FOUNDATIONONE®HEME

PATIENT

TUMOR TYPE
Bone osteosarcoma

REPORT DATE

COUNTRY CODE
BR

ORDERED TEST #

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	PHYSICIAN	SPECIMEN
DISEASE Bone osteosarcoma	ORDERING PHYSICIAN	SPECIMEN SITE
NAME	MEDICAL FACILITY	SPECIMEN ID
DATE OF BIRTH	ADDITIONAL RECIPIENT	SPECIMEN TYPE
SEX	MEDICAL FACILITY ID	DATE OF COLLECTION
MEDICAL RECORD #	PATHOLOGIST	SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]
Tumor Mutational Burden - 7 Muts/Mb

Genomic Findings

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

KIT amplification
PDGFRA amplification
CDK4 amplification
FGFR1 amplification - equivocal[†]
MDM2 amplification
CCND3 amplification
FRS2 amplification
KDR amplification
RAD21 amplification
TP53 R337H
ZNF703 amplification - equivocal[†]

† See About the Test in appendix for details.
α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***CDK4*** **amplification** (p. 5), ***MDM2*** **amplification** (p. 6)
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Sorafenib** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 7 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KIT **-** amplification	none	Sorafenib 2A
		Imatinib
		Nilotinib
10 Trials *see p. 17*		Sunitinib
PDGFRA **-** amplification	none	Imatinib
1 Trial *see p. 20*		
CDK4 **-** amplification	none	none
10 Trials *see p. 13*		
FGFR1 **-** amplification - equivocal	none	none
10 Trials *see p. 15*		
MDM2 **-** amplification	none	none
1 Trial *see p. 19*		

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

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BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[1-2] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab[3-8] and PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[9-11] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

In osteosarcoma, MSI at any level has been reported in 14% (3/21) to 44% (8/18) of cases with high MSI observed in 11% (2/18) of cases[12-13]. However, other studies have reported an absence of MSI in osteosarcoma (0/7 and 0/68)[14-15] and bone sarcoma (0/29)[16]. The prognostic significance of MSI in osteosarcoma or other bone mesenchymal tumors is unknown (PubMed, Sep 2021).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[17]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[17-19]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

POTENTIAL GERMLINE IMPLICATIONS

While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[17], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[20]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[20-22] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[23-25]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
7 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[26-28], anti-PD-1 therapies[26-29], and combination nivolumab and ipilimumab[30-35]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[26-29,36]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[26]. 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[27]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[29,36]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Osteosarcoma harbors a median TMB of 2.5 mutations per megabase (muts/Mb), and 0.4% of cases have high TMB (>20 muts/Mb)[38]. Undifferentiated pleomorphic sarcomas reportedly have an increased mutation burden compared to Ewing sarcomas or rhabdomyosarcomas[39-41]. The association of mutation burden with prognosis of bone sarcoma has not been studied extensively (PubMed, Sep 2021); however, one study of 31 patients with high-grade osteosarcoma reported a significant association of high TMB and improved median OS by multivariate analysis (HR=0.05, p=0.03)[42].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[43-44] and cigarette smoke in lung cancer[7,45], treatment with temozolomide-based chemotherapy in glioma[46-47], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[48-52], and microsatellite instability (MSI)[48,51-52]. 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[27-28,36].

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GENE
KIT

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, primarily in GIST, AML, and systemic mastocytosis, KIT activating alterations are associated with sensitivity to KIT tyrosine kinase inhibitors including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, pazopanib, regorafenib, ponatinib, midostaurin, avapritinib, and ripretinib[53-60]. The use of mTOR inhibitors as an alternative therapeutic strategy has demonstrated limited success in KIT-mutated, imatinib-resistant melanoma, with 1 PR and 3 SD observed for 4 patients treated with everolimus[61]. However, no responses were observed for 10 patients with mastocytosis following everolimus monotherapy, with 8/10 patients harboring the KIT D816V mutation[62]. The role of KIT amplification as a biomarker for response to mTOR inhibitors has not been investigated (PubMed, Mar 2021). Clinical benefit has been observed for patients with KIT amplified or overexpressing tumors following treatment with imatinib[63-73], nilotinib[74], sorafenib[75-78], and sunitinib[79-80], suggesting that KIT amplification may be sensitive to these inhibitors. However, evidence demonstrating clinical benefit for regorafenib, dasatinib, pazopanib, or ponatinib in the context of KIT amplified or overexpressing tumors is limited.

FREQUENCY & PROGNOSIS

KIT amplification has been reported in 20% (13/66)[81] to 35% (24/74)[82] of osteosarcoma cases. Relative to all tumor types analyzed, co-amplification of KIT, KDR, and PDGFRA on the 4q12 locus has been reported to be enriched in osteosarcomas; although primarily bone-derived (6.4%; 27/420), 1 of 15 soft tissue osteosarcoma (extraskeletal) samples also harbored this amplicon[83]. Studies have observed KIT amplification and overexpression in pediatric osteosarcomas; KIT expression has been reported to correlate with a poor response to chemotherapy, but not with overall survival or disease-free survival, in pediatric osteosarcoma[82,84]. KIT amplification and overexpression have also been reported in pediatric patients with osteosarcoma, and KIT expression has been reported to correlate with poor response to chemotherapy, but not with overall survival or disease-free survival[82,84].

FINDING SUMMARY

KIT (also called c-KIT) encodes a cell surface tyrosine kinase receptor that, upon ligand binding and dimerization, activates the PI3K-AKT and RAS-MAPK signaling pathways[85]. KIT aberrations, including point mutations, translocations, amplification, and overexpression, have been associated with various malignancies, and KIT is considered an oncoprotein[86]. KIT has been reported to be amplified in cancer[87] and may be biologically relevant in this context[88-89].

GENE
PDGFRA

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence in solid tumors and hematologic cancers, PDGFRA activating alterations are associated with sensitivity to imatinib[90-127]. Sorafenib has shown clinical and preclinical activity against the FIP1L1-PDGFRA fusion in chronic eosinophilic leukemia (CEL) and mutations associated with clinical resistance to imatinib and sunitinib in both CEL and gastrointestinal stromal tumor (GIST)[128-133]. Complete responses to nilotinib have been reported in patients with CEL or hypereosinophilic syndrome with FIP1L1-PDGFRA or activating mutations[106,134-135]; preclinical evidence has reported efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[136-137]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[138] or regorafenib[139-140]. Preclinical studies have reported sensitivity of activating PDGFRA mutations and FIP1L1-PDGFRA fusion to dasatinib[130,136]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[53] and preclinical[53] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[141].

FREQUENCY & PROGNOSIS

Relative to all tumor types analyzed, co-amplification of KIT, KDR, and PDGFRA on the 4q12 locus has been reported to be enriched in osteosarcomas; although primarily bone-derived (6.4%; 27/420), 1 of 15 soft tissue osteosarcoma (extraskeletal) samples also harbored this amplicon[83]. High PDGFRA expression was detected in 42% (40/96) of osteosarcoma samples in one study; none of the 40 cases with high PDGFRA expression harbored mutation of PDGFRA exons 12 or 18[142]. PDGFRA mutation was not detected in any of the 243 osteosarcoma cases analyzed in COSMIC (Mar 2021)[143]. PDGFR-alpha expression has been reported in patients with osteosarcoma but was not correlated with overall or disease-free survival[142,144-145].

FINDING SUMMARY

PDGFRA encodes platelet-derived growth factor receptor alpha (PDGFR-alpha), a tyrosine kinase receptor that, upon binding of cognate ligands (PDGFA or PDGFB), activates several signaling pathways, including PI3K and MAPK[146]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[86]. Amplification of PDGFRA, frequently occurring with amplification of the genes KDR and KIT, has been associated with increased PDGFRA expression[147-150] and poor prognosis[147,151-153] in some subtypes of glioma.

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GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[154-157]. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib[158], palbociclib[154,159], and ribociclib[160].

FREQUENCY & PROGNOSIS

Amplification of CDK4 has been reported in a subset of osteosarcoma samples[161-165]. CDK4 amplification has been reported to be relatively rare in conventional high-grade osteosarcoma but frequent in low-grade osteosarcomas, including parosteal osteosarcomas and low-grade central osteosarcomas, suggesting that CDK4 expression may help facilitate subclassification in osteosarcoma[163-165]. Deregulation of the G1/S checkpoint genes, including CDK4, and expression of the cyclin D1/CDK4 complex have been associated with poor prognosis in osteosarcoma patients[166-167].

FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[168]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[169-170]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[154,163,171-176].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Amplification of 12q13–q15, including CDK4 and MDM2, is characteristic of well-differentiated liposarcoma (WDLPS) and dedifferentiated (DDLPS) liposarcoma (NCCN Soft Tissue Sarcoma Guidelines, v2.2021)[176-179], and low-grade osteosarcomas, including parosteal osteosarcomas and low-grade central osteosarcomas as opposed to conventional high-grade osteosarcoma (NCCN Soft Tissue Sarcoma Guidelines, v2.2021)[163-165,180-181].

GENE
FGFR1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors including erdafitinib[182-184], pemigatinib[185], infigratinib[186-187], rogaratinib[188], Debio 1347[189-190], futibatinib[191], and derazantinib[192], or multikinase inhibitors such as pazopanib[193] and ponatinib[194-196]. The activity and efficacy of selective FGFR inhibitors for FGFR1-amplified tumors has been modest with limited responses reported in FGFR1-amplified lung squamous cell carcinoma (SCC) treated with infigratinib[197] or AZD457[198] and no responses reported among patients with FGFR1-amplified breast cancer treated with infigratinib[197]. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[193].

— Potential Resistance —

Preclinical studies suggest that overexpression of FGFR1 may be a mechanism of acquired resistance to gefitinib; addition of an FGFR inhibitor restored gefitinib sensitivity in lung cancer cell lines[199-200].

FREQUENCY & PROGNOSIS

Putative amplification of FGFR1 has been detected in 4.4% of sarcoma cases, although this dataset only included soft tissue sarcoma (cBioPortal, Jun 2021)[87,201]. FGFR1 amplification was reported in osteosarcoma cell lines and in 1/17 primary osteosarcoma samples[202]. In one study, FGFR1 protein expression was observed in 82% (45/55) of phosphaturic mesenchymal tumors (PMTs) analyzed, and expression was independent of FGFR1 fusion status; positive expression was also observed in a subset of PMT-mimicking tumors (10 samples per tumor type), such as solitary fibrous tumors (40%, 4/10), chondrosarcomas (40%), giant cell tumors of bone (38%), non-ossifying fibromas (20%), osteosarcomas (10%), and osteoblastomas (10%)[203]. Published data investigating the prognostic implications of FGFR1 alterations in osteosarcoma are limited (PubMed, Jun 2021).

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[204]. Amplification of FGFR1 has been correlated with protein expression[205-206] and may predict pathway activation and sensitivity to therapies targeting this pathway[207-208].

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GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[209]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[210-211]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[212-213] . A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[214]. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[215-216] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[217]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[218]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[219-220] .

FREQUENCY & PROGNOSIS

Amplification of MDM2 has been reported in 19-80% of osteosarcomas[180-181,221]. MDM2 amplification has been reported to be relatively rare in conventional high-grade osteosarcoma but frequent in low-grade osteosarcomas, including parosteal osteosarcomas and low-grade central osteosarcomas, suggesting that MDM2 expression may help facilitate subclassification in osteosarcoma[163-165]. Deregulation of the G1/S checkpoint genes, including amplification of CDK4 and MDM2, has been found to be correlated with decreased survival and poor prognosis in osteosarcoma patients[166].

FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[222-224]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[225-226]. Overexpression or amplification of MDM2 is frequent in cancer[89]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[227] and 2/3 patients with MDM2 or MDM4 amplification[228] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[229]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[229].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Amplification of 12q13–q15, including CDK4 and MDM2, is characteristic of well-differentiated liposarcoma (WDLPS) and dedifferentiated (DDLPS) liposarcoma (NCCN Soft Tissue Sarcoma Guidelines, v2.2021)[176-179], and low-grade osteosarcomas, including parosteal osteosarcomas and low-grade central osteosarcomas as opposed to conventional high-grade osteosarcoma (NCCN Soft Tissue Sarcoma Guidelines, v2.2021)[163-165,180-181].

GENE
CCND3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or activation of CCND3 may predict sensitivity to CDK4/6 inhibitors[230-232], such as abemaciclib, palbociclib, and ribociclib[154-157,233-234]. As supported by strong preclinical studies, tumors with CCND3 activation depend on CDK4/6[230-232].

FREQUENCY & PROGNOSIS

One study reported frequent high-level amplification of CCND3 in 83% (5/6) of aggressive osteosarcomas studied[235]. Another study reports consistent overexpression of CCND3 in all 13 osteosarcoma patient samples analyzed and gene amplification in 2 out of 4 samples, although overexpression was not correlated with increased cyclin D3 protein levels[236]. Increased expression of Cyclin D3 has been reported in bone and soft tissue sarcomas compared with leiomyomas and normal tissue, suggesting a role for this protein in bone and soft tissue tumors[237]. The prognostic significance of CCND3 alteration in osteosarcoma have not been extensively studied (PubMed, Sep 2021).

FINDING SUMMARY

CCND3 encodes cyclin D3, a G1/S-specific cell cycle regulator. Cyclin D3 interacts with and regulates the cyclin-dependent kinases CDK4 and CDK6, resulting in the phosphorylation and inactivation of Rb and the progression of the cell cycle[238]. CCND3 amplification has been associated with increased cyclin D3 expression[239].

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GENE
FRS2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that target alterations in FRS2. Amplification of FRS2 can lead to activation of the FGFR and MAPK-ERK pathways, and preliminary studies in liposarcoma cell lines have shown that cells with this alteration are sensitive to FGFR inhibitors[175,240].

FREQUENCY & PROGNOSIS

FRS2 amplification is particularly prevalent in liposarcoma, where amplification of the 12q13-15 region of chromosome 12 is considered to be a hallmark genetic alteration, although the effects of amplification of CDK4 and MDM2, also located in this region, have been studied in more detail than FRS2 in this context[241-242]. Amplification of FRS2 has been observed in 93%-100% of dedifferentiated liposarcoma, 32% of undifferentiated high-grade pleomorphic sarcoma, and 100% of well-differentiated liposarcoma[175,243]. Amplification of the 12p15 chromosomal region containing FRS2, but not CDK4 or MDM2, was found in 12.5% of high-grade serous ovarian carcinomas, and knockdown of FRS2 in these cells resulted in apoptosis, indicating that cells with 12p15 amplification require FRS2[240].

FINDING SUMMARY

FRS2 encodes the fibroblast growth factor receptor (FGFR) substrate 2, an adaptor protein involved in FGFR signaling, which may also mediate signaling through EGFR, NTRK, and VEGF receptors[244-247]. FRS2 amplification was found to correlate with overexpression in high-grade serous ovarian tumors, and FRS2 overexpression promoted tumorigenesis in a preclinical study[240].

GENE
KDR

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical benefit for patients with ccRCC[248-252] and a patient with breast angiosarcoma[253], high VEGFR-2 expression has been associated with sensitivity to sunitinib. However, because data supporting concordance between VEGFR-2 expression and KDR genomic biomarkers are limited, it is unclear whether these therapeutic strategies would be beneficial in this case. On the basis of extensive clinical evidence across multiple tumor types, expression of plasma or tumor VEGFR-1 or VEGFR-2 has not been established as a reliable biomarker to predict response to the VEGFA-targeted agent bevacizumab[254-273].

FREQUENCY & PROGNOSIS

Relative to all tumor types analyzed, co-amplification of KIT, KDR, and PDGFRA on the 4q12 locus has been reported to be enriched in osteosarcomas; although primarily bone-derived (6.4%; 27/420), 1 of 15 soft tissue osteosarcoma (extraskeletal) samples also harbored this amplicon[83]. KDR expression, mutation and amplification have been reported in various subtypes of sarcoma, most commonly in undifferentiated pleomorphic sarcoma of bone and angiosarcoma[274]. The Sarcoma Genome Project has reported KDR amplification in 2% of sarcoma samples[179]. In the scientific literature, KDR mRNA expression has been reported in 67% of osteosarcoma specimens analyzed[275]. Another study reports frequent gain of KDR in pleomorphic sarcoma of bone[145]. The prognostic significance of KDR amplification in osteosarcoma has not been extensively studied (PubMed, Feb 2021). One retrospective IHC analysis of 30 pediatric osteosarcoma samples reported significantly poorer metastasis-free survival for patients with high versus low KDR protein expression[276].

FINDING SUMMARY

KDR encodes vascular endothelial growth factor receptor 2 (VEGFR2), a member of the vascular endothelial growth factor receptor (VEGFR) family. It is a receptor tyrosine kinase that transmits signals from VEGFA and is involved in both tumor angiogenesis and vasculogenesis during development[277]. KDR amplification has been reported in many tumor types and may be oncogenic[277].

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GENE
RAD21

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS

RAD21 amplifications, point mutations, and truncating mutations have been reported in various cancers[278]. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes[279-280], including sporadic Grade 3 but not Grade 1 cancers[279], as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers[279]. Furthermore, SNPs in or near RAD21 have been linked with risk of breast cancer development[281-282]. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer[283] and in colorectal cancer (CRC), especially in KRAS-mutant CRC[284]. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer[285]. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression[286]. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic[287]. Downregulation of RAD21 expression resulted in sensitization of cultured breast[280,288] and CRC[284] cells to chemotherapy, thereby suggesting that RAD21 overexpression confers resistance to chemotherapy.

FINDING SUMMARY

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[289-292]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[293], but also leads to an increase in deletions, insertions, and other rearrangements[294]. High RAD21 expression has also been associated with increased genomic instability[279]. Cohesin complex also organizes chromatin domains and regulates gene expression[295-296]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[297]. RAD21 amplification has been correlated with increased expression in breast[279-280,298] and endometrial[283] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

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GENE
TP53

ALTERATION
R337H

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
1010G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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[299-302], or p53 gene therapy and immunotherapeutics such as SGT-53[303-307] and ALT-801[308]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[309]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[310]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[311]. 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[312]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[313]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[314]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[307]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[315]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[316-318]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[319]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[320-321]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[322-323]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

Mutations of TP53 have been reported in 16% of bone tumors, including 25-50% of osteosarcomas (COSMIC, Sep 2021)[143,324-325]. TP53 rearrangements affecting the 5' UTR have been identified as recurrent alterations in 11-55% of osteosarcomas (n = 11-215) and have been reported in the context of Li-Fraumeni syndrome[326-330]. Both TP53 alterations and increased expression of p53 have been reported to correlate with worse survival of patients with osteosarcoma[324,331].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[225]. Alterations such as seen here may disrupt TP53 function or expression[332-336].

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, Sep 2021)[337]. 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[338-340], including sarcomas[341-342]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[343] to 1:20,000[342]. 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[344]. 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[345-350]. 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[345-346]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[351]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[349,352-353]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
ZNF703

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available targeted therapies to directly address ZNF703 alterations in cancer. One preclinical study suggested that ZNF703 expression in breast cancer cell lines is associated with reduced sensitivity to tamoxifen through AKT-mTOR activation[354], although these findings have not been verified in the clinical setting.

FREQUENCY & PROGNOSIS

Amplification and high expression of ZNF703 has been observed in luminal B breast tumors, a subtype associated with aggressive disease progression and poor patient outcomes[355-357]. ZNF703 expression has also been linked with aggressive tumor characteristics in patients with gastric and colorectal cancers[358-359]. Putative high-level amplification of ZNF703 has been reported with the highest frequency in breast carcinoma, bladder urothelial carcinoma, uterine carcinosarcoma, lung squamous cell carcinoma (SCC), esophageal carcinoma and head and neck SCC (5-13% of samples)(cBioPortal, 2021)[87,201].

FINDING SUMMARY

ZNF703 encodes a transcriptional repressor that plays roles in stem cell proliferation, cell cycle progression, and other key cellular functions[356,360]. Amplification of ZNF703 has been correlated with protein expression[355-356]. ZNF703 was established as a breast cancer oncoprotein by studies showing that ZNF703 expression resulted in transformation and increased proliferation of cultured cells[355-356,361], as well as increased lung metastases in a breast cancer xenograft model[361].

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Imatinib

Assay findings association

KIT
amplification

PDGFRA
amplification

AREAS OF THERAPEUTIC USE

Imatinib targets the BCR-ABL fusion protein, PDGFR, and KIT. It is FDA approved for the treatment of KIT-positive gastrointestinal stromal tumors (GIST), Ph+ chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL), myelodysplastic syndrome/ myeloproliferative syndrome (MDS/MPS), aggressive systemic mastocytosis without a D816V KIT mutation, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[64-65,102,362] , KIT-amplified[63-66] , or KIT-expressing tumors[68-73,363-364] , KIT activating alterations may confer sensitivity to imatinib. PDGFRA amplification may predict sensitivity to tyrosine kinase inhibitors such as imatinib; a patient with Merkel cell carcinoma expressing PDGFRA achieved a complete response to imatinib[100].

SUPPORTING DATA

A Phase 2 study of imatinib for children with refractory or relapsed solid tumors did not report any objective responses for the included osteosarcoma cases[365]. Genomically unselected patients with osteosarcoma experienced a 4-month progression-free survival rate of 18% (3/17) on imatinib[366].

Nilotinib

Assay findings association

KIT
amplification

AREAS OF THERAPEUTIC USE

Nilotinib targets tyrosine kinases such as ABL (including BCR-ABL), PDGFRs, KIT, CSF1R, DDR1, and DDR2. It is FDA approved to treat newly diagnosed pediatric or adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, adults with Ph+ CML in chronic or accelerated phase with resistance or intolerance to prior therapy including imatinib, and pediatric patients with Ph+ CML in chronic phase with resistance or intolerance to prior tyrosine-kinase inhibitor therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[74,367-370] , KIT-amplified[74], or KIT-expressing tumors[371], KIT activating alterations may confer sensitivity to nilotinib.

SUPPORTING DATA

Clinical data on the efficacy of nilotinib for the treatment of bone sarcoma are limited (PubMed, Jun 2021). Nilotinib has been primarily investigated as a therapeutic option for the treatment of CML or gastrointestinal stromal tumors (GIST). In the context of CML, a Phase 3 clinical trial of Ph+ patients treated with imatinib or nilotinib (300 mg or 400 mg) reported progression-free survival (PFS) rates of 93% and 97-98% and overall survival (OS) rates of 93% and 94-97%, respectively, at 4 years[372]. For imatinib-resistant Japanese patients with CML, a Phase 2 trial reported a 47.8% major medical response rate to treatment with nilotinib at 12 months[373]. A Phase 3 clinical trial of single-agent nilotinib in 240 patients with advanced GIST who failed prior treatment with imatinib or sunitinib reported no significant difference in progression-free survival between nilotinib and the best supportive care, but did report increased overall survival for nilotinib-treated patients[374]. A Phase 2 trial has shown that nilotinib was well tolerated and suggested it may be particularly useful for treating patients with GIST harboring mutations in KIT exon 17[375]. Preclinical, cell-based assays have reported efficacy for nilotinib alone and in combination with additional therapies in the context of leiomyosarcoma and synovial sarcoma[376].

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Sorafenib

Assay findings association

KIT
amplification

AREAS OF THERAPEUTIC USE

Sorafenib is a kinase inhibitor that targets the RAF kinases, KIT, FLT3, RET, VEGFRs, and PDGFRs. It is FDA approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and recurrent or metastatic differentiated thyroid carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical and preclinical data in KIT-mutated[377-384] or KIT-expressing tumors[75-78] , KIT activating alterations may predict sensitivity to sorafenib.

SUPPORTING DATA

A retrospective study of osteosarcoma reported 3 SD in 4 patients treated with sorafenib[385]. Phase 2 studies in non-small cell lung cancer (NSCLC) report that single-agent sorafenib improved disease control rates and that the addition of sorafenib to erlotinib increased survival in EGFR wild-type patients[386-387] . A Phase 1 trial of everolimus combined with sorafenib reported 11% partial responses and 77% stable disease[388]. In the context of small cell lung carcinoma, sorafenib combined with cisplatin plus etoposide was highly toxic and ineffective[389]. In HER2-negative breast cancer, Phase 2b trials found improved progression-free survival for sorafenib added to capecitabine, but not when added to paclitaxel[390-391] . Phase 2 studies of sorafenib in biliary tract cancer reported disease control rates of 33-39%[392]. Three patients with cholangiocarcinoma derived clinical benefit from sorafenib[393-394] . However, the addition of sorafenib to gemcitabine did not improve outcome in patients with biliary tract tumors compared with gemcitabine alone[395]. A Phase 2 study of sorafenib and bicalutamide in castration-resistant prostate cancer (CRPC) observed a PSA response or stable disease (>6 months) in 47% (18/39) of patients[396]. Single-agent sorafenib was moderately active as second-line treatment for CRPC (3.7 months PFS and 18.0 months OS)[397]. For the treatment of glioblastoma or high-grade gliomas, sorafenib alone or combined with temozolomide/radiotherapy or erlotinib did not show efficacy[398-401] .

Sunitinib

Assay findings association

KIT
amplification

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

On the basis of clinical and preclinical data in KIT-mutated[79,402-406] or KIT-expressing tumors[79-80] , KIT activating alterations may predict sensitivity to sunitinib.

SUPPORTING DATA

A retrospective study of osteosarcoma reported 1 partial response and 1 stable disease in 5 patients treated with sunitinib[385] and a patient with breast osteosarcoma did not report clinical benefit from sunitinib[407]. A preclinical study of osteosarcoma reported a significant reduction of tumor growth and vasculature in response to sunitinib[408].

Phase 1 and 2 studies of sunitinib, alone or in combination with capecitabine, reported partial responses in patients with cancer of the biliary tract (6 responses), pancreas (3 responses), breast, thyroid, neuroendocrine, bladder, and large intestine (1 response each)[409-410] . Partial responses have also been observed in patients with melanoma (3/36)[411] and were more frequent in melanomas with KIT mutation (3/4) than in melanomas with KIT amplification (1/6)[79]. Sunitinib has been evaluated as maintenance therapy for non-small cell lung cancer (NSCLC)[412]. A Phase 3 study in NSCLC reported that sunitinib plus erlotinib was associated with better response rate and progression-free survival, as compared with erlotinib alone[413]. Sunitinib has shown preliminary activity against soft tissue sarcomas[414-415] and sunitinib-involving regimens have provided significant benefit to at least 5 patients with angiosarcoma, including one complete response[253,416-419] . In a Phase 2 study of patients with cervical carcinoma, no objective response to sunitinib was observed in 19 patients, but 84% (16/19) patients had stable disease[420]. In several Phase 2 trials of patients with glioblastoma, sunitinib did not achieve objective responses or improve clinical outcome[421-424] .

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

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CLINICAL TRIALS

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

GENE
CDK4

ALTERATION
amplification

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

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT02693535

PHASE 2

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

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, North Carolina, Georgia, Virginia, Alabama, Pennsylvania, New Hampshire, Maine

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Florida, North Carolina

NCT03310879

PHASE 2

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

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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CLINICAL TRIALS

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT03242382

PHASE 2

Phase II Multicenter Trial of Palbociclib in Second Line of Advanced Sarcomas With CDK4 Overexpression.

TARGETS
CDK4, CDK6

LOCATIONS: Sevilla (Spain)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04040205

PHASE 2

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

TARGETS
CDK4, CDK6

LOCATIONS: Missouri, Wisconsin, Iowa

NCT04594005

PHASE 1/2

CDK4/6 Tumor, Abemaciclib, Paclitaxel

TARGETS
CDK4, CDK6

LOCATIONS: Seoul (Korea, Republic of)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

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CLINICAL TRIALS

GENE
FGFR1

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

ALTERATION
amplification - equivocal

NCT02549937

PHASE 1/2

A Multi-Center, Open-Label Study of Sulfatinib(HMPL-012) in Patients With Advanced Solid Tumors

TARGETS
CSF1R, FGFR1, VEGFRs

LOCATIONS: Florida, Virginia, New York, Tennessee, Texas, Wisconsin, Colorado, Milano (Italy), California

NCT04042116

PHASE 1/2

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

TARGETS
FGFRs, VEGFRs, PD-1

LOCATIONS: Florida, North Carolina, New York, Massachusetts, Tennessee, Pennsylvania, Ohio, Cordoba (Spain), Madrid (Spain), Oklahoma

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4

LOCATIONS: Florida, Minnesota, Arizona, Colorado

NCT04784247

PHASE 2

Lenvatinib and Pembrolizumab in People With Advanced Soft Tissue Sarcoma

TARGETS
FGFRs, KIT, PD-1, PDGFRA, RET, VEGFRs

LOCATIONS: New Jersey, New York

NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

TARGETS
FGFRs, KIT, PD-1, PDGFRA, RET, VEGFRs

LOCATIONS: Massachusetts

NCT02272998

PHASE 2

Ponatinib for Patients Whose Advanced Solid Tumor Cancer Has Activating Mutations Involving the Following Genes: FGFR1, FGFR2, FGFR3, FGFR4, RET, KIT.

TARGETS
ABL, FGFRs, FLT3, KIT, RET, VEGFRs

LOCATIONS: Ohio

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CLINICAL TRIALS

NCT04169672

PHASE 2

Study of Surufatinib Combined With Toripalimab in Patients With Advanced Solid Tumors

TARGETS
CSF1R, FGFR1, VEGFRs, PD-1

LOCATIONS: Beijing (China), Shanghai (China)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Cape Town (South Africa), Johannesburg (South Africa), Durban (South Africa), New York, New Jersey, Ohio, Texas, Hamilton (Canada), Toronto (Canada), Ottawa (Canada)

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

TARGETS
FGFR1, FGFR2, FGFR3, FLT3, LCK, LYN, SRC, VEGFRs, PD-1

LOCATIONS: Villejuif (France)

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GENE
KIT

ALTERATION
amplification

RATIONALE
KIT amplification or activating mutations may predict sensitivity to small molecule tyrosine kinase inhibitors. Also, because KIT activation leads to activation of the PI3K-AKT-mTOR pathway, PI3K and mTOR pathway inhibitors may be relevant in a tumor with KIT activation.

NCT03277924

PHASE 1/2

Trial of Sunitinib Plus Nivolumab After Standard Treatment in Advanced Soft Tissue and Bone Sarcomas

TARGETS
PD-1, CSF1R, FLT3, KIT, RET, VEGFRs

LOCATIONS: La Laguna (Spain), Sevilla (Spain), Madrid (Spain), Valencia (Spain), Zaragoza (Spain), Barcelona (Spain), Candiolo (Italy), Milano (Italy)

NCT04449549

PHASE 2

Rapid Analysis and Response Evaluation of Combination Anti-Neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 1 Nilotinib and Paclitaxel

TARGETS
ABL, KIT

LOCATIONS: Maryland

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT04784247

PHASE 2

Lenvatinib and Pembrolizumab in People With Advanced Soft Tissue Sarcoma

TARGETS
FGFRs, KIT, PD-1, PDGFRA, RET, VEGFRs

LOCATIONS: New Jersey, New York

NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

TARGETS
FGFRs, KIT, PD-1, PDGFRA, RET, VEGFRs

LOCATIONS: Massachusetts

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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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

CLINICAL TRIALS

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT02461849

PHASE 2

Patients With Refractory, Metastatic Cancer Harboring KIT Mutation or Amplification to Investigate the Clinical Efficacy and Safety of Imatinib Therapy

TARGETS
KIT, ABL

LOCATIONS: Seoul (Korea, Republic of)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Cape Town (South Africa), Johannesburg (South Africa), Durban (South Africa), New York, New Jersey, Ohio, Texas, Hamilton (Canada), Toronto (Canada), Ottawa (Canada)

NCT03502733

PHASE 1

Copanlisib and Nivolumab in Treating Patients With Metastatic Solid Tumors or Lymphoma

TARGETS
PI3K, PD-1

LOCATIONS: Maryland, Texas

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GENE
MDM2

ALTERATION
amplification

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

NCT03611868

PHASE 1/2

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

TARGETS
MDM2, PD-1

LOCATIONS: Florida, Virginia, District of Columbia, Pennsylvania, New York, Tennessee, Texas, Missouri

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GENE
PDGFRA

ALTERATION
amplification

RATIONALE
PDGFRA amplification may predict sensitivity to imatinib and to anti-PDGFRA antibodies.

NCT01738139

PHASE 1

Ipilimumab and Imatinib Mesylate in Advanced Cancer

TARGETS
KIT, ABL, CTLA-4

LOCATIONS: Texas

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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.

FLCN T22M	***HDAC7*** amplification	***INPP4B*** V594A	***KDM5A*** P1237H
NCOR2 Q510_P511insQQQQ	***RICTOR*** R1202fs*4	***SOX10*** E359D	***WT1*** amplification

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APPENDIX Genes Assayed in FoundationOne®Heme

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

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

ABL1	*ACTB*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	*APC*
APH1A	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*		*ARID1A*	*ARID2*	*ASMTL*
ASXL1	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*	*B2M*
BAP1	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*	*BCL7A*	*BCOR*
BCORL1	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BRSK1*
BTG2	*BTK*	*BTLA*	*C11orf30 (EMSY)*	*CAD*	*CALR**	*CARD11*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CCT6B*	*CD22*	*CD274 (PD-L1)*	*CD36*	*CD58*
CD70	*CD79A*	*CD79B*	*CDC73*	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*
CDKN1B	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*	*CIC*
CIITA	*CKS1B*	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*	*DNMT3A*
DOT1L	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*	*EGFR*	*ELP2*
EP300	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*	*ERG*
ESR1	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*	*FAF1*	*FAM46C*	*FANCA*	*FANCC*
FANCD2	*FANCE*	*FANCF*	*FANCG*	*FANCL*	*FAS (TNFRSF6)*	*FBXO11*	*FBXO31*	*FBXW7*
FGF10	*FGF14*	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*
FGFR3	*FGFR4*	*FHIT*	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*	*FOXL2*
FOXO1	*FOXO3*	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*	*GID4 (C17orf39)*
GNA11	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GSK3B*	*GTSE1*
HDAC1	*HDAC4*	*HDAC7*	*HGF*	*HIST1H1C*	*HIST1H1D*	*HIST1H1E*	*HIST1H2AC*	*HIST1H2AG*
HIST1H2AL	*HIST1H2AM*	*HIST1H2BC*	*HIST1H2BJ*	*HIST1H2BK*	*HIST1H2BO*	*HIST1H3B*	*HNF1A*	*HRAS*
HSP90AA1	*ICK*	*ID3*	*IDH1*	*IDH2*	*IGF1R*	*IKBKE*	*IKZF1*	*IKZF2*
IKZF3	*IL7R*	*INHBA*	*INPP4B*	*INPP5D (SHIP)*	*IRF1*	*IRF4*	*IRF8*	*IRS2*
JAK1	*JAK2*	*JAK3*	*JARID2*	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*
KRAS	*LEF1*	*LRP1B*	*LRRK2*	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*
MAP2K2	*MAP2K4*	*MAP3K1*	*MAP3K14*	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*	*MDM2*
MDM4	*MED12*	*MEF2B*	*MEF2C*	*MEN1*	*MET*	*MIB1*	*MITF*	*MKI67*
MLH1	*MPL*	*MRE11A*	*MSH2*	*MSH3*	*MSH6*	*MTOR*	*MUTYH*	*MYC*
MYCL (MYCL1)	*MYCN*	*MYD88*	*MYO18A*	*NCOR2*	*NCSTN*	*NF1*	*NF2*	*NFE2L2*
NFKBIA	*NKX2-1*	*NOD1*	*NOTCH1*	*NOTCH2*	*NPM1*	*NRAS*	*NT5C2*	*NTRK1*
NTRK2	*NTRK3*	*NUP93*	*NUP98*	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*
PAX5	*PBRM1*	*PC*	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*
PTPN2	*PTPN6 (SHP-1)*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*	*RARA*	*RASGEF1A*
RB1	*RELN*	*RET*	*RHOA*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*RUNX1*
S1PR2	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SERP2*	*SETBP1*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA1*	*SMARCA4*	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*
SOCS1	*SOCS2*	*SOCS3*	*SOX10*	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*
STAG2	*STAT3*	*STAT4*	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*
TAF1	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*	
TMSB4XP8 (TMSL3)		*TNFAIP3*	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*
TRAF2	*TRAF3*	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*
U2AF2	*VHL*	*WDR90*	*WHSC1 (MMSET or NSD2)*		*WISP3*	*WT1*	*XBP1*	*XPO1*
YY1AP1	*ZMYM3*	*ZNF217*	*ZNF24 (ZSCAN3)*	*ZNF703*	*ZRSR2*			

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

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

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

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

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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The median exon coverage for this sample is 664x

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

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

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

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

ABOUT FOUNDATIONONE HEME

FoundationOne®Heme is a comprehensive genomic profiling test for hematologic malignancies and sarcomas. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials, and quantitative markers that may support immunotherapy clinical trial enrollment. FoundationOne Heme is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across more than 250 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas.

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of 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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

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

FoundationOne Heme fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium.

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REPORT HIGHLIGHTS

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

SELECT ABBREVIATIONS

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

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1. Histopathology (2007) pmid: 17204026
2. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
3. Overman MJ, et al. Lancet Oncol. (2017) pmid: 28734759
4. Overman MJ, et al. J. Clin. Oncol. (2018) pmid: 29355075
5. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
6. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
7. Rizvi NA, et al. Science (2015) pmid: 25765070
8. Oaknin A, et al. JAMA Oncol (2020) pmid: 33001143
9. Hochster et al., 2017; ASCO Abstract 673
10. Fleming et al., 2018; ASCO Abstract 5585
11. Bang et al., 2018; ASCO Abstract 92
12. Heinsohn S, et al. Int. J. Oncol. (2007) pmid: 17390023
13. Belchis DA, et al. Diagn. Mol. Pathol. (1996) pmid: 8866236
14. Suwa K, et al. J Orthop Sci (1999) pmid: 10370164
15. Entz-Werlé N, et al. J. Clin. Oncol. (2005) pmid: 15800315
16. Tarkkanen M, et al. Br. J. Cancer (1996) pmid: 8695363
17. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
18. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
19. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
20. Lynch HT, et al. Clin. Genet. (2009) pmid: 19659756
21. Pande M, et al. Fam. Cancer (2012) pmid: 22714864
22. Kastrinos F, et al. Semin. Oncol. (2007) pmid: 17920897
23. Silva FC, et al. Sao Paulo Med J (2009) pmid: 19466295
24. Sehgal R, et al. Genes (Basel) (2014) pmid: 24978665
25. Fam. Cancer (2005) pmid: 16136383
26. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
27. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
28. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
29. Cristescu R, et al. Science (2018) pmid: 30309915
30. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
31. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
32. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
33. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
34. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
35. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
36. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
37. Legrand et al., 2018; ASCO Abstract 12000
38. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
39. Lim J, et al. Clin. Cancer Res. (2015) pmid: 26330427
40. Brohl AS, et al. PLoS Genet. (2014) pmid: 25010205
41. Chen X, et al. Cancer Cell (2013) pmid: 24332040
42. Xie L, et al. Front Oncol (2020) pmid: 33898301
43. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
44. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
45. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
46. Johnson BE, et al. Science (2014) pmid: 24336570
47. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
48. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
49. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
50. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
51. Nature (2012) pmid: 22810696
52. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
53. Evans EK, et al. Sci Transl Med (2017) pmid: 29093181
54. Abbaspour Babaei M, et al. Drug Des Devel Ther (2016) pmid: 27536065
55. Ramaswamy A, et al. J Gastrointest Oncol (2016) pmid: 27563456
56. Demetri GD, et al. Lancet (2013) pmid: 23177515
57. Gotlib J, et al. N. Engl. J. Med. (2016) pmid: 27355533
58. Jawhar M, et al. Blood (2017) pmid: 28424161
59. Xu X, et al. Int J Clin Exp Pathol (2014) pmid: 25031773
60. Gotlib J, et al. Blood (2005) pmid: 15972446
61. Si L, et al. J. Clin. Oncol. (2012) pmid: 22162580
62. Parikh SA, et al. Leuk Lymphoma (2010) pmid: 20038218
63. Wei X, et al. Oncol. Res. (2019) pmid: 30075827
64. Hodi FS, et al. J. Clin. Oncol. (2013) pmid: 23775962
65. Carvajal RD, et al. JAMA (2011) pmid: 21642685
66. Guo J, et al. J. Clin. Oncol. (2011) pmid: 21690468
67. Debiec-Rychter M, et al. Gastroenterology (2005) pmid: 15685537
68. Dematteo RP, et al. Lancet (2009) pmid: 19303137
69. Faivre S, et al. J. Clin. Oncol. (2005) pmid: 16135502
70. Hotte SJ, et al. J. Clin. Oncol. (2005) pmid: 15659505
71. Alcedo JC, et al. Head Neck (2004) pmid: 15350030
72. Brandwein JM, et al. Leukemia (2011) pmid: 21403650
73. Reardon DA, et al. Br. J. Cancer (2009) pmid: 19904263
74. Lee SJ, et al. Oncologist (2015) pmid: 26424760
75. Llovet JM, et al. Clin. Cancer Res. (2012) pmid: 22374331
76. Zhang HL, et al. Clin Genitourin Cancer (2013) pmid: 23058498
77. Seino S, et al. Gastroenterology (2014) pmid: 25450081
78. Li XF, et al. Med. Oncol. (2009) pmid: 18846437
79. Minor DR, et al. Clin. Cancer Res. (2012) pmid: 22261812
80. Mahipal A, et al. Melanoma Res. (2012) pmid: 23114504
81. Suehara Y, et al. Clin. Cancer Res. (2019) pmid: 31175097
82. Entz-Werle N, et al. Int. J. Cancer (2007) pmid: 17294449
83. Disel U, et al. Oncologist (2020) pmid: 31604903
84. Miiji LN, et al. Int J Clin Exp Pathol (2011) pmid: 22135725
85. Int. J. Biochem. Cell Biol. (1999) pmid: 10582339
86. Semin. Oncol. (2004) pmid: 15175998
87. Gao J, et al. Sci Signal (2013) pmid: 23550210
88. Zack TI, et al. Nat. Genet. (2013) pmid: 24071852
89. Beroukhim R, et al. Nature (2010) pmid: 20164920
90. Arefi M, et al. Int. J. Hematol. (2012) pmid: 22806436
91. Baccarani M, et al. Haematologica (2007) pmid: 17666373
92. Cassier PA, et al. Clin. Cancer Res. (2012) pmid: 22718859
93. Chalmers ZR, et al. Blood Cancer J (2015) pmid: 25658984
94. Cools J, et al. N. Engl. J. Med. (2003) pmid: 12660384
95. Curtis CE, et al. Br. J. Haematol. (2007) pmid: 17555450
96. Debiec-Rychter M, et al. Eur. J. Cancer (2004) pmid: 15010069
97. Dileo P, et al. Int. J. Cancer (2011) pmid: 20473908
98. Fanta PT, et al. J. Clin. Oncol. (2015) pmid: 24638008
99. Florian S, et al. Leuk. Res. (2006) pmid: 16406018
100. Frenard C, et al. JAAD Case Rep (2016) pmid: 27051816
101. Griffin JH, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808148
102. Heinrich MC, et al. J. Clin. Oncol. (2003) pmid: 14645423
103. Helbig G, et al. Br. J. Haematol. (2009) pmid: 19120352
104. Helbig G, et al. Am. J. Hematol. (2014) pmid: 24009127
105. Hus M, et al. Leuk. Res. (2011) pmid: 21093052
106. Ikezoe T, et al. Leuk. Res. (2010) pmid: 20303172
107. Intermesoli T, et al. Br. J. Haematol. (2009) pmid: 19735261
108. Jain N, et al. Leuk. Res. (2009) pmid: 19013640
109. Jovanovic JV, et al. Blood (2007) pmid: 17299092
110. Kang HJ, et al. Acta Oncol (2012) pmid: 22150077
111. Klion AD, et al. Blood (2004) pmid: 14504092
112. Kobayashi M, et al. Respirology (2009) pmid: 19192229
113. Kocáková I, et al. Klin Onkol (2014) pmid: 24635438
114. Metzgeroth G, et al. Br. J. Haematol. (2008) pmid: 18950453
115. Murayama Y, et al. World J Gastrointest Oncol (2012) pmid: 22645636
116. Ogbogu PU, et al. J. Allergy Clin. Immunol. (2009) pmid: 19910029
117. Ohnishi H, et al. Br. J. Haematol. (2006) pmid: 16856885
118. Pardanani A, et al. Blood (2003) pmid: 12842979
119. Pardanani A, et al. Blood (2004) pmid: 15284118
120. Qu SQ, et al. Oncotarget (2016) pmid: 27120808
121. Score J, et al. Leukemia (2006) pmid: 16498388
122. Shah S, et al. J Hematol Oncol (2014) pmid: 24669761
123. Sugimoto Y, et al. Cancer Genet (2015) pmid: 26319757
124. Volz HC, et al. Int. J. Cardiol. (2011) pmid: 20609486
125. von Bubnoff N, et al. Leukemia (2005) pmid: 15618966
126. Walz C, et al. Genes Chromosomes Cancer (2006) pmid: 16845659
127. Yoo C, et al. Cancer Res Treat (2016) pmid: 26130666
128. Al-Riyami AZ, et al. Leuk. Lymphoma (2013) pmid: 23157309
129. Lierman E, et al. Blood (2006) pmid: 16645167
130. Lierman E, et al. Leukemia (2009) pmid: 19212337
131. Metzgeroth G, et al. Leukemia (2012) pmid: 21818111
132. Roubaud G, et al. Ann. Oncol. (2012) pmid: 22294526
133. von Bubnoff N, et al. Oncogene (2011) pmid: 20972453
134. Hochhaus A, et al. J. Cancer Res. Clin. Oncol. (2013) pmid: 24057647
135. Tabouret E, et al. Leuk. Res. (2011) pmid: 20832858
136. Dewaele B, et al. Clin. Cancer Res. (2008) pmid: 18794084
137. Weisberg E, et al. Gastroenterology (2006) pmid: 17087936
138. Brohl AS, et al. Clin Sarcoma Res (2015) pmid: 26396737
139. Grellety T, et al. Future Sci OA (2015) pmid: 28031906
140. Kollàr A, et al. Clin Sarcoma Res (2014) pmid: 25905001
141. Jaku et al., 2017; ASCO Abstract 2515
142. Sulzbacher I, et al. Pathology (2010) pmid: 21080877
143. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
144. Kubo T, et al. Cancer (2008) pmid: 18338812
145. Niini T, et al. Genes Chromosomes Cancer (2011) pmid: 21254299
146. Andrae J, et al. Genes Dev. (2008) pmid: 18483217
147. Burford A, et al. PLoS ONE (2013) pmid: 23990986
148. Flavahan WA, et al. Nature (2016) pmid: 26700815
149. Roszik J, et al. Sci Rep (2016) pmid: 26787600
150. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
151. Koschmann C, et al. Oncotarget (2016) pmid: 27582545
152. Phillips JJ, et al. Brain Pathol. (2013) pmid: 23438035
153. Puget S, et al. PLoS ONE (2012) pmid: 22389665
154. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
155. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
156. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
157. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
158. Dickson et al., 2019; ASCO Abstract 11004
159. Dickson MA, et al. JAMA Oncol (2016) pmid: 27124835

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160. Peguero et al., 2016; ASCO Abstract 2528
161. Wei G, et al. Int. J. Cancer (1999) pmid: 9935200
162. Smida J, et al. Clin. Cancer Res. (2010) pmid: 20610556
163. Dujardin F, et al. Mod. Pathol. (2011) pmid: 21336260
164. Mejia-Guerrero S, et al. Genes Chromosomes Cancer (2010) pmid: 20196171
165. Yoshida A, et al. Am. J. Surg. Pathol. (2012) pmid: 22301501
166. López-Guerrero JA, et al. Diagn. Mol. Pathol. (2004) pmid: 15167009
167. Benassi MS, et al. Int. J. Cancer (1999) pmid: 10502725
168. Choi YJ, et al. Oncogene (2014) pmid: 23644662
169. Cell (1995) pmid: 7736585
170. Musgrove EA, et al. Nat. Rev. Cancer (2011) pmid: 21734724
171. Wikman H, et al. Genes Chromosomes Cancer (2005) pmid: 15543620
172. Rao SK, et al. J. Neurooncol. (2010) pmid: 19609742
173. Chung L, et al. Am. J. Surg. Pathol. (2009) pmid: 19574885
174. Ragazzini P, et al. Histol. Histopathol. (2004) pmid: 15024701
175. Zhang K, et al. Cancer Res. (2013) pmid: 23393200
176. Horvai AE, et al. Mod. Pathol. (2009) pmid: 19734852
177. Oliner JD, et al. Nature (1992) pmid: 1614537
178. Kashima T, et al. Mod. Pathol. (2012) pmid: 22699518
179. Barretina J, et al. Nat. Genet. (2010) pmid: 20601955
180. Park HR, et al. Pathol. Res. Pract. (2004) pmid: 15310147
181. Wunder JS, et al. Oncogene (1999) pmid: 9989829
182. Loriot Y, et al. N. Engl. J. Med. (2019) pmid: 31340094
183. Tabernero J, et al. J. Clin. Oncol. (2015) pmid: 26324363
184. Karkera JD, et al. Mol. Cancer Ther. (2017) pmid: 28416604
185. Necchi et al., 2018; ESMO Abstract 900P
186. Pal SK, et al. Cancer Discov (2018) pmid: 29848605
187. Pal SK, et al. Cancer (2020) pmid: 32208524
188. Schuler M, et al. Lancet Oncol. (2019) pmid: 31405822
189. Farouk Sait S, et al. JCO Precis Oncol (2021) pmid: 34250399
190. Voss MH, et al. Clin. Cancer Res. (2019) pmid: 30745300
191. Bahleda R, et al. Ann Oncol (2020) pmid: 32622884
192. Papadopoulos KP, et al. Br. J. Cancer (2017) pmid: 28972963
193. Cheng FT, et al. J Natl Compr Canc Netw (2017) pmid: 29223982
194. Khodadoust MS, et al. Leukemia (2016) pmid: 26055304
195. Tanasi I, et al. Blood (2019) pmid: 31434701
196. Strati P, et al. Leuk. Lymphoma (2018) pmid: 29119847
197. Nogova L, et al. J. Clin. Oncol. (2017) pmid: 27870574
198. Aggarwal C, et al. J Thorac Oncol (2019) pmid: 31195180
199. Ware KE, et al. Oncogenesis (2013) pmid: 23552882
200. Terai H, et al. Mol. Cancer Res. (2013) pmid: 23536707
201. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
202. Guagnano V, et al. Cancer Discov (2012) pmid: 23002168
203. Lee JC, et al. Mod. Pathol. (2016) pmid: 27443518
204. Turner N, et al. Nat. Rev. Cancer (2010) pmid: 20094046
205. Kohler LH, et al. Virchows Arch. (2012) pmid: 22648708
206. Kim HR, et al. J. Clin. Oncol. (2013) pmid: 23182986
207. André F, et al. Lancet Oncol. (2014) pmid: 24508104
208. Dienstmann R, et al. Ann. Oncol. (2014) pmid: 24265351
209. Cheok CF, et al. Nat Rev Clin Oncol (2011) pmid: 20975744
210. Ohnstad HO, et al. Cancer (2013) pmid: 23165797
211. Gamble LD, et al. Oncogene (2012) pmid: 21725357
212. Zhang et al., 2019; ASCO Abstract 3124
213. Rasco et al., 2019; ASCO Abstract 3126
214. Tolcher et al., 2021; ASCO Abstract 2506
215. Martinelli et al., 2016; EHA21 Abstract S504
216. Daver et al., 2018; ASH Abstract 767
217. Mascarenhas et al., 2019; ASH Abstract 134
218. Shustov et al., 2018; ASH Abstract 1623
219. Sallman et al., 2018; ASH Abstract 4066
220. Meric-Bernstam et al., 2017; ASCO Abstract 2505
221. Yoshida A, et al. Mod. Pathol. (2010) pmid: 20601938
222. Sdek P, et al. Mol. Cell (2005) pmid: 16337594
223. Brady M, et al. Mol. Cell. Biol. (2005) pmid: 15632057
224. Li M, et al. Mol. Cell (2004) pmid: 15053880
225. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
226. Cordon-Cardo C, et al. Cancer Res. (1994) pmid: 8306343
227. Kato S, et al. Clin. Cancer Res. (2017) pmid: 28351930
228. Singavi et al., 2017; ESMO Abstract 1140PD
229. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
230. Schmitz R, et al. Nature (2012) pmid: 22885699
231. Choi YJ, et al. Cancer Cell (2012) pmid: 23079655
232. Sawai CM, et al. Cancer Cell (2012) pmid: 23079656
233. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
234. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
235. Kanamori M, et al. J. Exp. Clin. Cancer Res. (2012) pmid: 23199169
236. Lu XY, et al. Mol. Cancer Res. (2008) pmid: 18567798
237. Bui MM, et al. In Vivo () pmid: 18019405
238. Sridhar J, et al. AAPS J (2006) pmid: 16584130
239. Kasugai Y, et al. Clin. Cancer Res. (2005) pmid: 16322284
240. Luo LY, et al. Mol. Cancer Res. (2015) pmid: 25368431
241. Pilotti S, et al. J. Pathol. (1998) pmid: 9713346
242. Segura-Sánchez J, et al. Anticancer Res. () pmid: 17214366
243. Wang X, et al. Genes Chromosomes Cancer (2011) pmid: 21793095
244. Kanodia J, et al. Cell Commun. Signal (2014) pmid: 24885272
245. Wu Y, et al. Biol. Chem. (2003) pmid: 12974390
246. Chen PY, et al. Proc. Natl. Acad. Sci. U.S.A. (2014) pmid: 24706887
247. Yan KS, et al. J. Biol. Chem. (2002) pmid: 11877385
248. Beuselinck B, et al. Acta Oncol (2018) pmid: 29095068
249. Song Y, et al. Chin. Med. J. (2015) pmid: 26228213
250. Dornbusch J, et al. PLoS ONE (2013) pmid: 24086736
251. Terakawa T, et al. Urol. Oncol. (2013) pmid: 21478036
252. You D, et al. World J Urol (2015) pmid: 24710685
253. Silva E, et al. Breast J () pmid: 25639617
254. Baumgarten P, et al. Neuro-oncology (2016) pmid: 26627848
255. Sathornsumetee S, et al. J. Clin. Oncol. (2008) pmid: 18182667
256. Olafson LR, et al. J Clin Neurosci (2019) pmid: 31582283
257. Duda DG, et al. Oncologist (2010) pmid: 20484123
258. Stremitzer S, et al. Mol. Cancer Ther. (2016) pmid: 27535973
259. Weickhardt AJ, et al. Br. J. Cancer (2015) pmid: 26125443
260. Kopetz S, et al. J. Clin. Oncol. (2010) pmid: 20008624
261. Miles DW, et al. Br. J. Cancer (2013) pmid: 23422754
262. Fountzilas G, et al. Anticancer Res. (2011) pmid: 21868552
263. Gianni L, et al. J. Clin. Oncol. (2013) pmid: 23569311
264. Sánchez-Rovira P, et al. Clin Transl Oncol (2013) pmid: 23397155
265. Cameron D, et al. Lancet Oncol. (2013) pmid: 23932548
266. Mok T, et al. J Thorac Oncol (2014) pmid: 24807156
267. An SJ, et al. Cancer Gene Ther. (2014) pmid: 24577128
268. Bais C, et al. J. Natl. Cancer Inst. (2017) pmid: 29059426
269. Cohen EE, et al. Lancet Oncol. (2009) pmid: 19201650
270. Van Cutsem E, et al. J. Clin. Oncol. (2012) pmid: 22565005
271. Lee EQ, et al. Clin. Cancer Res. (2018) pmid: 29941486
272. Xu L, et al. Cancer Res. (2009) pmid: 19826039
273. Heist RS, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25605928
274. Biochem. Pharmacol. (2012) pmid: 22387046
275. Lee YH, et al. Eur. J. Cancer (1999) pmid: 10533453
276. Negri GL, et al. J Pathol (2019) pmid: 31236944
277. Biol. Pharm. Bull. (2011) pmid: 22130231
278. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
279. Yan M, et al. Breast Cancer Res. (2012) pmid: 22537934
280. Xu H, et al. Breast Cancer Res. (2011) pmid: 21255398
281. Stevens KN, et al. Breast Cancer Res. Treat. (2011) pmid: 21607584
282. Sehl ME, et al. Clin. Cancer Res. (2009) pmid: 19276285
283. Supernat A, et al. Oncol Lett (2012) pmid: 23205091
284. Deb S, et al. Br. J. Cancer (2014) pmid: 24548858
285. Supernat A, et al. Transl Oncol (2014) pmid: 25048628
286. Porkka KP, et al. Genes Chromosomes Cancer (2004) pmid: 14603436
287. Davis SJ, et al. Mol. Cancer Ther. (2015) pmid: 25852062
288. Atienza JM, et al. Mol. Cancer Ther. (2005) pmid: 15767545
289. Xu H, et al. Nat. Rev. Cancer (2011) pmid: 21326324
290. Hill VK, et al. Biochim. Biophys. Acta (2016) pmid: 27207471
291. Solomon DA, et al. BMB Rep (2014) pmid: 24856830
292. Bauerschmidt C, et al. Nucleic Acids Res. (2010) pmid: 19906707
293. Yun J, et al. Nucleic Acids Res. (2016) pmid: 26420833
294. Gelot C, et al. Nucleus (2016) pmid: 27326661
295. Sofueva S, et al. EMBO J. (2013) pmid: 24185899
296. Deng Z, et al. EMBO J. (2012) pmid: 23010778
297. Yun J, et al. EMBO Rep. (2016) pmid: 27466323
298. Mahmood SF, et al. Carcinogenesis (2014) pmid: 24148822
299. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
300. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
301. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
302. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
303. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
304. Xu L, et al. Mol. Med. (2001) pmid: 11713371
305. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
306. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
307. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
308. Hajdenberg et al., 2012; ASCO Abstract e15010
309. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
310. Moore et al., 2019; ASCO Abstract 5513
311. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
312. Oza et al., 2015; ASCO Abstract 5506
313. Lee J, et al. Cancer Discov (2019) pmid: 31315834
314. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
315. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
316. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
317. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967

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318. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
319. Gourley et al., 2016; ASCO Abstract 5571
320. Kwok M, et al. Blood (2016) pmid: 26563132
321. Boudny M, et al. Haematologica (2019) pmid: 30975914
322. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
323. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
324. Tsuchiya T, et al. Cancer Genet. Cytogenet. (2000) pmid: 10942797
325. Ito M, et al. Clin. Cancer Res. (2011) pmid: 21159888
326. Lorenz S, et al. Oncotarget (2016) pmid: 26672768
327. Ribi S, et al. Oncotarget (2015) pmid: 25762628
328. Miller CW, et al. Cancer Res (1990) pmid: 2253237
329. Chen X, et al. Cell Rep (2014) pmid: 24703847
330. Chandar N, et al. Br J Cancer (1992) pmid: 1739619
331. Wu X, et al. Cancer Epidemiol (2012) pmid: 21890444
332. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
333. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
334. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
335. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
336. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
337. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
338. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
339. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
340. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
341. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
342. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
343. Lalloo F, et al. Lancet (2003) pmid: 12672316
344. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
345. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
346. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
347. Xie M, et al. Nat. Med. (2014) pmid: 25326804
348. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
349. Severson EA, et al. Blood (2018) pmid: 29678827
350. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
351. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
352. Chabon JJ, et al. Nature (2020) pmid: 32269342
353. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
354. Zhang X, et al. PLoS ONE (2013) pmid: 23991038
355. Holland DG, et al. EMBO Mol Med (2011) pmid: 21337521
356. Sircoulomb F, et al. EMBO Mol Med (2011) pmid: 21328542
357. Reynisdottir I, et al. Cancer Med (2013) pmid: 24156016
358. Yang G, et al. Oncol. Rep. (2014) pmid: 24481460
359. Ma F, et al. Oncol. Rep. (2014) pmid: 25017610
360. Bazarov AV, et al. Breast Cancer Res. (2011) pmid: 21635707
361. Slorach EM, et al. Genes Dev. (2011) pmid: 21317240
362. Debiec-Rychter M, et al. Eur. J. Cancer (2006) pmid: 16624552
363. Kamenz T, et al. World J. Gastroenterol. (2006) pmid: 16570351
364. Wang YY, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15650049
365. Bond M, et al. Pediatr Blood Cancer (2008) pmid: 17262795
366. Chugh et al., 2004; ASCO Abstract 9001
367. Carvajal RD, et al. Clin. Cancer Res. (2015) pmid: 25695690
368. Hochhaus A, et al. J. Cancer Res. Clin. Oncol. (2015) pmid: 26002753
369. Blay JY, et al. Lancet Oncol. (2015) pmid: 25882987
370. Kajimoto N, et al. Int J Clin Exp Pathol (2015) pmid: 26722383
371. Sako H, et al. PLoS ONE (2014) pmid: 25221952
372. Hughes TP, et al. Blood (2014) pmid: 24335106
373. Takahashi N, et al. Biomark Res (2014) pmid: 24650752
374. Reichardt P, et al. Ann. Oncol. (2012) pmid: 22357255
375. Cauchi C, et al. Cancer Chemother. Pharmacol. (2012) pmid: 22119758
376. Villar VH, et al. PLoS ONE (2012) pmid: 22662203
377. Quintás-Cardama A, et al. Nat Clin Pract Oncol (2008) pmid: 18936790
378. Bisagni G, et al. J Thorac Oncol (2009) pmid: 19461405
379. Handolias D, et al. Br. J. Cancer (2010) pmid: 20372153
380. Dişel U, et al. Lung Cancer (2011) pmid: 20970876
381. Park SH, et al. Invest New Drugs (2012) pmid: 22270258
382. Catania C, et al. Onco Targets Ther (2014) pmid: 24855380
383. Guo T, et al. Clin. Cancer Res. (2007) pmid: 17699867
384. Hu S, et al. Mol. Cancer Ther. (2008) pmid: 18483300
385. Penel-Page M, et al. BMC Cancer (2015) pmid: 26541413
386. Wakelee HA, et al. J Thorac Oncol (2012) pmid: 22982658
387. Spigel DR, et al. J. Clin. Oncol. (2011) pmid: 21576636
388. You et al., 2016; ASCO Abstract 2532
389. Sharma N, et al. Invest New Drugs (2014) pmid: 24420556
390. Baselga J, et al. J. Clin. Oncol. (2012) pmid: 22412143
391. Gradishar WJ, et al. Eur. J. Cancer (2013) pmid: 22954665
392. Bengala C, et al. Br. J. Cancer (2010) pmid: 19935794
393. Qun W, et al. Hepatogastroenterology () pmid: 20698202
394. LaRocca RV, et al. J Gastrointest Cancer (2007) pmid: 19089671
395. Moehler M, et al. Eur. J. Cancer (2014) pmid: 25446376
396. Beardsley EK, et al. Invest New Drugs (2012) pmid: 21785998
397. Aragon-Ching JB, et al. BJU Int. (2009) pmid: 19154507
398. Reardon DA, et al. J. Neurooncol. (2011) pmid: 20443129
399. Lee EQ, et al. Neuro-oncology (2012) pmid: 23099651
400. Peereboom DM, et al. Neuro-oncology (2013) pmid: 23328813
401. Hottinger AF, et al. Br. J. Cancer (2014) pmid: 24786603
402. Heinrich MC, et al. J. Clin. Oncol. (2008) pmid: 18955458
403. Buchbinder EI, et al. Cancer (2015) pmid: 26264378
404. Reichardt P, et al. BMC Cancer (2016) pmid: 26772734
405. Hirai F, et al. Mol Clin Oncol (2016) pmid: 27073655
406. Goemans BF, et al. Leuk. Res. (2010) pmid: 20435347
407. Guo W, et al. Oncol Lett (2016) pmid: 26870284
408. Kumar RM, et al. Am J Cancer Res (2015) pmid: 26328246
409. Sweeney CJ, et al. J. Clin. Oncol. (2010) pmid: 20837944
410. Yi JH, et al. Eur. J. Cancer (2012) pmid: 22176869
411. Decoster et al., 2010; ASCO Abstract 8518
412. Gervais R, et al. Lung Cancer (2011) pmid: 21680048
413. Scagliotti GV, et al. J. Clin. Oncol. (2012) pmid: 22564989
414. Mahmood ST, et al. Int. J. Cancer (2011) pmid: 21154746
415. George S, et al. J. Clin. Oncol. (2009) pmid: 19451429
416. Lu HJ, et al. Br. J. Dermatol. (2013) pmid: 23383874
417. Eberst L, et al. BMC Cancer (2014) pmid: 25420707
418. Simas A, et al. Case Rep Oncol (2010) pmid: 20740188
419. Yoo C, et al. Sarcoma (2009) pmid: 19478954
420. Mackay HJ, et al. Gynecol. Oncol. (2010) pmid: 19740535
421. Pan E, et al. J. Neurooncol. (2012) pmid: 22832897
422. Kreisl TN, et al. J. Neurooncol. (2013) pmid: 23086433
423. Balaña C, et al. Target Oncol (2014) pmid: 24424564
424. Hutterer M, et al. Neuro-oncology (2014) pmid: 24311637

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