FOUNDATIONONE®HEME

PATIENT
Wang, Fu Ting

TUMOR TYPE
Soft tissue perivascular epithelioid cell tumor (PEComa)

COUNTRY CODE
TW

REPORT DATE
26 Apr 2023

ORDERED TEST #
ORD-1611555-01

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

PATIENT
DISEASE Soft tissue perivascular epithelioid cell tumor (PEComa)
NAME Wang, Fu Ting
DATE OF BIRTH 18 April 1996
SEX Female
MEDICAL RECORD # 49390887

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

SPECIMEN
SPECIMEN SITE Vagina
SPECIMEN ID S112-66474 N (PF23038)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 07 April 2023
SPECIMEN RECEIVED 17 April 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

TFE3 **NONO-TFE3 fusion**

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***TFE3*** **NONO-TFE3 fusion** (p. 3)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Sunitinib** (p. 4)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 5)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 0 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)
TFE3 **-** NONO-TFE3 fusion	none	Sunitinib
10 Trials see p. 5		

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

Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

Electronically signed by Lena Stuart, M.D. | 26 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., 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

— 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, of which 25% were liposarcomas, only 0.8% (2/255) of samples were MSI-high (MSI-H)[6]. However, reports of MSI in sarcomas in the literature are conflicting and varied due to substantial heterogeneity, lack of consensus on the markers and methods used for MSI assessment, and small sample size in most studies[7]. In these smaller studies of soft tissue sarcoma, reports of MSI at any level have been rare, with the highest incidences between 11% (2/18) to 25% (10/40) of cases[8-13]. In one study, MSI was reported to occur more frequently in high-grade soft tissue sarcomas compared with lower grade[14]. However, published data investigating the prognostic implications of MSI in sarcoma are limited (PubMed, Jan 2023).

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
0 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[21-23], anti-PD-1 therapies[21-24], and combination nivolumab and ipilimumab[25-30]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[21-24,31-35]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[31]; similar findings were observed in the KEYNOTE 028 and 012 trials[24]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[35]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[36]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[34]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[37] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[22].

FREQUENCY & PROGNOSIS

Perivascular epithelioid cell tumors harbor a median TMB of 1.6 mutations per megabase (muts/Mb) in a study of 31 cases[38]. Soft tissue sarcomas harbor a median tumor mutational burden (TMB) of 2.4-2.5 mutations per megabase (muts/Mb), with angiosarcoma (up to 15%) and malignant peripheral nerve sheath tumor (up to 11%) having the highest percentage of cases with high TMB[39-40]. In a study, 3.9% of soft tissue sarcoma samples analyzed harbor TMB ≥10 muts/Mb[39]; in addition, increased mutational burden has been reported in undifferentiated pleomorphic sarcomas as compared with Ewing sarcomas or rhabdomyosarcomas[41-43]. Published data investigating the prognostic implications of tissue TMB in sarcoma are conflicting (PubMed, Feb 2023). High tissue TMB was associated with improved PFS and metastasis-free survival in a study of undifferentiated sarcomas[44], but with reduced survival in a study of patients with rhabdomyosarcoma[45].

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[46-47] and cigarette smoke in lung cancer[48-49], treatment with temozolomide-based chemotherapy in glioma[50-51], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[52-56], and microsatellite instability (MSI)[52,55-56]. 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].

GENE
TFE3

ALTERATION
NONO-TFE3 fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical benefit in certain TFE3-rearranged solid tumors has been reported in response to anti-angiogenic agents such as sunitinib[57-64], sorafenib[57-58], and cediranib[65-66]; to mTOR inhibitors[58,67-72]; and to MET inhibitors[73-74]. Clinical studies have shown high response rates to treatment with sunitinib for patients with TFE3 fusion-associated cancers, including alveolar soft part sarcoma (ASPS)[62-64] and translocation renal cell carcinoma (tRCC or Xp11.2 RCC)[57-61]. In addition, TFE3 fusions result in increased MET expression[73,75-76] and clinical and preclinical sensitivity to MET inhibitors[73-75]; a Phase 2 study of crizotinib to treat advanced or metastatic ASPS reported 1 PR and 35 SDs out of 40 MET-expressing cases[73]. Two patients with Xp11.2 RCC experienced clinical benefit from immune checkpoint inhibitors, with ongoing time on treatments of 37 and 15.7 months in a retrospective analysis (n=8)[67].

FREQUENCY & PROGNOSIS

TFE3 rearrangements have been observed in a variety of types of perivascular epithelioid cell tumors (PEComa), including those of cervical, renal, and uterine origin[77-79]. Due to the low frequency of PEComa cases, the incidence of TFE3 rearrangement or mutation in PEComa is unclear. However, one study tested 29 PEComa patients for TFE3 alteration and identified 4 (14%) patients with TFE3 rearrangements and concomitant increased TFE3 expression as well as an additional 4 (14%) patients with increased TFE3 expression[78]. Another study reported TFE3 rearrangement in 23% (9/38) of PEComa patients and identified TFE3 rearrangements as being mutually exclusive from TSC2 mutation, a frequent mutation found in PEComa[80]. TFE3 rearrangements are generally rare in human cancer but characterize Xp11 translocation cancers, which include renal cell carcinoma, perivascular epithelioid cell tumor (PEComa), epithelioid hemangioendothelioma, alveolar soft part sarcoma, and melanotic Xp11 neoplasm, with a variety of TFE3 fusion partners reported in these diseases[81]. An analysis of 3 PEComa patients with TFE3 rearrangement and increased expression reported that 2 of the 3 patients exhibited histological malignancy and aggressive growth, while the other patient exhibited a benign course[82].

FINDING SUMMARY

TFE3 encodes the transcription factor for immunoglobulin heavy chain enhancer 3 protein. Multiple fusions with TFE3 as a 3' partner have been reported in cancer and characterized as activating[76,83-87]. NONO-TFE3 fusions have been reported in renal cell carcinomas[85,88-90] and neoplasms with melanocytic differentiation including melanocytic perivascular epithelioid cell neoplasms (PEComas)[90-92] and are likely activating[88,93-94], although one in vitro study found NONO-TFE3 was unable to activate transcription[87].

POTENTIAL DIAGNOSTIC IMPLICATIONS

TFE3 rearrangements are characteristic of a group of neoplasms known as Xp11 translocation cancers, which include renal cell carcinoma, PEComa, epithelioid hemangioendothelioma, alveolar soft part sarcoma, and melanotic Xp11 neoplasm[81,95-101].

Sunitinib

Assay findings association

TFE3
NONO-TFE3 fusion

AREAS OF THERAPEUTIC USE

Sunitinib is a small-molecule tyrosine kinase inhibitor that targets PDGFRs, VEGFRs, KIT, FLT3, CSF-1R, and RET. It is FDA approved for the treatment of advanced or metastatic pancreatic neuroendocrine tumors, gastrointestinal stromal tumors (GISTs) in patients who have progressed on or are intolerant to imatinib, and advanced renal cell carcinoma (RCC) as well as for the adjuvant treatment of patients at high risk of recurrent RCC after nephrectomy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

TFE3 fusions may confer sensitivity to sunitinib, based on both clinical[57-64] and preclinical[76,102-104] evidence.

SUPPORTING DATA

Clinical data on the efficacy of sunitinib for the treatment of PEComa and angiomyolipoma are limited (PubMed, Apr 2023). A patient with malignant PEComa of the kidney treated with sunitinib for 4 weeks followed by resection exhibited a durable response before progressing[105]. A patient with epithelioid angiomyolipoma (EAML) of kidney treated with sunitinib had a short response for 2 months[106]. Another patient with kidney EAML who was treated with sunitinib for a short time and then switched to everolimus experienced favorable response for 30 months[107].

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

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
TFE3

ALTERATION
NONO-TFE3 fusion

RATIONALE
TFE3 fusions may activate angiogenic pathways and increase expression of the MET oncogene and may therefore confer sensitivity to MET inhibitors or to tyrosine kinase inhibitors such as sunitinib, sorafenib, or cediranib. TFE3 fusions may also predict sensitivity to mTOR inhibitors.

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), North Adelaide (Australia), Bedford Park (Australia)

NCT05439993

PHASE 1/2

Tepotinib Plus Paclitaxel in MET Amplified or MET Exon 14 Alterated Gastric and GEJ Carcinoma

TARGETS
MET

LOCATIONS: Gyeonggi-do (Korea, Republic of)

NCT03784014

PHASE 3

MOLECULAR PROFILING OF ADVANCED SOFT-TISSUE SARCOMAS

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

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

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT04220229

PHASE 1/2

Cabozantinib With Radiation Therapy for the Treatment of Sarcomas of the Extremities

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Washington

NCT04200443

PHASE 2

Cabozantinib and Temozolomide for the Treatment of Unresectable or Metastatic Leiomyosarcoma or Other Soft Tissue Sarcoma

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: California, Iowa, Wisconsin, Illinois, Missouri

NCT05135975

PHASE 2

A Study of Cabozantinib as a Maintenance Agent to Prevent Progression or Recurrence in High-Risk Pediatric Solid Tumors

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Ohio

NCT05468359

PHASE 1/2

Safety and Efficacy of Cyclophosphamide, Sorafenib, Bevacizumab, and Atezolizumab in Pediatric Solid Tumor Patients

TARGETS
RET, KIT, RAFs, FLT3, VEGFRs, VEGFA, PD-L1

LOCATIONS: Tennessee

NCT02484404

PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, VEGFRs, PDGFRA, PDGFRB, KIT, PD-L1

LOCATIONS: Maryland

NCT05038839

PHASE 1

Cabozantinib and Pamiparib for the Treatment of Advanced of Refractory Solid Tumors

TARGETS
MET, ROS1, RET, VEGFRs, PARP

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
NM_000038.4: c.3374T>C
(p.V1125A)
chr5:112174665

ASXL1
NM_015338.5: c.342T>G
(p.N114K)
chr20:31016020

FLT1
NM_002019.4: c.2434C>T
(p.R812W)
chr13:28913359

MAP3K14
NM_003954.4: c.295C>T
(p.R99C)
chr17:43366633

NUP98
NM_016320.4: c.4891A>C
(p.K1631Q)
chr11:3704457

PRKDC
NM_006904.6: c.9844C>A
(p.R3282S)
chr8:48715945

SOCS1
NM_003745.1: c.44C>T
(p.T15I)
chr16:11349292

FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies and sarcomas that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay utilizes DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACTB*	*ADGRA2 (GPR124)*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	
APC	*APH1A*	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*		*ARID1A*	*ARID2*
ASMTL	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*
B2M	*BAP1*	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*	*BCL7A*
BCOR	*BCORL1*	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*
BRSK1	*BTG2*	*BTK*	*BTLA*	*CAD*	*CALR**	*CARD11*	*CBFB*	*CBL*
CCN6 (WISP3)	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CCT6B*	*CD22*	*CD274 (PD-L1)*	*CD36*
CD58	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*	*CDK12*	*CDK4*	*CDK6*
CDK8	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*
CIC	*CIITA*	*CKS1B*	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*
DNMT3A	*DOT1L*	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*	*EGFR*
ELP2	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*
ERBB4	*ERG*	*ESR1*	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*	*FAF1*	*FANCA*
FANCC	*FANCD2*	*FANCE*	*FANCF*	*FANCG*	*FANCL*	*FAS (TNFRSF6)*	*FBXO11*	*FBXO31*
FBXW7	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*
FGFR2	*FGFR3*	*FGFR4*	*FHIT*	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*
FOXL2	*FOXO1*	*FOXO3*	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*
GID4 (C17orf39)	*GNA11*	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GRIN2A*	*GSK3B*	*GTSE1*
HDAC1	*HDAC4*	*HDAC7*	*HGF*	*H1-2 (HIST1H1C)*		*H1-3 (HIST1H1D)*		
H1-4 (HIST1H1E)		*H2AC6 (HIST1H2AC)*		*H2AC11 (HIST1H2AG)*		*H2AC16 (HIST1H2AL)*		
H2AC17 (HIST1H2AM)		*H2BC4 (HIST1H2BC)*		*H2BC11 (HIST1H2BJ)*		*H2BC12 (HIST1H2BK)*		
H2BC17 (HIST1H2BO)		*H3C2 (HIST1H3B)*		*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*
IDH1	*IDH2*	*IGF1R*	*IKBKE*	*IKZF1*	*IKZF2*	*IKZF3*	*IL7R*	*INHBA*
INPP4B	*INPP5D (SHIP)*	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*
KEAP1	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LEF1*	*LRP1B*
LRRK2	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*
MAP3K14	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEF2C	*MEN1*	*MET*	*MIB1*	*MITF*	*MKI67*	*MLH1*	*MPL*	*MRE11 (MRE11A)*
MSH2	*MSH3*	*MSH6*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
MYO18A	*NCOR2*	*NCSTN*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*
NOTCH1	*NOTCH2*	*NPM1*	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NT5C2*	*NTRK1*	*NTRK2*
NTRK3	*NUP93*	*NUP98*	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*	*PAX5*
PBRM1	*PC*	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*		*PDGFRA*
PDGFRB	*PDK1*	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*
PTPN2	*PTPN6 (SHP-1)*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*	*RARA*	*RASGEF1A*
RB1	*RELN*	*RET*	*RHOA*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*RUNX1*
S1PR2	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SERP2*	*SETBP1*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA1*	*SMARCA4*	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*
SOCS1	*SOCS2*	*SOCS3*	*SOX10*	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*
STAG2	*STAT3*	*STAT4*	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*
TAF1	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TENT5C (FAM46C)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*
TMSB4XP8 (TMSL3)		*TNFAIP3*	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*
TRAF2	*TRAF3*	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*

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

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

HEMATOLOGICAL MALIGNANCY DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*	*EPOR*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FGFR2*	*IGH*	*IGK*	*IGL*
JAK1	*JAK2*	*KMT2A (MLL)*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*	*RARA*
RET	*ROS1*	*TMPRSS2*	*TRG*					

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

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFDN (MLLT4 or AF6)*		*AFF1*	*AFF4*	*ALK*
ARHGAP26 (GRAF)		*ARHGEF12*	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*
BCL10	*BCL11A*	*BCL11B*	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*
BCR	*BIRC3*	*BRAF*	*BTG1*	*CAMTA1*	*CARS1 (CARS)*	*CBFA2T3*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CD274 (PD-L1)*	*CDK6*	*CDX2*	*CEP43 (FGFR1OP)*	*CHIC2*	*CHN1*
CIC	*CIITA*	*CLP1*	*CLTC*	*CLTCL1*	*CNTRL (CEP110)*	*COL1A1*	*CREB3L1*	*CREB3L2*
CREBBP	*CRLF2*	*CSF1*	*CTNNB1*	*DDIT3*	*DDX10*	*DDX6*	*DEK*	*DUSP22*
EGFR	*EIF4A2*	*ELF4*	*ELL*	*ELN*	*EML4*	*EP300*	*EPOR*	*EPS15*
ERBB2	*ERG*	*ETS1*	*ETV1*	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*
FCRL4	*FEV*	*FGFR1*	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*
FOXO4	*FOXP1*	*FSTL3*	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*H4C9 (HIST1H4I)*
HERPUD1	*HEY1*	*HIP1*	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*	*HOXA3*
HOXA9	*HOXC11*	*HOXC13*	*HOXD11*	*HOXD13*	*HSP90AA1*	*HSP90AB1*	*IGH*	*IGK*
IGL	*IKZF1*	*IL21R*	*IL3*	*IRF4*	*ITK*	*JAK1*	*JAK2*	*JAK3*
JAZF1	*KAT6A (MYST3)*	*KDSR*	*KIF5B*	*KMT2A (MLL)*	*LASP1*	*LCP1*	*LMO1*	*LMO2*
LPP	*LYL1*	*MAF*	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MLF1*	*MLLT1 (ENL)*
MLLT10 (AF10)	*MLLT3*	*MLLT6*	*MN1*	*MNX1*	*MRTFA (MKL1)*	*MSI2*	*MSN*	*MUC1*
MYB	*MYC*	*MYH11*	*MYH9*	*NACA*	*NBEAP1 (BCL8)*	*NCOA2*	*NDRG1*	*NF1*
NF2	*NFKB2*	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NSD2 (WHSC1 or MMSET)*	
NSD3 (WHSC1L1)	*NTRK1*	*NTRK2*	*NTRK3*	*NUMA1*	*NUP214*	*NUP98*	*NUTM2A*	*OMD*
P2RY8	*PAFAH1B2*	*PAX3*	*PAX5*	*PAX7*	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2 (PD-L2)*
PDE4DIP	*PDGFB*	*PDGFRA*	*PDGFRB*	*PER1*	*PHF1*	*PICALM*	*PIM1*	*PLAG1*
PML	*POU2AF1*	*PPP1CB*	*PRDM1*	*PRDM16*	*PRRX1*	*PSIP1*	*PTCH1*	*PTK7*
RABEP1	*RAF1*	*RALGDS*	*RAP1GDS1*	*RARA*	*RBM15*	*RET*	*RHOH*	*RNF213*
RNF217-AS1 (STL)		*ROS1*	*RPL22*	*RPN1*	*RUNX1*	*RUNX1T1 (ETO)*	*RUNX2*	*SEC31A*
SEPTIN5 (SEPT5)	*SEPTIN6 (SEPT6)*	*SEPTIN9 (SEPT9)*	*SET*	*SH3GL1*	*SLC1A2*	*SNX29 (RUNDC2A)*		*SRSF3*
SS18	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*SYK*	*TAF15*	*TAL1*	*TAL2*
TBL1XR1	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TEC*	*TET1*	*TFE3*	*TFG*	*TFPT*	*TFRC*
TLX1	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*	*TPM3*	*TPM4*	*TRIM24*
TRIP11	*TTL*	*TYK2*	*USP6*	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*	*ZNF521*

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

The median exon coverage for this sample is 668x

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

*95% Confidence Interval

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

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

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

ABOUT FOUNDATIONONE HEME

FoundationOne®Heme is a comprehensive genomic profiling test for hematologic malignancies and sarcomas. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials, and quantitative markers that may support immunotherapy clinical trial enrollment. FoundationOne Heme is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across 265 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas.

FoundationOne Heme was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne Heme identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that FoundationOne Heme data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne Heme for identifying a copy number amplification is five (5) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that FoundationOne Heme data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that FoundationOne Heme analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne Heme.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne Heme is performed using DNA and RNA derived from tumor, and as such germline events may not be reported.

The following targets typically have low coverage resulting in a reduction in sensitivity: SDHD exon 4, TNFRSF11A exon1, and TP53 exon 1.

FoundationOne Heme fulfills the requirements of the European Directive 98/79 EC for in vitro

diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium.

CE

REPORT HIGHLIGHTS

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.8.0

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. Bonneville R, et al. JCO Precis Oncol (2017) pmid: 29850653
7. Monument MJ, et al. ISRN Oncol (2012) pmid: 23401795
8. Wooster R, et al. Nat. Genet. (1994) pmid: 8162069
9. Kawaguchi K, et al. Oncol. Rep. (2005) pmid: 15643505
10. Saito T, et al. Hum. Pathol. (2003) pmid: 14562278
11. Suwa K, et al. J Orthop Sci (1999) pmid: 10370164
12. Garcia JJ, et al. Mod. Pathol. (2006) pmid: 16619000
13. Aue G, et al. Cancer Genet. Cytogenet. (1998) pmid: 9689926
14. Rucińska M, et al. Med. Sci. Monit. (2005) pmid: 15668629
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. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
33. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
34. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
35. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
36. Schenker at al., 2022; AACR Abstract 7845
37. Legrand et al., 2018; ASCO Abstract 12000
38. Akumalla S, et al. Oncology (2020) pmid: 32966992
39. Gounder MM, et al. Nat Commun (2022) pmid: 35705558
40. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
41. Lim J, et al. Clin. Cancer Res. (2015) pmid: 26330427
42. Brohl AS, et al. PLoS Genet. (2014) pmid: 25010205
43. Chen X, et al. Cancer Cell (2013) pmid: 24332040
44. Steele CD, et al. Cancer Cell (2019) pmid: 30889380
45. Casey DL, et al. Clin Cancer Res (2020) pmid: 31699828
46. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
47. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
48. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
49. Rizvi NA, et al. Science (2015) pmid: 25765070
50. Johnson BE, et al. Science (2014) pmid: 24336570
51. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
52. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
53. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
54. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
55. Nature (2012) pmid: 22810696
56. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
57. Choueiri TK, et al. Cancer (2010) pmid: 20665500
58. Malouf GG, et al. Ann. Oncol. (2010) pmid: 20154303
59. Numakura K, et al. Int. J. Clin. Oncol. (2011) pmid: 21161315
60. Liu YC, et al. Jpn. J. Clin. Oncol. (2011) pmid: 21965162
61. Chowdhury T, et al. J. Pediatr. Hematol. Oncol. (2013) pmid: 22995920
62. Stacchiotti S, et al. Clin. Cancer Res. (2009) pmid: 19188185
63. Stacchiotti S, et al. Ann. Oncol. (2011) pmid: 21242589
64. Orbach D, et al. Pediatr Blood Cancer (2013) pmid: 23857870
65. Kummar S, et al. J. Clin. Oncol. (2013) pmid: 23630200
66. Judson I, et al. Clin. Cancer Res. (2014) pmid: 24714778
67. Marcon J, et al. Clin Cancer Res (2020) pmid: 32220885
68. Qu Y, et al. Sci Rep (2016) pmid: 27026382
69. Rua Fernández OR, et al. Urology (2018) pmid: 29702156
70. Koh Y, et al. Ann Oncol (2013) pmid: 23180114
71. Kakoki K, et al. Clin Genitourin Cancer (2017) pmid: 28190703
72. Parikh J, et al. Rare Tumors (2009) pmid: 21139932
73. Schöffski P, et al. Ann. Oncol. (2018) pmid: 29216400
74. Wedekind MF, et al. Pediatr Blood Cancer (2017) pmid: 28417541
75. Tsuda M, et al. Cancer Res. (2007) pmid: 17283122
76. Kobos R, et al. J. Pathol. (2013) pmid: 23288701
77. Liu F, et al. Int J Clin Exp Pathol (2014) pmid: 25337301
78. Argani P, et al. Am. J. Surg. Pathol. (2010) pmid: 20871214
79. Schoolmeester JK, et al. Am. J. Surg. Pathol. (2015) pmid: 25517951
80. Agaram NP, et al. Am. J. Surg. Pathol. (2015) pmid: 25651471
81. Wang XT, et al. Mod. Pathol. (2018) pmid: 29713041
82. Shen Q, et al. Virchows Arch. (2014) pmid: 25239799
83. Gotoh M, et al. Genes Chromosomes Cancer (2014) pmid: 25230976
84. Argani P, et al. Am. J. Pathol. (2001) pmid: 11438465
85. Clark J, et al. Oncogene (1997) pmid: 9393982
86. Weterman MJ, et al. Oncogene (2000) pmid: 10644981
87. Skalsky YM, et al. Oncogene (2001) pmid: 11313942
88. Sato Y, et al. Nat. Genet. (2013) pmid: 23797736
89. Xia QY, et al. Mod Pathol (2017) pmid: 27934879
90. Argani P, et al. Am. J. Surg. Pathol. (2016) pmid: 26975036
91. McGregor SM, et al. Am J Surg Pathol (2017) pmid: 28009605
92. Wang XT, et al. Histopathology (2016) pmid: 26844676
93. Davis IJ, et al. Cancer Cell (2006) pmid: 16766266
94. Kauffman EC, et al. Nat Rev Urol (2014) pmid: 25048860
95. Weterman MA, et al. Proc Natl Acad Sci U S A (1996) pmid: 8986805
96. Argani P, et al. Oncogene (2003) pmid: 12917640
97. Bruder E, et al. Am. J. Surg. Pathol. (2004) pmid: 15316311
98. Trpkov K, et al. Mod Pathol (2021) pmid: 33664427
99. Moch H, et al. Eur Urol (2016) pmid: 26935559
100. Warren TE, et al. Heart Lung (1983) pmid: 6575003
101. Cajaiba MM, et al. Cancer (2018) pmid: 29905933
102. Vistica DT, et al. J. Pediatr. Hematol. Oncol. (2009) pmid: 19636271
103. Covell DG, et al. PLoS ONE (2012) pmid: 23226201
104. Ford KM, et al. Mol. Vis. (2012) pmid: 22419845
105. AlAzab RS, et al. Res Rep Urol (2019) pmid: 32010646
106. Citak EC, et al. Can Urol Assoc J () pmid: 26279736
107. Huľová S, et al. Klin Onkol (2018) pmid: 30545225