
40. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
41. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
42. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
43. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
44. Nature (2012) pmid: 22810696
45. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
46. Dombi E, et al. N. Engl. J. Med. (2016) pmid: 28029918
47. Gross AM, et al. N. Engl. J. Med. (2020) pmid: 32187457
48. Fangusaro J, et al. Lancet Oncol. (2019) pmid: 31151904
49. Ameratunga M, et al. J Clin Pharm Ther (2016) pmid: 26936308
50. Woodfield SE, et al. BMC Cancer (2016) pmid: 26925841
51. Jousma E, et al. Pediatr Blood Cancer (2015) pmid: 25907661
52. Nissan MH, et al. Cancer Res. (2014) pmid: 24576830
53. Jessen WJ, et al. J. Clin. Invest. (2013) pmid: 23221341
54. Chang T, et al. J. Clin. Invest. (2013) pmid: 23221337
55. See WL, et al. Cancer Res. (2012) pmid: 22573716
56. Lim SM, et al. Oncotarget (2016) pmid: 26859683
57. Weiss B, et al. Neuro-oncology (2015) pmid: 25314964
58. Janku F, et al. Oncotarget (2014) pmid: 24931142
59. Johannessen CM, et al. Curr. Biol. (2008) pmid: 18164202
60. Johannessen CM, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15937108
61. Malone CF, et al. Cancer Discov (2014) pmid: 24913553
62. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
63. Patterson et al., 2018; AACR Abstract 3891
64. Barretina J, et al. Nat. Genet. (2010) pmid: 20601955
65. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
66. Biochem. Pharmacol. (2012) pmid: 22387046
67. Liew MA, et al. Pediatr. Dev. Pathol. () pmid: 11910511
68. Kluger N, et al. Cases J (2009) pmid: 19946501
69. Bień E, et al. Med Wieku Rozwoj () pmid: 18663267
70. Hattori S, et al. Biochem. Biophys. Res. Commun. (1991) pmid: 1904223
71. Morcos P, et al. Mol. Cell. Biol. (1996) pmid: 8628317
72. Ballester R, et al. Cell (1990) pmid: 2121371
73. Xu GF, et al. Cell (1990) pmid: 2116237
74. Martin GA, et al. Cell (1990) pmid: 2121370
75. Thomas L, et al. Hum. Mutat. (2012) pmid: 22807134
76. Skuse GR, et al. Hum. Mol. Genet. (1997) pmid: 9300663
77. Messiaen LM, et al. Genet. Med. () pmid: 11258625
78. Ars E, et al. Hum. Mol. Genet. (2000) pmid: 10607834
79. Messiaen LM, et al. J. Med. Genet. (2005) pmid: 15863657
80. Poullet P, et al. Mol. Cell. Biol. (1994) pmid: 8264648
81. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
82. Jett K, et al. Genet. Med. (2010) pmid: 20027112
83. Patil S, et al. Oncologist (2012) pmid: 22240541
84. Evans DG, et al. Clin Sarcoma Res (2012) pmid: 23036231
85. Upadhyaya M, et al. J. Med. Genet. (1995) pmid: 8544190
86. Williams VC, et al. Pediatrics (2009) pmid: 19117870
87. van Dartel M, et al. Cancer Genet. Cytogenet. (2004) pmid: 15193436
88. Both J, et al. PLoS ONE (2012) pmid: 22292074
89. van Dartel M, et al. Cancer Genet. Cytogenet. (2003) pmid: 12645656
90. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
91. Gao J, et al. Sci Signal (2013) pmid: 23550210
92. Menssen R, et al. J. Biol. Chem. (2012) pmid: 22645139
93. Santt O, et al. Mol. Biol. Cell (2008) pmid: 18508925
94. Schmitz R, et al. Nature (2012) pmid: 22885699
95. Choi YJ, et al. Cancer Cell (2012) pmid: 23079655
96. Sawai CM, et al. Cancer Cell (2012) pmid: 23079656
97. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
98. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
99. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
100. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
101. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
102. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
103. Bui MM, et al. In Vivo () pmid: 18019405
104. Dei Tos AP, et al. Am. J. Pathol. (1996) pmid: 8644845
105. Sridhar J, et al. AAPS J (2006) pmid: 16584130
106. Kasugai Y, et al. Clin. Cancer Res. (2005) pmid: 16322284
107. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
108. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
109. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
110. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
111. Elvin JA, et al. Oncologist (2017) pmid: 28283584
112. Gao J, et al. Curr Oncol (2015) pmid: 26715889
113. Gopalan et al., 2014; ASCO Abstract 8077
114. Peguero et al., 2016; ASCO Abstract 2528
115. Konecny et al., 2016; ASCO Abstract 5557
116. Johnson DB, et al. Oncologist (2014) pmid: 24797823
117. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
118. Gamble LD, et al. Oncogene (2012) pmid: 21725357
119. Shapiro et al., 2013; ASCO Abstract 2500
120. Louis-Brennetot C, et al. Genes Chromosomes Cancer (2011) pmid: 21910158
121. Endo M, et al. Clin. Cancer Res. (2011) pmid: 21262917
122. Paulson V, et al. Genes Chromosomes Cancer (2011) pmid: 21412928
123. Park JY, et al. Int. J. Gynecol. Cancer (2013) pmid: 23221606
124. Kawaguchi K, et al. J. Pathol. (2003) pmid: 14595762
125. Seidel C, et al. Int. J. Cancer (2005) pmid: 15551306
126. Bodner-Adler B, et al. Gynecol. Oncol. (2005) pmid: 15589581
127. Schütz A, et al. J. Oral Maxillofac. Surg. (2013) pmid: 23434173
128. Obana K, et al. Int. J. Oncol. (2003) pmid: 12963998
129. Quelle DE, et al. Cell (1995) pmid: 8521522
130. Mutat. Res. (2005) pmid: 15878778
131. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
132. Oncogene (1999) pmid: 10498883
133. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
134. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
135. Ruas M, et al. Oncogene (1999) pmid: 10498896
136. Jones R, et al. Cancer Res. (2007) pmid: 17909018
137. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
138. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
139. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
140. Gombart AF, et al. Leukemia (1997) pmid: 9324288
141. Yang R, et al. Cancer Res. (1995) pmid: 7780957
142. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
143. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
144. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
145. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
146. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
147. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
148. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
149. Koh J, et al. Nature (1995) pmid: 7777061
150. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
151. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
152. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
153. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
154. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
155. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
156. Rutter JL, et al. Oncogene (2003) pmid: 12853981

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

157. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
158. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
159. Zhang Y, et al. Cell (1998) pmid: 9529249
160. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
161. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
162. Adv Exp Med Biol (2010) pmid: 20687502
163. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
164. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
165. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
166. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
167. Kaufman DK, et al. Neurology (1993) pmid: 8414022
168. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
169. Chan AK, et al. Clin Neuropathol () pmid: 28699883
170. Straubhar A, et al. Gynecol Oncol Rep (2017) pmid: 28560298
171. Thangavelu A, et al. Gynecol. Oncol. (2013) pmid: 24076063
172. Gershenson DM, et al. J. Clin. Oncol. (2017) pmid: 28221866
173. Esfahani K, et al. BMJ Case Rep (2014) pmid: 24925537
174. Ramirez PT, et al. Gynecol. Oncol. (2008) pmid: 18457865
175. Turner NC, et al. N. Engl. J. Med. (2018) pmid: 30345905
176. Thanopoulou E, et al. Clin Sarcoma Res (2014) pmid: 25018868
177. O'Cearbhaill R, et al. Gynecol. Oncol. (2010) pmid: 19932916
178. George S, et al. Cancer (2014) pmid: 24222211
179. Bodner K, et al. Anticancer Res. () pmid: 12680175
180. Leitao MM, et al. Gynecol. Oncol. (2012) pmid: 22085894
181. Tsiambas E, et al. Med. Oncol. (2011) pmid: 20458558
182. Pearce ST, et al. Crit. Rev. Oncol. Hematol. (2004) pmid: 15094156
183. Eroglu Z, et al. Br. J. Cancer (2015) pmid: 25897676
184. Subbiah V, et al. Clin. Cancer Res. (2017) pmid: 28377484

Electronically signed by Chelsea Marcus, M.D. | 12 July 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531