FOUNDATIONONE®HEME

PATIENT
Wei, Ming Yeh

TUMOR TYPE
Soft tissue sarcoma (NOS)
COUNTRY CODE
TW

REPORT DATE
14 Jul 2023
ORDERED TEST #
ORD-1665268-01

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 sarcoma (NOS)
NAME Wei, Ming Yeh
DATE OF BIRTH 14 August 1980
SEX Male
MEDICAL RECORD # 49476053

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 Bone
SPECIMEN ID S112-20200A (PF23085)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 04 May 2023
SPECIMEN RECEIVED 30 June 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

BRIP1 P488S
IDH1 R132C
TP53 Y220C
PHF6 loss
SGK1 rearrangement intron 1

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Ivosidenib** (p. 7), **Niraparib** (p. 7), **Olaparib** (p. 8), **Rucaparib** (p. 9), **Talazoparib** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 3 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)**
BRIP1 - P488S	none	Niraparib
		Olaparib
		Rucaparib
10 Trials see p. 11		Talazoparib
IDH1 - R132C	none	Ivosidenib
10 Trials see p. 13		
TP53 - Y220C	none	none
1 Trial see p. 15		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

PHF6 - loss ..... p. 6
SGK1 - rearrangement intron 1 ..... p. 6

Electronically signed by Douglas A. Mata, MD, MPH | 14 July 2023
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NOTE Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type.

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

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. 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
3 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

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[38-39]. In a study, 3.9% of soft tissue sarcoma samples analyzed harbor TMB ≥10 muts/Mb[38]; in addition, increased mutational burden has been reported in undifferentiated pleomorphic sarcomas as compared with Ewing sarcomas or rhabdomyosarcomas[40-42]. 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[43], but with reduced survival in a study of patients with rhabdomyosarcoma[44].

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[45-46] and cigarette smoke in lung cancer[47-48], treatment with temozolomide-based chemotherapy in glioma[49-50], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[51-55], and microsatellite instability (MSI)[51,54-55]. 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
BRIP1

ALTERATION
P488S

HGVS VARIANT
NM_032043.2:c.1462C>T (p.P488S)

VARIANT CHROMOSOMAL POSITION
chr17:59870969

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical responses in ovarian cancer[56] and prostate cancer[57], as well as clinical benefit in breast cancer[58], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. 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

BRIP1 alterations are rare in sarcomas, with 1 mutation and 0 losses detected among 413 patients with sarcoma in two genomic studies[59-60]. Published data investigating the prognostic implications of BRIP1 alterations in sarcoma are limited (PubMed, Feb 2023).

FINDING SUMMARY

BRIP1, also known as FANCJ (Fanconi Anemia complementation group J) and BACH1, encodes a DNA helicase required for DNA repair and the maintenance of chromosomal stability[61-63]. 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.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in BRIP1 are associated with increased risk of breast, ovarian, and cervical cancers[64-68]. Germline mutations in BRIP1 are also associated with Fanconi anemia (FA), a rare autosomal disorder that predisposes patients to a subset of cancers, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), gynecological malignancies, and head and neck tumors[69-71]; frequency estimates suggest an incidence of 3/1,000,000 individuals in Europe and the US, and a heterozygote carrier frequency of 1/181 to 1/300 in the US and Europe, respectively, with slightly higher rates in some populations, such as the Ashkenazi Jewish population (1/89)[70,72]. In the appropriate clinical context, germline testing of BRIP1 is recommended.

GENE
IDH1

ALTERATION
R132C

HGVS VARIANT
NM_005896.2:c.394C>T (p.R132C)

VARIANT CHROMOSOMAL POSITION
chr2:209113113

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib[73] and olutasidenib[74]. A Phase 1B/2 basket study of the IDH1 inhibitor olutasidenib reported a DCR of 48% (12/25, 2 PR) in patients with glioma; patients with other solid tumors including intrahepatic cholangiocarcinoma and chondrosarcoma achieved SD[74]. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)[75]. Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors[76-79].

FREQUENCY & PROGNOSIS

In the TCGA Sarcoma dataset, IDH1 mutations have been reported in fewer than 1% of samples[80]. Published data investigating the prognostic implications of IDH1 mutations in soft tissue sarcoma are limited (PubMed, Sep 2022). Research suggests that IDH gene mutations could be early stage events in specific cancers; in central conventional cartilaginous cancer, benign tumors (enchondromas), which are known for their ability to transform into chondrosarcomas, have been reported to possess IDH mutations in 87% of reviewed cases[81-82]. Assessment of IDH1 and IDH2 mutation status has been suggested to be of potential value for aiding in diagnosis of chondrosarcomas, including differentiation of chondrosarcoma from chondroblastic osteosarcoma and of intracranial chondrosarcoma from chordoma[83-84].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis[85]. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer[85-89]. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)[87-91], which promotes tumorigenesis[87,92-95].

GENE
TP53

ALTERATION
Y220C

HGVS VARIANT
NM_000546.4:c.659A>G (p.Y220C)

VARIANT CHROMOSOMAL POSITION
chr17:7578190

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data suggest that solid tumors with TP53 mutations, such as R175H, Y220C, G245S, and R248W, may benefit from adoptive cell therapy targeting these specific TP53 mutations[96]. Clinical benefit has been reported for patients with breast cancer (2 PRs)[96], ovarian cancer (1 PR)[96], and colorectal cancer (CRC; 1 SD)[97] treated with tumor infiltrating lymphocyte-based or modified T-cell receptor-based adoptive cell therapy. For patients with TP53 Y220C-mutated disease, a Phase 1 study of the Y220C-specific reactivator PC14586 reported an ORR of 32% (8/25) and DCR of 88% (22/25) at higher doses across a variety of solid tumor types[98]. There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[99-102] or p53 gene therapy such as SGT53[103-107]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[108]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[109]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[110]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[111]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[112]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[113]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[114]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[107]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[115]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[116].

FREQUENCY & PROGNOSIS

TP53 mutations and homozygous deletion have been observed in 33% and 9.4% of sarcoma samples in the TCGA dataset, respectively (cBioPortal, Feb 2023)[117-118]. TP53 alterations appear to lead to chromosomal instability and drive oncogenesis in soft tissue sarcomas[119]. One study of soft tissue sarcomas reported that TP53 non-frameshift mutations correlated with poor prognosis, including lymph node metastasis, increased rate of relapse, and decreased OS[120].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[121]. Alterations such as seen here may disrupt TP53 function or expression[122-126]. TP53 Y220C is targetable by mutation-specific inhibitors such as PC14586[98].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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 Li-Fraumeni syndrome (ClinVar, Apr 2023)[127]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[128-130], including sarcomas[131-132]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[133] to 1:20,000[132]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[134]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[135-140]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[135-136]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[141]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[139,142-143]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
PHF6

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials directly targeting the loss of PHF6 activity.

FREQUENCY & PROGNOSIS

PHF6 mutations have been reported in up to 40% of T-cell acute lymphoblastic leukemias (T-ALLs)[144-151]. PHF6 mutations are more commonly found in adult T-ALL than pediatric T-ALL and may be associated with reduced overall survival, although this has not been consistently observed[144,148]. PHF6 mutations have been seen in approximately 2-3% of acute myeloid leukemias (AMLs)[145,149] and associated with poorer outcome for patients with AML[152]; they have been observed to affect males with a greater frequency than females[145].

FINDING SUMMARY

PHF6 encodes PHD finger protein 6, which has been implicated in ribosomal RNA biogenesis and chromatin remodeling[153-154]. PHF6 loss-of-function mutations have been associated with hematopoietic malignancies[145,155]. Mutations in PHF6 underlie the X-linked disorder Börjeson-Forssman-Lehmann syndrome[156-157].

GENE
SGK1

ALTERATION
rearrangement intron 1

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The PI3K inhibitor LY294002 has been reported to block SGK1 activity in a preclinical study[158]. Several SGK1 inhibitors[159-164] have been developed but are not suitable for clinical use. SGK1 and NDRG1 expression were reported to be increased in three PIK3CA-mutated breast cancer samples from patients who did not respond to treatment with the PI3K inhibitor BYL719 in combination with aromatase inhibitor[160]. Additionally, preclinical studies have reported that SGK1 expression confers resistance to BYL719 in breast cancer cells harboring PIK3CA activating mutations[160] and to the AKT inhibitors AZD5363 and MK2206 in breast cancer cells[165].

FREQUENCY & PROGNOSIS

SGK1 mutation has been observed in 6-16% of diffuse large B-cell lymphomas[166], 5/7 cases of variant nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), and 1/6 cases of typical NLPHL[167]. SGK1 amplification and mutation have rarely been observed in other tumor types (cBioPortal, COSMIC, 2023)[117-118,168]. Increased SGK1 expression has been reported in lung squamous cell carcinoma[169], endometrioid endometrial carcinoma[170], glioblastoma[171], and breast cancer[172].

FINDING SUMMARY

SGK1 encodes serum/glucocorticoid regulated kinase 1, which activates ion channels in response to cellular stress. SGK1 can be activated by PI3K-mTORC2 signaling[173] and can in turn activate mTORC1[160].

Ivosidenib

Assay findings association

IDH1
R132C

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML) or previously treated locally advanced or metastatic cholangiocarcinoma. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML[174] and cholangiocarcinoma[175-176] and limited clinical data in myelodysplastic syndrome (MDS)[174] and glioma[73,177] , IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

Ivosidenib has shown clinical activity in diverse IDH1-mutated solid tumor types. In the Phase 3 ClaIDHy trial, patients with IDH1 R132-mutated cholangiocarcinoma treated with ivosidenib, compared to placebo, had a significantly increased PFS (HR=0.37, p<0.001) and numerically increased OS (HR=0.79, p=0.093) that became significant once adjusted for crossover (HR=0.49, p<0.0001)[176,178] . For patients with glioma, treatment with ivosidenib resulted in high rates of SD (72.7% [8/11] and 87.5% [21/24] for patients in the dose escalation and expansion cohorts, respectively)[179]. A cohort of patients with chondrosarcoma that harbored a high incidence of IDH1 R132 mutation (n=15/21) achieved a high rate of SD (55.0% [11/20]), including 3 SDs >1.5 years[180]. In a Phase 1 trial for patients with IDH1-mutated solid tumors, including chondrosarcoma, cholangiocarcinoma, and glioma, ivosidenib led to 4 PRs[73].

Niraparib

Assay findings association

BRIP1
P488S

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian[56,181-182] , breast[58], endometrial[183], and prostate cancer[57], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 1 study of niraparib with temozolomide or irinotecan for patients with Ewing sarcoma reported an ORR of 8.3%, with 1/12 patient achieving a PR; the median PFS was 16.3 weeks[184]. Niraparib has primarily been evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS compared with placebo in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months), as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[185]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer experienced SD[186]. A Phase 1 study of the combination of niraparib and bevacizumab for patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[187]. A Phase 2 study of niraparib reported 1 PR and 8 SDs, with 78% (7/9) of patients with BAP1-mutated cholangiocarcinoma, mesothelioma, uveal melanoma, or clear cell renal cell carcinoma (ccRCC) experiencing SD[188]. A case study reported a patient with BAP1-mutated pretreated ccRCC experienced a PR of 5 months on niraparib[189].

Olaparib

Assay findings association

BRIP1
P488S

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian[56,181-182], breast[58], endometrial[183], and prostate cancer[57], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Olaparib has been evaluated in a Phase 1b study for the treatment of patients with advanced and unresectable bone and soft tissue sarcomas with radiographic progression after first- or further-line therapy; among 22 evaluable patients, 18% (4/22) with synovial sarcoma or leiomyosarcoma achieved PR, and 23% (5/22) with liposarcoma, Ewing sarcoma, solitary fibrous tumor or malignant peripheral nerve sheath tumor achieved SD[190]. However, a Phase 2 study of olaparib for patients (n=12) with genomically unselected advanced Ewing sarcoma and failure of standard chemotherapy did not observe any objective responses or durable disease control; the median PFS was 5.7 weeks[191]. A Phase 1 trial combining olaparib with trabectidin for patients with bone (n=11) or soft tissue (n=39) sarcomas who had progressed on standard treatment reported PRs for 14% (7/50) and SD for 32% (16/50) of patients, with all responders harboring soft tissue sarcomas[192]. Higher baseline PARP1 expression associated with significantly improved PFS relative to that for patients with low baseline PARP1 expression (59% vs. 8%, HR=0.37)[192].

Rucaparib

Assay findings association

BRIP1
P488S

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian[56,181-182] , breast[58], endometrial[183], and prostate cancer[57], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of sarcoma are limited (PubMed, May 2023). Rucaparib has primarily been evaluated in the context of patients with ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for patients with recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer for patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared with patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[56]. For heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression-free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[109]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed for 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported for patients with breast cancer (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[193]. In a Phase 1 study of rucaparib treatment for patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[194]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (1 unconfirmed), and 4/19 SD. 79% (15/19) of patients treated in the study had a BRCA2 mutation[195]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 17% (8/46) of patients achieved a PR and 17% (8/46) experienced SD[196]. A Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer for patients with metastatic melanoma[197]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of patients with advanced solid tumors reported a disease control rate of 69% (53/77), including 1 CR and 9 PRs[198].

Talazoparib

Assay findings association

BRIP1
P488S

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian[56,181-182], breast[58], endometrial[183], and prostate cancer[57], loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A study of talazoparib plus irinotecan for children and young adults with recurrent solid tumors reported an ORR of 12.5% and a CBR of 45.8%, with PRs in synovial sarcoma and Ewing sarcoma and a CR in Ewing sarcoma[199]. However, a study of single-agent talazoparib reported an ORR of 0% (0/13) and SD in 23% (3/13) of patients with Ewing sarcoma[200]. Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[201-202]. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[203]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[200,204-206].

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
BRIP1

ALTERATION
P488S

RATIONALE
BRIP1 inactivation may predict sensitivity to inhibitors of other DNA repair pathways, including inhibitors of PARP. 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.

NCT04434482

PHASE 1

IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Gyeonggi-do (Korea, Republic of), Orange (Australia), Blacktown (Australia), Albury (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT05021367

PHASE 1

A Clinical Study of TQB3823 in Patients With Advanced Malignant Tumor

TARGETS
PARP

LOCATIONS: Guangzhou (China)

NCT04170153

PHASE 1

M1774 in Participants With Metastatic or Locally Advanced Unresectable Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Beijing (China), Chuo-ku (Japan), Kashiwa-shi (Japan), Newcastle upon Tyne (United Kingdom), Cambridge (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom), Barcelona (Spain), Valencia (Spain), Madrid (Spain)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT03784014

PHASE 3

MOLECULAR PROFILING OF ADVANCED SOFT-TISSUE SARCOMAS

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

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

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Colorado, Illinois, Texas, North Carolina, Georgia

GENE
IDH1

ALTERATION
R132C

RATIONALE
IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP inhibitors in solid tumors.

NCT04434482

PHASE 1

IMP4297 in Combination With Temozolomide in Patients With Advanced Solid Tumors and Small Cell Lung Cancer

TARGETS
PARP

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Gyeonggi-do (Korea, Republic of), Orange (Australia), Blacktown (Australia), Albury (Australia)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT05021367

PHASE 1

A Clinical Study of TQB3823 in Patients With Advanced Malignant Tumor

TARGETS
PARP

LOCATIONS: Guangzhou (China)

NCT04170153

PHASE 1

M1774 in Participants With Metastatic or Locally Advanced Unresectable Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Beijing (China), Chuo-ku (Japan), Kashiwa-shi (Japan), Newcastle upon Tyne (United Kingdom), Cambridge (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom), Barcelona (Spain), Valencia (Spain), Madrid (Spain)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

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)

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Colorado, Illinois, Texas, North Carolina, Georgia

NCT04056910

PHASE 2

Ivosidenib (AG-120) With Nivolumab in IDH1 Mutant Tumors

TARGETS
PD-1, IDH1

LOCATIONS: Pennsylvania

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

GENE
TP53

ALTERATION
Y220C

RATIONALE
Clinical and preclinical evidence suggests that TP53 hotspot mutations may predict sensitivity to TP53-targeted adoptive cell therapies. Clinical evidence suggests patients with TP53 Y220C mutations may benefit from Y220C-specific reactivators of TP53.

NCT04585750

PHASE 1/2

The Evaluation of PC14586 in Patients With Advanced Solid Tumors Harboring a p53 Y220C Mutation

TARGETS
TP53

LOCATIONS: Washington, Oregon, California, Ohio, Massachusetts, Connecticut, New York, Texas, Tennessee

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.95A>G
(p.N32S)
chr5:112090682

ASXL1
NM_015338.5: c.341A>G
(p.N114S)
chr20:31016019

CSF1R
NM_005211.3: c.224C>T
(p.T75I)
chr5:149460413

CSF3R
NM_156039.3: c.911C>G
(p.T304S)
chr1:36937925

GTSE1
NM_016426.6: c.1988C>G
(p.P663R)
chr22:46725316

KDM4C
NM_015061.3: c.1304C>G
(p.A435G)
chr9:6984354

KDM5C
amplification

LRP1B
NM_018557.2: c.9418C>G
(p.Q3140E)
chr2:141242919

MAP3K1
NM_005921.1: c.4469A>C
(p.E1490A)
chr5:56189437

MITF
NM_198159.2: c.38T>C
(p.V13A)
chr3:69788786

PCLO
NM_033026.5: c.15159A>G
(p.I5053M)
chr7:82390084

PRKDC
NM_006904.6: c.935C>T
(p.A312V)
chr8:48855800

SETD2
NM_014159.6: c.3612T>G
(p.I1204M)
chr3:47162514

SMC1A
amplification

TSC2
NM_000548.3: c.2032G>A
(p.A678T)
chr16:2121870

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 678x

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 was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research.

INTENDED USE

FoundationOne Heme is a next generation sequencing-based *in vitro* diagnostic device for hematologic malignancies and sarcomas. The test is intended for the detection of substitutions, insertion and deletion alterations (indels), copy number alterations (CNAs), and select rearrangements from the complete coding DNA sequences of 406 genes, as well as selected introns of 31 genes using DNA isolated from peripheral blood, bone marrow aspirate (BMA), and formalinfixed paraffin embedded (FFPE) tumor tissue specimens. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across 265 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas. FoundationOne Heme is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with hematologic malignancies and sarcomas.

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) 7.10.0

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. Gounder MM, et al. Nat Commun (2022) pmid: 35705558
39. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
40. Lim J, et al. Clin. Cancer Res. (2015) pmid: 26330427
41. Brohl AS, et al. PLoS Genet. (2014) pmid: 25010205
42. Chen X, et al. Cancer Cell (2013) pmid: 24332040
43. Steele CD, et al. Cancer Cell (2019) pmid: 30889380
44. Casey DL, et al. Clin Cancer Res (2020) pmid: 31699828
45. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
46. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
47. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
48. Rizvi NA, et al. Science (2015) pmid: 25765070
49. Johnson BE, et al. Science (2014) pmid: 24336570
50. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
51. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
52. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
53. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
54. Nature (2012) pmid: 22810696
55. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
56. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
57. Abida W, et al. Clin. Cancer Res. (2020) pmid: 32086346
58. Dhawan et al., 2017; ASCO Abstract 2527
59. Barretina J, et al. Nat. Genet. (2010) pmid: 20601955
60. Cancer Genome Atlas Research Network. Electronic address: elizabeth.demicco@sinaihealthsystem.ca, et al. Cell (2017) pmid: 29100075
61. Cantor SB, et al. Cell (2001) pmid: 11301010
62. Litman R, et al. Cancer Cell (2005) pmid: 16153896
63. Bridge WL, et al. Nat. Genet. (2005) pmid: 16116421
64. Filippini SE, et al. Front Biosci (Landmark Ed) (2013) pmid: 23747889
65. Ren LP, et al. Genet. Mol. Res. (2013) pmid: 24301948
66. Seal S, et al. Nat. Genet. (2006) pmid: 17033622
67. Rafnar T, et al. Nat. Genet. (2011) pmid: 21964575
68. Ma XD, et al. Biochem. Biophys. Res. Commun. (2013) pmid: 23473757
69. Hematology Am Soc Hematol Educ Program (2007) pmid: 18024606
70. Khincha PP, et al. Semin. Hematol. (2013) pmid: 24246701
71. Chandrasekharappa SC, et al. Blood (2013) pmid: 23613520
72. Tischkowitz MD, et al. J. Med. Genet. (2003) pmid: 12525534
73. Fan B, et al. Invest New Drugs (2019) pmid: 31028664
74. de la Fuente MI, et al. Neuro Oncol (2022) pmid: 35639513
75. Mellinghoff et al., 2020; ASCO Abstract 2504
76. Philip B, et al. Cell Rep (2018) pmid: 29719265
77. Molenaar RJ, et al. Clin. Cancer Res. (2018) pmid: 29339439
78. Lu Y, et al. Cancer Res. (2017) pmid: 28202508
79. Sulkowski PL, et al. Sci Transl Med (2017) pmid: 28148839
80. Sanchez-Vega F, et al. Cell (2018) pmid: 29625050
81. Amary MF, et al. J. Pathol. (2011) pmid: 21598255
82. Pansuriya TC, et al. Nat. Genet. (2011) pmid: 22057234
83. Arai M, et al. Brain Tumor Pathol (2012) pmid: 22323113
84. Kerr DA, et al. Am. J. Surg. Pathol. (2013) pmid: 23598960
85. Reitman ZJ, et al. J. Natl. Cancer Inst. (2010) pmid: 20513808
86. Jin G, et al. PLoS ONE (2011) pmid: 21326614
87. Gross S, et al. J. Exp. Med. (2010) pmid: 20142433
88. Ward PS, et al. Cancer Cell (2010) pmid: 20171147
89. Leonardi R, et al. J. Biol. Chem. (2012) pmid: 22442146
90. Dang L, et al. Nature (2009) pmid: 19935646
91. Ward PS, et al. Oncogene (2012) pmid: 21996744
92. Figueroa ME, et al. Cancer Cell (2010) pmid: 21130701
93. Xu W, et al. Cancer Cell (2011) pmid: 21251613
94. Turcan S, et al. Nature (2012) pmid: 22343889
95. Duncan CG, et al. Genome Res. (2012) pmid: 22899282
96. Kim SP, et al. Cancer Immunol Res (2022) pmid: 35749374
97. Morelli et al., 2023; ASCO Abstract 2547
98. Dumbrava et al., 2022; ASCO Abstract 3003
99. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
100. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
101. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
102. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
103. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
104. Xu L, et al. Mol. Med. (2001) pmid: 11713371
105. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
106. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
107. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
108. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
109. Moore et al., 2019; ASCO Abstract 5513
110. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
111. Oza et al., 2015; ASCO Abstract 5506
112. Lee J, et al. Cancer Discov (2019) pmid: 31315834
113. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
114. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
115. Gourley et al., 2016; ASCO Abstract 5571
116. Park H, et al. ESMO Open (2022) pmid: 36084396
117. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
118. Gao J, et al. Sci Signal (2013) pmid: 23550210
119. Pérot G, et al. Am. J. Pathol. (2010) pmid: 20884963
120. Taubert H, et al. Cancer Res. (1996) pmid: 8797580
121. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
122. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
123. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
124. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
125. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
126. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
127. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
128. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
129. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
130. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
131. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
132. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
133. Lalloo F, et al. Lancet (2003) pmid: 12672316
134. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
135. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
136. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
137. Xie M, et al. Nat. Med. (2014) pmid: 25326804
138. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
139. Severson EA, et al. Blood (2018) pmid: 29678827
140. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
141. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
142. Chabon JJ, et al. Nature (2020) pmid: 32269342
143. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
144. Van Vlierberghe P, et al. Nat. Genet. (2010) pmid: 20228800
145. Van Vlierberghe P, et al. Leukemia (2011) pmid: 21030981
146. Grossmann V, et al. Genes Chromosomes Cancer (2013) pmid: 23341344
147. Zhang J, et al. Nature (2012) pmid: 22237106

148. Wang Q, et al. Haematologica (2011) pmid: 21880637
149. Yoo NJ, et al. Acta Oncol (2012) pmid: 21736506
150. Holmfeldt L, et al. Pediatr Blood Cancer (2010) pmid: 20589626
151. Huh HJ, et al. Ann. Hematol. (2013) pmid: 23354995
152. Patel JP, et al. N. Engl. J. Med. (2012) pmid: 22417203
153. Wang J, et al. J. Biol. Chem. (2013) pmid: 23229552
154. Todd MA, et al. J. Proteome Res. (2012) pmid: 22720776
155. Todd MA, et al. Genes (Basel) (2015) pmid: 26103525
156. Lower KM, et al. Nat. Genet. (2002) pmid: 12415272
157. Gécz J, et al. Eur. J. Hum. Genet. (2006) pmid: 16912705
158. Park J, et al. EMBO J. (1999) pmid: 10357815
159. Ackermann TF, et al. Cell. Physiol. Biochem. (2011) pmid: 21865856
160. Castel P, et al. Cancer Cell (2016) pmid: 27451907
161. Halland N, et al. ACS Med Chem Lett (2015) pmid: 25589934
162. Mansley MK, et al. Br. J. Pharmacol. (2010) pmid: 20880397
163. O'Neill D, et al. Oncotarget (2015) pmid: 26267320
164. Sherk AB, et al. Cancer Res. (2008) pmid: 18794135
165. Sommer EM, et al. Biochem. J. (2013) pmid: 23581296
166. Lohr JG, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22343534
167. Hartmann S, et al. Leukemia (2016) pmid: 26658840
168. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
169. Abbruzzese C, et al. J. Exp. Clin. Cancer Res. (2012) pmid: 22240294
170. Conza D, et al. J. Cell. Physiol. (2017) pmid: 28177128
171. Talarico C, et al. Oncotarget (2016) pmid: 26908461
172. Sahoo S, et al. Eur. J. Cancer (2005) pmid: 16246546
173. García-Martínez JM, et al. Biochem. J. (2008) pmid: 18925875
174. DiNardo CD, et al. N. Engl. J. Med. (2018) pmid: 29860938
175. Lowery MA, et al. Lancet Gastroenterol Hepatol (2019) pmid: 31300360
176. Abou-Alfa GK, et al. Lancet Oncol. (2020) pmid: 32416072
177. Mellinghoff IK, et al. J. Clin. Oncol. (2020) pmid: 32530764
178. Abou-Alfa et al., 2021; ASCO Abstract 4069
179. Mellinghoff et al., 2017; SNO Abstract ACTR-46
180. Tap et al., 2016; CTOS Abstract P1-138
181. Dougherty et al., 2014; ASCO Abstract 5536
182. Piha-Paul et al., 2018; AACR Abstract A096
183. Nakamura et al., 2020; DOI: 10.1200/PO.19.00368
184. Chugh R, et al. Cancer (2021) pmid: 33289920
185. Mirza MR, et al. N. Engl. J. Med. (2016) pmid: 27717299
186. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
187. Mirza et al., 2016; ASCO Abstract 5555
188. George et al., 2022; ASCO Abstract 3122
189. Lian BJ, et al. Front Oncol (2022) pmid: 35875073
190. Grignani et al., 2016; ASCO Abstract 11018
191. Choy E, et al. BMC Cancer (2014) pmid: 25374341
192. Grignani G, et al. Lancet Oncol. (2018) pmid: 30217671
193. Drew Y, et al. Br. J. Cancer (2016) pmid: 27002934
194. Kristeleit et al., 2014; ASCO Abstract 2573
195. Domcheck et al., 2016; ASCO Abstract 4110
196. Plummer R, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23423489
197. Plummer R, et al. Clin. Cancer Res. (2008) pmid: 19047122
198. Wilson RH, et al. Br. J. Cancer (2017) pmid: 28222073
199. Federico et al., 2017; ASCO Abstract 10542
200. de Bono J, et al. Cancer Discov (2017) pmid: 28242752
201. Litton JK, et al. N. Engl. J. Med. (2018) pmid: 30110579
202. Ettl J, et al. Ann. Oncol. (2018) pmid: 30124753
203. Gruber et al., 2019; ASCO Abstract 3006
204. Lu E, et al. J Natl Compr Canc Netw (2018) pmid: 30099369
205. Piha-Paul et al., 2017; EORTC-NCI-AACR Abstract A096
206. Meehan et al., 2017; AACR Abstract 4687