ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Brain glioblastoma (GBM)
NAME Kuo, Chin-Chuan
DATE OF BIRTH 20 March 1961
SEX Male
MEDICAL RECORD # 46795442

PHYSICIAN

ORDERING PHYSICIAN Hsu, Pin-Chuan
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Brain
SPECIMEN ID S110-24512 A
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 24 August 2021
SPECIMEN RECEIVED 14 September 2021

Biomarker Findings

Microsatellite status - Cannot Be Determined
Tumor Mutational Burden - 25 Muts/Mb

Genomic Findings

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

NF1 S340fs*12
KRAS V14I - subclonal†
PDGFRA S847L
PTEN R233* - subclonal†
RNF43 G659fs*41
TSC2 R1438Q
ATR Y2025fs*2
CDKN2A/B p16INK4a R58* and p14ARF P72L
ERCC4 A428V
PTPN11 M504V - subclonal, R498W†
SETD2 W1640fs*26
TP53 R110C, R175H

2 Disease relevant genes with no reportable alterations: ***EGFR, IDH1***

† See About the Test in appendix for details.

2 Therapies with Clinical Benefit
0 Therapies with Resistance
38 Clinical Trials

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 25 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)
NF1 **-** S340fs*12	none	Selumetinib
10 Trials *see p. 17*		Trametinib
KRAS **-** V14I - subclonal	none	none
10 Trials *see p. 15*		
PDGFRA **-** S847L	none	none
8 Trials *see p. 19*		
PTEN **-** R233* - subclonal	none	none
10 Trials *see p. 21*		
RNF43 **-** G659fs*41	none	none
3 Trials *see p. 23*		
TSC2 **-** R1438Q	none	none
10 Trials *see p. 24*		

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 approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. 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. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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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, MSI and associated increased mutational burden[1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[2-6], including the approved therapies nivolumab (alone or in combination with ipilimumab)[7-9], pembrolizumab[10-11], atezolizumab, avelumab, and durvalumab[3-5] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[12-14]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[12], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[15]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[12], in GBMs with a previous lower grade astrocytoma[13], and in giant cell GBM compared to classic GBM[14].

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[16]. 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[16-18]. 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[16], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[19]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[19-21] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[22-24]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
25 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[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-34]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[25,35-36]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[37-38] or anti-PD-L1[39] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)[40]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[41-42]. Increased TMB has been reported to correlate with higher tumor grade in glioma[43] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[37], as well as with shorter OS of patients with diffuse glioma[44].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[45-46] and cigarette smoke in lung cancer[11,47], treatment with temozolomide-based chemotherapy in glioma[48-49], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[50-54], and microsatellite instability (MSI)[50,53-54]. This sample harbors a TMB that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in POLE-mutated glioma. Although efficacy of immune checkpoint inhibitors has been observed for patients with other solid tumor types harboring TMB levels such as seen here[25-28,55], an association between TMB and clinical benefit has generally not been observed for patients with glioma[25,35-36], except for those with ultramutated glioma with POLE mutation[37-39]. Therefore, these agents may have efficacy for patients with this cancer type harboring both high TMB and POLE mutation.

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GENE
NF1

ALTERATION
S340fs*12

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
1019_1020delCT

VARIANT ALLELE FREQUENCY (% VAF)
41.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[56-59], glioma or glioblastoma[59-63], non-small cell lung cancer[64], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including the approved agents everolimus and temsirolimus, based on limited clinical data[65-67] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[68-69]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[70]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[71], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[72].

FREQUENCY & PROGNOSIS

NF1 mutation has been observed in 5-6% of lower grade gliomas and 9-14% of glioblastoma multiforme (GBM) cases; homozygous deletion of NF1 was observed in 1% of lower grade gliomas and 2-3% of GBMs[48,73-75]. Among GBM subtypes, NF1 mutation and loss were reported most frequently in the mesenchymal subtype, 37% (14/28) and 38% (21/55) of cases, respectively[76]. NF1 loss was significantly associated with decreased overall and disease-specific survival in patients with lower grade gliomas (II-III), but not in those with GBM[77].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[78]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[79]. Alterations such as seen here may disrupt NF1 function or expression[79-88].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the NF1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with neurofibromatosis type 1 (ClinVar, Mar 2021)[89]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[90-92]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[93-94], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE
KRAS

ALTERATION
V14I - subclonal

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
40G>A

VARIANT ALLELE FREQUENCY (% VAF)
2.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[95-96]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[97]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[98]. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[99-104]. While clinical responses have been reported for patients with KRAS-mutated ovarian[105-108], cervical small cell neuroendocrine[109], or uterine cancer[107] treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC[110-113], pancreatic cancer[114-116], and NSCLC[111,117-118]. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer[119]. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer[120-122] and KRAS-mutated endometrioid adenocarcinoma[123].

FREQUENCY & PROGNOSIS

In the TCGA dataset, KRAS mutations or amplification was detected in 1.8% of glioblastomas (GBM)[74] and 2.8% of lower grade gliomas[73]. In other studies KRAS mutations were observed in 2 out of 125 pilocytic astrocytomas, 1 out 25 grade 1 and 2 astrocytomas[124-125], and 2 out of 94 patients with GBM[126]. While the importance of RAS signaling in astrocytomas has been established, there is very little information regarding clinical implications of KRAS alterations in human astrocytoma[124,127]. In mouse models of cancer, activating KRAS mutation in combination with AKT mutation was sufficient to induce GBM in astrocytes and neural progenitors[128]. Furthermore, mutant KRAS-driven signaling was required for the maintenance of mouse GBM tumors[129], suggesting that targeting KRAS signaling may be an appropriate therapeutic strategy in KRAS-driven GBMs.

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[100,130]. KRAS mutations K5N, V14I, P34L/R, T58I, G60R, Y71H, K147E, and F156L have been characterized as activating and identified as germline mutations associated with Noonan, Costello and cardio-faciocutaneous syndromes[131-138].

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GENE
PDGFRA

ALTERATION
S847L

TRANSCRIPT ID
NM_006206

CODING SEQUENCE EFFECT
2540C>T

VARIANT ALLELE FREQUENCY (% VAF)
24.2%

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[139-176]. 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)[177-182]. Complete responses to nilotinib have been reported in patients with CEL or hypereosinophilic syndrome with FIP1L1-PDGFRA or activating mutations[155,183-184]; preclinical evidence has reported efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[185-186]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[187] or regorafenib[188-189]. Preclinical studies have reported sensitivity of activating PDGFRA mutations and FIP1L1-PDGFRA fusion to dasatinib[179,185]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[190] and preclinical[190] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[191]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

PDGFRA mutation has been identified in 5.6% of Grade 3 and 5.4% of Grade 4 astrocytomas, 2.4% of Grade 3 oligodendrogliomas, and 12% (3/25) of gliosarcomas analyzed in COSMIC (Jun 2021)[192]. PDGFRA mutations have been reported in 0-5% of lower grade glioma and glioblastoma samples[74-75,193-198], Ceccarelli et al., 2016; 26824661, Cancer Genome Atlas Research Network., 2015; 26061751, cBio-Johnson et al., 2014; 24336570, cBio-Thomas et al., 2017; 28472509, cBio-Jones et al., 2013; 23817572). A retrospective analysis of TCGA glioma samples reported elevated expression of ERBB3 correlated with PDGFRA expression and co-expression of these genes was an indicator of poor prognosis in a GBM patient cohort[199]. Amplification of PDGFRA has been associated with tumor grade and poor progression-free and overall survival in patients with glioblastoma[200-202]. In addition, PDGFRA amplification has been reported to occur in conjunction with IDH1 mutation in glioblastoma, and both alterations in the same tumor have been associated with poor patient prognosis[202].

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[203]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[204]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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GENE
PTEN

ALTERATION
R233* - subclonal

TRANSCRIPT ID
NM_000314

CODING SEQUENCE EFFECT
697C>T

VARIANT ALLELE FREQUENCY (% VAF)
1.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[205-208]. Clinical studies in glioblastoma have not observed an association between PTEN deficiency and response to everolimus or temsirolimus[209-211]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[212-216], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[217], ovarian cancer[218], uterine leiomyosarcoma[219], and endometrial cancer[216] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[220-221].

— Potential Resistance —

On the basis of a Phase 1b study, PTEN loss of expression may be associated with resistance to combination therapy with CDK4/6 inhibitors such as ribociclib and aromatase inhibitors such as letrozole[222]. Limited clinical evidence in glioblastoma[35], leiomyosarcoma[223], and melanoma[224] suggests that PTEN alterations may predict a lack of response to anti-PD-1 therapy. In an analysis of 39 patients with metastatic melanoma treated with pembrolizumab or nivolumab, patients with PTEN-expressing tumors achieved significantly greater reduction of tumor size than those with reduction or loss of PTEN expression[224]. In a retrospective analysis of 66 patients with glioblastoma, tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations[35]. In a patient with uterine leiomyosarcoma treated with pembrolizumab monotherapy, a treatment-resistant tumor arose that harbored PTEN loss[223].

FREQUENCY & PROGNOSIS

Studies in the literature have indicated that PTEN alterations (mutation or homozygous deletion) occur most frequently in glioblastoma (GBM), less frequently in anaplastic astrocytoma, and rarely in lower grade glioma subtypes including low grade astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma[225-232]. One study detected PTEN mutation in 42% (97/232) and loss in 10% (24/232) of IDH-wildtype GBM samples analyzed[233]. In the TCGA dataset, PTEN mutation was observed in 23% of GBM cases and PTEN deletion was reported in 7% of cases[74], while in the Lower Grade Glioma TCGA dataset, PTEN mutation was observed in 4% of cases and homozygous deletion observed in 1.2% of cases[73]. Decreased PTEN expression is associated with the higher grade GBM tumors[234]. Loss of PTEN correlated with significantly worse prognosis in all grades of gliomas[229,235].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[206]. Alterations such as seen here may disrupt PTEN function or expression[231,236-275].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the PTEN 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 hamartoma tumor syndrome (ClinVar, Mar 2021)[89]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[276-277]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[276,278]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[276]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

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GENE
RNF43

ALTERATION
G659fs*41

TRANSCRIPT ID
NM_017763

CODING SEQUENCE EFFECT
1976delG

VARIANT ALLELE FREQUENCY (% VAF)
18.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies have reported that RNF43 is a negative regulator of WNT signaling, and RNF43 loss or inactivation leads to WNT activation and confers sensitivity to WNT pathway inhibitors, particularly Porcupine inhibitors, in multiple tumor types[279-283]. Therefore, patients whose tumors harbor inactivating alterations in RNF43 may benefit from WNT pathway inhibitors, which are under investigation in clinical trials.

FREQUENCY & PROGNOSIS

Mutations in RNF43 have been reported in 18-27% of endometrial cancers[284-285], 3-5% of pancreatic cancers[286], 21% of ovarian mucinous carcinomas[287], 9% of liver fluke-associated cholangiocarcinomas[288], and up to 18% of colorectal cancers[53,285]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[285], endometrial[285], and gastric cancers[289-290]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[289].

FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[291] that was discovered because it is overexpressed in colon cancer[292]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[279-283]. An additional tumor-suppressor-like role for RNF43 in colon cancer is hypothesized to occur via its interaction with the ubiquitin-protein ligase NEDL1, which is predicted to enhance the pro-apoptotic effects of p53[293].

GENE
TSC2

ALTERATION
R1438Q

TRANSCRIPT ID
NM_000548

CODING SEQUENCE EFFECT
4313G>A

VARIANT ALLELE FREQUENCY (% VAF)
22.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss or inactivation of TSC2 can activate mTOR signaling[294-295]. MTOR inhibitors such as everolimus, temsirolimus, and sirolimus have shown activity against tumors associated with the genetic disease tuberous sclerosis complex (TSC), including subependymal giant-cell astrocytomas and renal angiomyolipomas[296-300]. In the context of TSC2-altered malignancies unrelated to TSC, MTOR inhibitor activity has been limited[301-303], with the exception of perivascular epithelioid cell tumors (PEComas)[304-305] and anecdotal reports across various solid tumors including anaplastic thyroid cancer[306], renal cell carcinoma (RCC)[307-308], glioblastoma[309], and CNS embryonal tumor[310], as well as a case of Hodgkin lymphoma[311]. In the prospective NCI-MATCH study, only 6.7% (1/15) of patients with TSC2-mutated solid tumors responded to everolimus, with the single response reported for a patient with uterine leiomyosarcoma[301]. Retrospective analyses of the RECORD-3, GRANITE-1, and EVOLVE-1 studies of everolimus to treat patients with RCC, gastric cancer, or hepatocellular carcinoma, respectively, showed no significant association between alterations in MTOR, TSC1, or TSC2 and median PFS[312]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

Hemizygous loss of TSC2 has been reported in one of 15 GBM samples in one study[313] and homozygous deletion in 0.2% of cases analyzed in the TCGA datasets[74]. TSC2 mutation has been observed in 0.4-3.0% of grade I-II glioma, 2.8% of grade III glioma, and <0.5% of glioblastomas (cBioPortal, COSMIC, Jan 2021)[73-74]. Loss of Tuberin expression has been reported in high-grade astrocytomas[314]. Inactivation of TSC2 and Tuberin has been associated with numerous cancers, including astrocytomas and glioblastomas[315-316].

FINDING SUMMARY

The tumor suppressor protein Tuberin (TSC2) binds with Hamartin (TSC1) to inhibit mTOR signaling and cell growth[294,317]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in TSC2 are associated with the autosomal dominant disorder tuberous sclerosis complex, which results in the development of hamartomas in multiple organ systems and an increased risk of developing renal cell carcinoma (RCC)[318-320]. TSC2 mutations account for approximately 75 to 80% of reported sporadic cases[321]. Prevalence for this disorder in the general population is estimated to be 1/6,000 from birth and 1/12,000 to 1/14,000 in children under 10 years of age[321]. In the appropriate clinical context, germline testing of TSC2 is recommended.

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

GENE
ATR

ALTERATION
Y2025fs*2

TRANSCRIPT ID
NM_001184

CODING SEQUENCE EFFECT
6072_6073insA

VARIANT ALLELE FREQUENCY (% VAF)
24.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 2 study reported talazoparib led to a SD lasting over 6 months for a patient with ATR-mutated breast cancer[322]. Based on preclinical evidence, ATR-deficient tumors may be sensitive to PARP inhibitors[323-324].

— Nontargeted Approaches —

ATR inactivation has been associated with increased sensitivity to 5-fluorouracil and cisplatin, but not to oxaliplatin, in cancer cell lines[325-327]; however, this has not been demonstrated clinically.

FREQUENCY & PROGNOSIS

ATR mutations have been reported in 1% of glioblastoma multiforme (GBM) samples[74-75]. In the COSMIC database, ATR mutations were not detected in any of 70 low-grade gliomas, but were identified in 2% of glioblastomas (Apr 2021)[192]. Expression of ATR has been reported to be reduced in gliomas compared to normal brain tissue[328]. It has also been reported that in glioma cells the level of phosphorylated ATR decreases in response to hypoxia[329]. The prognostic significance of ATR alterations in glioma has not been extensively investigated (PubMed, Mar 2021).

FINDING SUMMARY

ATR encodes the protein ataxia telangiectasia and RAD3 related, which phosphorylates the tumor suppressor BRCA1, and several cell cycle checkpoint proteins including CHK1; it plays a key role in maintaining genome integrity via regulation of DNA repair and replication[330-331]. Alterations such as seen here may disrupt ATR function or expression[332].

GENE
CDKN2A/B

ALTERATION
p16INK4a R58* and p14ARF P72L

TRANSCRIPT ID
NM_000077

CODING SEQUENCE EFFECT
172C>T

VARIANT ALLELE FREQUENCY (% VAF)
24.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[333-336]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[337-338], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[339-345]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[346-347], the clinical relevance of p14ARF as a predictive biomarker is not clear.

— Potential Resistance —

On the basis of a Phase 1b study, PTEN loss of expression may be associated with resistance to combination therapy with CDK4/6 inhibitors such as ribociclib and aromatase inhibitors such as letrozole[222].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[348] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[74] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[349-350]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[76,201,351]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[352]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[233]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[353]. Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression[201,354]. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas[355-356].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[357-358]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[359-360]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[361-362]. One or more alterations observed here are predicted to result in p16INK4a loss of function[363-384]. One or more alterations seen here have been observed in the context of cancer but have not been characterized and their effect on p14ARF function is unclear.

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[385]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[386-387]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[388-390]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[391-393]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENE
ERCC4

ALTERATION
A428V

TRANSCRIPT ID
NM_005236

CODING SEQUENCE EFFECT
1283C>T

VARIANT ALLELE FREQUENCY (% VAF)
26.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to address ERCC4 alterations in cancer. On the basis of limited preclinical and clinical data, loss of ERCC4 expression may predict response to platinum agents[394-395] or combination PARP and TOP1 inhibitors[396]. A patient with advanced-stage high-grade serous epithelial ovarian cancer and an ERCC4 A583T mutation with heterozygous loss of the wild-type allele exhibited an ongoing disease-free response (25 months post diagnosis) to first-line platinum chemotherapy[394].

FREQUENCY & PROGNOSIS

In the MSK-IMPACT pan-cancer dataset, ERCC4 mutation has been reported in 1.2% of more than 10,000 samples across 62 solid tumor types analyzed[397]. In lung adenocarcinoma, higher expression of XPF was observed in never smokers versus ever smokers[398]. High expression of the partner protein, ERCC1, has been associated with lack of response to platinum-based chemotherapy in several tumor types, including non-small cell lung cancer[399-400], head and neck squamous cell carcinoma[401], bladder cancer[402], and ovarian cancer[403-404].

FINDING SUMMARY

ERCC4 (also known as XPF) encodes a DNA endonuclease that forms an obligate partner for ERCC1; XPF-ERCC1 is involved in several DNA repair pathways, including nucleotide excision repair (NER), interstrand cross-link repair, single-stranded annealing branch of homologous recombination, and telomere maintenance[404-405]. Cells lacking ERCC4 exhibit heightened sensitivity to platinum agents[394-395]. Mutations in ERCC4 have been associated with xeroderma pigmentosum, Cockayne syndrome, Fanconi anemia, XFE progeria, and cerebro-oculo-facio-skeletal syndrome[406].

GENE
PTPN11

ALTERATION
M504V - subclonal, R498W

TRANSCRIPT ID
NM_002834, NM_002834

CODING SEQUENCE EFFECT
1510A>G, 1492C>T

VARIANT ALLELE FREQUENCY (% VAF)
2.0%, 20.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

SHP-2 has been reported to activate the RAS-MEK-ERK, PI3K-AKT-mTOR, and SRC kinase pathways[407-410]. Based on a case study of a patient with histiocytic sarcoma harboring an activating PTPN11 mutation who experienced a PR to trametinib[411], as well as preclinical data[412-414], PTPN11 activation may predict sensitivity to MEK inhibitors in histiocytic neoplasms. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

In the Brain Lower Grade Glioma and Glioblastoma Multiforme TCGA datasets, PTPN11 mutations have been reported in fewer than 1% of cases (cBioPortal, Jan 2021)[349-350]. PTPN11 mutations in glioma subtypes have also been reported in the scientific literature, and recurrent activating PTPN11 mutations have been detected in pilocytic astrocytomas[415-417]. PTPN11 mutations in glioblastoma have been associated with young patient age[418], but their prognostic significance in gliomas in general have not been extensively studied (PubMed, Aug 2021). While both oncogenic and tumor suppressor roles for PTPN11 has been described, its role in glioblastoma tumorigenesis is likely to be oncogenic[415-416,419-420].

FINDING SUMMARY

PTPN11 encodes the protein tyrosine-protein phosphatase non-receptor type 11, also known as SHP-2. PTPN11 plays a critical role in both embryonic development and cancer[421]. PTPN11 is also known to be somatically mutated in a variety of cancers, where both oncogenic and tumor suppressor roles for PTPN11 have been described[415,419-420]. The N-terminal SRC homology 2 (SH2) domain (aa 6-102) negatively regulates SHP-2 activity by binding to the active site of the SHP-2 protein tyrosine phosphatase (PTP) domain (aa 247-521)[422]. Alterations that disrupt this interaction or affect the specificity and structure of the SH2 and PTP domains, such as seen here, have been characterized as activating[409,419,423-435] and are predicted to be oncogenic[409,419,424-427,436-439]. The PTPN11 R498W mutation was reported in a patient with Noonan syndrome and characterized as inactivating[431].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in PTPN11 have been found in the developmental disorder Noonan syndrome, which predisposes individuals to various cancers, including embryonal rhabdomyosarcoma, neuroblastoma, and juvenile myelomonocytic leukemia[425,440-444].

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GENE
SETD2

ALTERATION
W1640fs*26

TRANSCRIPT ID
NM_014159

CODING SEQUENCE EFFECT
4912_4913insA

VARIANT ALLELE FREQUENCY (% VAF)
26.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS

Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[445]. SETD2 has been associated with favorable prognosis in gastric cancer[446]. SETD2 has also been associated with poor prognosis in RCC and MDS[447], while data in other tumor types is limited (PubMed, Jun 2021).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[448] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[449]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[450]. SETD2 alterations such as observed here have been shown to be inactivating[451-456].

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GENE
TP53

ALTERATION
R110C, R175H

TRANSCRIPT ID
NM_000546, NM_000546

CODING SEQUENCE EFFECT
328C>T, 524G>A

VARIANT ALLELE FREQUENCY (% VAF)
27.5%, 28.6%

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[457-460], or p53 gene therapy and immunotherapeutics such as SGT-53[461-465] and ALT-801[466]. 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) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[467]. 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 in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[468]. 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 in patients with platinum-refractory TP53-mutated ovarian cancer[469]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[120]. 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[470]. 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[471]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in 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[465]. 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[472]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[473-475]. 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[476]. 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[477-478]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[479-480]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs[75,481]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[233]. TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively[482-487]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[488]. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM[233]. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN[489].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[490]. Alterations such as seen here may disrupt TP53 function or expression[491-495].

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, Mar 2021)[89]. 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[496-498], including sarcomas[499-500]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[501] to 1:20,000[500]. 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[502]. 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[503-508]. 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[503-504]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[509]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[507,510-511]. 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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Selumetinib

Assay findings association

NF1
S340fs*12

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[56-59,512-516] , glioma[59-63,517] , and non-small cell lung cancer[64], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of selumetinib for the treatment of glioblastoma are limited (PubMed, Apr 2021). Selumetinib has demonstrated clinical activity in low-grade glioma. A Phase 2 study of selumetinib for patients with low-grade glioma (LGG) reported 8/25 PRs for patients with BRAF alterations and 10/25 PRs for those with NF1-associated LGG[60]; a Phase 1 study of selumetinib reported 5/25 PRs for patients with LGG[518]. A Phase 2 study of selumetinib for patients with tumors with activating alterations in the MAPK pathway evaluated 8 patients with high-grade glioma (HGG); 2 SDs and no objective responses were observed in this subset[519]. Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[57,512-513] and a Phase 1 study[56]. Phase 2 studies reported clinical responses in low-grade glioma[60,518] , melanoma[520-524] , and in lung[64,525-526] and endometrial cancer[527]. A Phase 2 study of selumetinib for patients with activating alterations in the MAPK pathway reported a DCR of 15% (3/20), with no objective responses observed[519]. Phase 1 studies of selumetinib to treat patients with solid tumors reported 1/15 PR for a patient with colorectal cancer (CRC) and 5/15 SDs for patients with tonsil squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and CRC[528]; 2/39 PRs (for patients with CRC) and 18/39 SDs were achieved when selumetinib was administered in combination with cyclosporin A[529]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[530], docetaxel or dacarbazine[531], AKT inhibitors[532], or cixutumumab (an anti-IGF-1R antibody)[533] reported clinical responses for patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

Trametinib

Assay findings association

NF1
S340fs*12

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[56-59,512-516] , glioma[59-63,517] , and non-small cell lung cancer[64], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Case studies of trametinib in NF1-associated low-grade glioma have reported 7 PRs, including 2 patients with pilocytic astrocytoma, 2 patients with diffuse astrocytoma, 3 patients with low-grade glioma experiencing PRs of over 6 months[59,61-62,517] . A study of four pediatric patients with BRAF mutation-positive non-operable astrocytoma reported a reduction in tumor volume in response to trametinib for the 3 optic gliomas with BRAF duplication[534-535] . A patient with pilocytic astrocytoma harboring an NFIA-RAF1 fusion that had progressed on multiple lines of prior treatment exhibited ongoing SD following treatment with trametinib[536]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[71], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[72].

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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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

KRAS

ALTERATION

V14I - subclonal

RATIONALE

KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors.

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)

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

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)

NCT03905148

PHASE 1/2

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

TARGETS RAFs, EGFR, MEK

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

NCT04111458

PHASE 1

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

TARGETS KRAS, SOS1, MEK

LOCATIONS: Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, Tennessee, Texas, North Carolina

NCT04800822

PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

TARGETS
SHP2, ROS1, ALK, BRAF, EGFR, MEK

LOCATIONS: California, Michigan, New York, Tennessee, Texas

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

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

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

NCT03065387

PHASE 1

Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification or HER3/4 Mutation

TARGETS
mTOR, EGFR, ERBB2, ERBB4, CDK4, CDK6, MEK

LOCATIONS: Texas

GENE
NF1

ALTERATION
S340fs*12

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

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)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (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)

NCT03834740

PHASE NULL

Ph0/2 Ribociclib & Everolimus

TARGETS
CDK6, CDK4, mTOR

LOCATIONS: Arizona

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)

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

ORDERED TEST # ORD-1188306-01

CLINICAL TRIALS

NCT03158389

PHASE 1/2

NCT Neuro Master Match - N²M² (NOA-20)

TARGETS
ALK, RET, CDK4, CDK6, mTOR, MDM2, PD-L1, SMO

LOCATIONS: Berlin (Germany), Dresden (Germany), Regensburg (Germany), Bochum (Germany), Frankfurt am Main (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Cologne (Germany), Mannheim (Germany)

NCT04800822

PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

TARGETS
SHP2, ROS1, ALK, BRAF, EGFR, MEK

LOCATIONS: California, Michigan, New York, Tennessee, Texas

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

GENE
PDGFRA

ALTERATION
S847L

RATIONALE
PDGFRA activating mutations may predict sensitivity to certain PDGFRA-targeted therapies. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04704154

PHASE 2

A Trial to Learn Whether Regorafenib in Combination With Nivolumab Can Improve Tumor Responses and How Safe it is for Participants With Solid Tumors

TARGETS
BRAF, KIT, RET, VEGFRs, PD-1

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Kobe (Japan), Nagoya (Japan), Chuo-ku (Japan), Koto-ku (Japan), Kita-Adachigun (Japan), Padova (Italy)

NCT03025893

PHASE 2/3

A Phase II/III Study of High-dose, Intermittent Sunitinib in Patients With Recurrent Glioblastoma Multiforme

TARGETS
CSF1R, FLT3, KIT, RET, VEGFRs

LOCATIONS: Groningen (Netherlands), Nijmegen (Netherlands), Amsterdam (Netherlands)

NCT03970447

PHASE 2/3

A Trial to Evaluate Multiple Regimens in Newly Diagnosed and Recurrent Glioblastoma

TARGETS
BRAF, KIT, RET, VEGFRs

LOCATIONS: Washington, Utah, California, Colorado, Minnesota, Wisconsin, Montréal (Canada), Michigan

NCT04051606

PHASE 2

Regorafenib in Bevacizumab Refractory Recurrent Glioblastoma

TARGETS
BRAF, KIT, RET, VEGFRs

LOCATIONS: Ohio

NCT04200404

PHASE 1/2

A Study of CS1001 in Subjects With Advanced or Refractory Solid Tumors

TARGETS
BRAF, KIT, RET, VEGFRs, PD-L1

LOCATIONS: Kurralta Park (Australia)

NCT02379416

PHASE 1

Combination Nilotinib and Paclitaxel in Adults With Relapsed Solid Tumors

TARGETS
ABL, KIT

LOCATIONS: Maryland

ORDERED TEST # ORD-1188306-01

CLINICAL TRIALS

NCT03475251

PHASE 1

A Study of CS1003 in Subjects With Advanced Solid Tumors

TARGETS
PD-1, BRAF, KIT, RET, VEGFRs

LOCATIONS: Randwick (Australia)

NCT01738139

PHASE 1

Ipilimumab and Imatinib Mesylate in Advanced Cancer

TARGETS
KIT, ABL, CTLA-4

LOCATIONS: Texas

GENE
PTEN

ALTERATION
R233* - subclonal

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04740190

PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04001569

PHASE 1/2

AZD8186 and Paclitaxel in Advanced Gastric Cancer

TARGETS
PI3K-beta

LOCATIONS: Seongnam-si (Korea, Republic of)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT04715620

PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
PARP

LOCATIONS: Tianjin (China)

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

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)

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Alaska, Washington, Oregon, California, Montana

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee, Texas

GENE
RNF43

ALTERATION
G659fs*41

RATIONALE
Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway.

NCT02521844

PHASE 1

A Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours

TARGETS
PORCN

LOCATIONS: Singapore (Singapore), Colorado, Missouri, Texas, North Carolina

NCT01351103

PHASE 1

A Study of LGK974 in Patients With Malignancies Dependent on Wnt Ligands

TARGETS
PORCN, PD-1

LOCATIONS: Utrecht (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Hospitalet de LLobregat (Spain), Valencia (Spain), Madrid (Spain), California, Michigan, Massachusetts, New York

NCT03447470

PHASE 1

Study to Evaluate the Safety and Tolerability of RXC004 in Advanced Malignancies

TARGETS
PORCN

LOCATIONS: Newcastle (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

GENE
TSC2

ALTERATION
R1438Q

RATIONALE
Inactivating TSC2 alterations may lead to increased mTOR activation and predict sensitivity to mTOR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (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)

NCT03834740

PHASE NULL

Ph0/2 Ribociclib & Everolimus

TARGETS
CDK6, CDK4, mTOR

LOCATIONS: Arizona

NCT03158389

PHASE 1/2

NCT Neuro Master Match - N²M² (NOA-20)

TARGETS
ALK, RET, CDK4, CDK6, mTOR, MDM2, PD-L1, SMO

LOCATIONS: Berlin (Germany), Dresden (Germany), Regensburg (Germany), Bochum (Germany), Frankfurt am Main (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Cologne (Germany), Mannheim (Germany)

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

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.

AXIN1 A526V	***BAP1*** R700W	***BARD1*** P395S	***BCORL1*** D1015N
CALR K111E	***DOT1L*** D588E	***EGFR*** R255*	***FGFR1*** D501E
JAK3 R222H	***KIT*** R956Q	***MAP2K2 (MEK2)*** E167K	***MSH2*** G164W
MSH6 K854del	***MTOR*** G1431R	***NF1*** R1412G	***PAX5*** R38C
POLE R1839H	***PRKCI*** R130H	***RBM10*** R660H	***RPTOR*** P368L and V971I
SYK splice site 1582-1G>T	***TBX3*** A562V	***TNFAIP3*** P462L	***ZNF703*** G340S

Electronically signed by J. Keith Killian, M.D. | 22 September 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors 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 interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

Electronically signed by J. Keith Killian, M.D. | 22 September 2021
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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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 CDx 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 the FoundationOne CDx assay 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 CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx 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.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics

of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

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, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, 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.

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 CDx.

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

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Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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

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. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

The median exon coverage for this sample is 832x

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1. Histopathology (2007) pmid: 17204026
2. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
3. Hochster et al., 2017; ASCO Abstract 673
4. Fleming et al., 2018; ASCO Abstract 5585
5. Bang et al., 2018; ASCO Abstract 92
6. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
7. Overman MJ, et al. Lancet Oncol. (2017) pmid: 28734759
8. Overman MJ, et al. J. Clin. Oncol. (2018) pmid: 29355075
9. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
10. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
11. Rizvi NA, et al. Science (2015) pmid: 25765070
12. Martinez R, et al. Oncology (2004) pmid: 15331927
13. Martinez R, et al. J. Cancer Res. Clin. Oncol. (2005) pmid: 15672285
14. Martinez R, et al. Cancer Genet. Cytogenet. (2007) pmid: 17498554
15. Szybka M, et al. Clin. Neuropathol. () pmid: 12908754
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
18. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
19. Lynch HT, et al. Clin. Genet. (2009) pmid: 19659756
20. Pande M, et al. Fam. Cancer (2012) pmid: 22714864
21. Kastrinos F, et al. Semin. Oncol. (2007) pmid: 17920897
22. Silva FC, et al. Sao Paulo Med J (2009) pmid: 19466295
23. Sehgal R, et al. Genes (Basel) (2014) pmid: 24978665
24. Fam. Cancer (2005) pmid: 16136383
25. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
26. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
27. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
28. Cristescu R, et al. Science (2018) pmid: 30309915
29. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
30. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
31. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
32. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
33. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
34. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
35. Zhao J, et al. Nat. Med. (2019) pmid: 30742119
36. Touat M, et al. Nature (2020) pmid: 32322066
37. Bouffet E, et al. J. Clin. Oncol. (2016) pmid: 27001570
38. Johanns TM, et al. Cancer Discov (2016) pmid: 27683556
39. Lukas RV, et al. J. Neurooncol. (2018) pmid: 30073642
40. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
41. Patel RR, et al. Pediatr Blood Cancer (2020) pmid: 32386112
42. Johnson A, et al. Oncologist (2017) pmid: 28912153
43. Draaisma K, et al. Acta Neuropathol Commun (2015) pmid: 26699864
44. Wang L, et al. BMC Cancer (2020) pmid: 32164609
45. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
46. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
47. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
48. Johnson BE, et al. Science (2014) pmid: 24336570
49. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
50. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
51. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
52. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
53. Nature (2012) pmid: 22810696
54. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
55. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
56. Dombi E, et al. N. Engl. J. Med. (2016) pmid: 28029918
57. Schalkwijk S, et al. Cancer Chemother Pharmacol (2021) pmid: 33903938
58. Toledano H, et al. Childs Nerv Syst (2021) pmid: 33751171
59. Ronsley R, et al. Cancer Med (2021) pmid: 33939292
60. Fangusaro J, et al. Lancet Oncol. (2019) pmid: 31151904
61. Manoharan N, et al. J Neurooncol (2020) pmid: 32780261
62. Kondyli M, et al. J Neurooncol (2018) pmid: 30097824
63. Awada G, et al. Case Rep Oncol () pmid: 33082744
64. Middleton G, et al. Nature (2020) pmid: 32669708
65. Lim SM, et al. Oncotarget (2016) pmid: 26859683
66. Weiss B, et al. Neuro-oncology (2015) pmid: 25314964
67. Janku F, et al. Oncotarget (2014) pmid: 24931142
68. Johannessen CM, et al. Curr. Biol. (2008) pmid: 18164202
69. Johannessen CM, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15937108
70. Malone CF, et al. Cancer Discov (2014) pmid: 24913553
71. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
72. Patterson et al., 2018; AACR Abstract 3891
73. Cancer Genome Atlas Research Network, et al. N. Engl. J. Med. (2015) pmid: 26061751
74. Brennan CW, et al. Cell (2013) pmid: 24120142
75. Nature (2008) pmid: 18772890
76. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
77. Vizcaíno MA, et al. Hum. Pathol. (2015) pmid: 26190195
78. Hattori S, et al. Biochem. Biophys. Res. Commun. (1991) pmid: 1904223
79. Morcos P, et al. Mol. Cell. Biol. (1996) pmid: 8628317
80. Ballester R, et al. Cell (1990) pmid: 2121371
81. Xu GF, et al. Cell (1990) pmid: 2116237
82. Martin GA, et al. Cell (1990) pmid: 2121370
83. Thomas L, et al. Hum. Mutat. (2012) pmid: 22807134
84. Skuse GR, et al. Hum. Mol. Genet. (1997) pmid: 9300663
85. Messiaen LM, et al. Genet. Med. () pmid: 11258625
86. Ars E, et al. Hum. Mol. Genet. (2000) pmid: 10607834
87. Messiaen LM, et al. J. Med. Genet. (2005) pmid: 15863657
88. Poullet P, et al. Mol. Cell. Biol. (1994) pmid: 8264648
89. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
90. Jett K, et al. Genet. Med. (2010) pmid: 20027112
91. Patil S, et al. Oncologist (2012) pmid: 22240541
92. Evans DG, et al. Clin Sarcoma Res (2012) pmid: 23036231
93. Upadhyaya M, et al. J. Med. Genet. (1995) pmid: 8544190
94. Williams VC, et al. Pediatrics (2009) pmid: 19117870
95. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
96. Mainardi S, et al. Nat Med (2018) pmid: 29808006
97. Koczywas et al., 2021; AACR Abstract LB001
98. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
99. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
100. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
101. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
102. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
103. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
104. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
105. Monk BJ, et al. J Clin Oncol (2020) pmid: 32822286
106. Farley J, et al. Lancet Oncol. (2013) pmid: 23261356
107. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
108. Han C, et al. Gynecol Oncol Rep (2018) pmid: 29946554
109. Lyons YA, et al. Gynecol Oncol Rep (2014) pmid: 26075998
110. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
111. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
112. Bennouna J, et al. Invest New Drugs (2011) pmid: 20127139
113. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
114. Van Laethem JL, et al. Target Oncol (2017) pmid: 27975152
115. Infante JR, et al. Eur. J. Cancer (2014) pmid: 24915778
116. Van Cutsem E, et al. Int. J. Cancer (2018) pmid: 29756206
117. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
118. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
119. Liu JF, et al. Gynecol. Oncol. (2019) pmid: 31118140
120. Spreafico et al., 2014; ASCO Abstract 5506
121. Juric et al., 2014; ASCO Abstract 9051
122. Banerji et al., 2014; ASCO Abstract e13559
123. Shapiro GI, et al. Invest New Drugs (2019) pmid: 31020608
124. Cin H, et al. Acta Neuropathol. (2011) pmid: 21424530
125. Janzarik WG, et al. Neuropediatrics (2007) pmid: 17712732
126. Knobbe CB, et al. Acta Neuropathol. (2004) pmid: 15517309
127. Mellinghoff IK, et al. Curr. Top. Microbiol. Immunol. (2012) pmid: 22015553
128. Holland EC, et al. Nat. Genet. (2000) pmid: 10802656
129. Holmen SL, et al. Cancer Res. (2005) pmid: 16166301
130. Kahn S, et al. Anticancer Res. () pmid: 3310850
131. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
132. Lee SH, et al. Oncogene (2003) pmid: 14534542
133. Schubbert S, et al. Nat. Genet. (2006) pmid: 16474405
134. Schubbert S, et al. Mol. Cell. Biol. (2007) pmid: 17875937
135. Gripp KW, et al. Am. J. Med. Genet. A (2008) pmid: 18247425
136. Kratz CP, et al. J. Mol. Med. (2007) pmid: 17211612
137. Cirstea IC, et al. Hum. Mol. Genet. (2013) pmid: 23059812
138. Stark Z, et al. Clin. Genet. (2012) pmid: 21797849
139. Arefi M, et al. Int. J. Hematol. (2012) pmid: 22806436
140. Baccarani M, et al. Haematologica (2007) pmid: 17666373
141. Cassier PA, et al. Clin. Cancer Res. (2012) pmid: 22718859
142. Chalmers ZR, et al. Blood Cancer J (2015) pmid: 25658984
143. Cools J, et al. N. Engl. J. Med. (2003) pmid: 12660384
144. Curtis CE, et al. Br. J. Haematol. (2007) pmid: 17555450
145. Debiec-Rychter M, et al. Eur. J. Cancer (2004) pmid: 15010069
146. Dileo P, et al. Int. J. Cancer (2011) pmid: 20473908
147. Fanta PT, et al. J. Clin. Oncol. (2015) pmid: 24638008

148. Florian S, et al. Leuk. Res. (2006) pmid: 16406018
149. Frenard C, et al. JAAD Case Rep (2016) pmid: 27051816
150. Griffin JH, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808148
151. Heinrich MC, et al. J. Clin. Oncol. (2003) pmid: 14645423
152. Helbig G, et al. Br. J. Haematol. (2009) pmid: 19120352
153. Helbig G, et al. Am. J. Hematol. (2014) pmid: 24009127
154. Hus M, et al. Leuk. Res. (2011) pmid: 21093052
155. Ikezoe T, et al. Leuk. Res. (2010) pmid: 20303172
156. Intermesoli T, et al. Br. J. Haematol. (2009) pmid: 19735261
157. Jain N, et al. Leuk. Res. (2009) pmid: 19013640
158. Jovanovic JV, et al. Blood (2007) pmid: 17299092
159. Kang HJ, et al. Acta Oncol (2012) pmid: 22150077
160. Klion AD, et al. Blood (2004) pmid: 14504092
161. Kobayashi M, et al. Respirology (2009) pmid: 19192229
162. Kocáková I, et al. Klin Onkol (2014) pmid: 24635438
163. Metzgeroth G, et al. Br. J. Haematol. (2008) pmid: 18950453
164. Murayama Y, et al. World J Gastrointest Oncol (2012) pmid: 22645636
165. Ogbogu PU, et al. J. Allergy Clin. Immunol. (2009) pmid: 19910029
166. Ohnishi H, et al. Br. J. Haematol. (2006) pmid: 16856885
167. Pardanani A, et al. Blood (2003) pmid: 12842979
168. Pardanani A, et al. Blood (2004) pmid: 15284118
169. Qu SQ, et al. Oncotarget (2016) pmid: 27120808
170. Score J, et al. Leukemia (2006) pmid: 16498388
171. Shah S, et al. J Hematol Oncol (2014) pmid: 24669761
172. Sugimoto Y, et al. Cancer Genet (2015) pmid: 26319757
173. Volz HC, et al. Int. J. Cardiol. (2011) pmid: 20609486
174. von Bubnoff N, et al. Leukemia (2005) pmid: 15618966
175. Walz C, et al. Genes Chromosomes Cancer (2006) pmid: 16845659
176. Yoo C, et al. Cancer Res Treat (2016) pmid: 26130666
177. Al-Riyami AZ, et al. Leuk. Lymphoma (2013) pmid: 23157309
178. Lierman E, et al. Blood (2006) pmid: 16645167
179. Lierman E, et al. Leukemia (2009) pmid: 19212337
180. Metzgeroth G, et al. Leukemia (2012) pmid: 21818111
181. Roubaud G, et al. Ann. Oncol. (2012) pmid: 22294526
182. von Bubnoff N, et al. Oncogene (2011) pmid: 20972453
183. Hochhaus A, et al. J. Cancer Res. Clin. Oncol. (2013) pmid: 24057647
184. Tabouret E, et al. Leuk. Res. (2011) pmid: 20832858
185. Dewaele B, et al. Clin. Cancer Res. (2008) pmid: 18794084
186. Weisberg E, et al. Gastroenterology (2006) pmid: 17087936
187. Brohl AS, et al. Clin Sarcoma Res (2015) pmid: 26396737
188. Grellety T, et al. Future Sci OA (2015) pmid: 28031906
189. Kollàr A, et al. Clin Sarcoma Res (2014) pmid: 25905001
190. Evans EK, et al. Sci Transl Med (2017) pmid: 29093181
191. Jaku et al., 2017; ASCO Abstract 2515
192. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
193. Hoadley KA, et al. Cell (2018) pmid: 29625048
194. Ellrott K, et al. Cell Syst (2018) pmid: 29596782
195. Taylor AM, et al. Cancer Cell (2018) pmid: 29622463
196. Gao Q, et al. Cell Rep (2018) pmid: 29617662
197. Liu J, et al. Cell (2018) pmid: 29625055
198. Sanchez-Vega F, et al. Cell (2018) pmid: 29625050
199. Song K, et al. Am J Cancer Res (2018) pmid: 29888103
200. Alentorn A, et al. Neuro-oncology (2012) pmid: 23074200
201. Sottoriva A, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23412337
202. Phillips JJ, et al. Brain Pathol. (2013) pmid: 23438035
203. Andrae J, et al. Genes Dev. (2008) pmid: 18483217
204. Semin. Oncol. (2004) pmid: 15175998
205. Courtney KD, et al. J. Clin. Oncol. (2010) pmid: 20085938
206. Simpson L, et al. Exp. Cell Res. (2001) pmid: 11237521
207. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
208. Milella M, et al. Sci Rep (2017) pmid: 28220839
209. Galanis E, et al. J. Clin. Oncol. (2005) pmid: 15998902
210. Kreisl TN, et al. J. Neurooncol. (2009) pmid: 19018475
211. Mason WP, et al. Invest New Drugs (2012) pmid: 22160854
212. Mendes-Pereira AM, et al. EMBO Mol Med (2009) pmid: 20049735
213. Shen Y, et al. Clin. Cancer Res. (2013) pmid: 23881923
214. Chatterjee P, et al. PLoS ONE (2013) pmid: 23565244
215. McCormick A, et al. Int. J. Gynecol. Cancer (2016) pmid: 26905328
216. Forster MD, et al. Nat Rev Clin Oncol (2011) pmid: 21468130
217. Eikesdal HP, et al. Ann Oncol (2021) pmid: 33242536
218. Dougherty et al., 2014; ASCO Abstract 5536
219. Pan M, et al. Perm J (2021) pmid: 33970096
220. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
221. Romero I, et al. Gynecol Oncol (2020) pmid: 32988624
222. Costa C, et al. Cancer Discov (2019) pmid: 31594766
223. George S, et al. Immunity (2017) pmid: 28228279
224. Peng W, et al. Cancer Discov (2016) pmid: 26645196
225. Zhou XP, et al. Int. J. Cancer (1999) pmid: 10096247
226. Rasheed BK, et al. Cancer Res. (1997) pmid: 9331072
227. Davies MP, et al. Br. J. Cancer (1999) pmid: 10188904
228. Smith JS, et al. J. Natl. Cancer Inst. (2001) pmid: 11504770
229. Lin H, et al. Clin. Cancer Res. (1998) pmid: 9796977
230. Schmidt EE, et al. J. Neuropathol. Exp. Neurol. (1999) pmid: 10560660
231. Kato H, et al. Clin. Cancer Res. (2000) pmid: 11051241
232. Furnari FB, et al. Genes Dev. (2007) pmid: 17974913
233. Yan et al. 2020; DOI:10.1200/PO.19.00385
234. Sano T, et al. Cancer Res. (1999) pmid: 10213484
235. Srividya MR, et al. Neuropathology (2011) pmid: 21134002
236. Campbell RB, et al. J. Biol. Chem. (2003) pmid: 12857747
237. Rodríguez-Escudero I, et al. Hum. Mol. Genet. (2011) pmid: 21828076
238. He X, et al. Cancer Res. (2013) pmid: 23475934
239. Han SY, et al. Cancer Res. (2000) pmid: 10866302
240. Myers MP, et al. Proc. Natl. Acad. Sci. U.S.A. (1998) pmid: 9811831
241. Pradella LM, et al. BMC Cancer (2014) pmid: 24498881
242. Kim JS, et al. Mol. Cell. Biol. (2011) pmid: 21536651
243. Denning G, et al. Oncogene (2007) pmid: 17213812
244. Hlobilkova A, et al. Anticancer Res. () pmid: 16619501
245. Redfern RE, et al. Protein Sci. (2010) pmid: 20718038
246. Shenoy S, et al. PLoS ONE (2012) pmid: 22505997
247. Wang Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19329485
248. Okumura K, et al. J. Biol. Chem. (2006) pmid: 16829519
249. Lee JO, et al. Cell (1999) pmid: 10555148
250. Maxwell GL, et al. Cancer Res. (1998) pmid: 9635567
251. Risinger JI, et al. Clin. Cancer Res. (1998) pmid: 9865913
252. Fenton TR, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22891331
253. Ngeow J, et al. J. Clin. Endocrinol. Metab. (2012) pmid: 23066114
254. Lobo GP, et al. Hum. Mol. Genet. (2009) pmid: 19457929
255. Liu J, et al. Oncogene (2014) pmid: 23995781
256. Maehama T, et al. Annu. Rev. Biochem. (2001) pmid: 11395408
257. De Vivo I, et al. J. Med. Genet. (2000) pmid: 10807691
258. Ramaswamy S, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10051603
259. Liu JL, et al. Mol. Cell. Biol. (2005) pmid: 15988030
260. Karoui M, et al. Br. J. Cancer (2004) pmid: 15026806
261. Gil A, et al. PLoS ONE (2015) pmid: 25875300
262. Furnari FB, et al. Cancer Res. (1998) pmid: 9823298
263. Spinelli L, et al. J. Med. Genet. (2015) pmid: 25527629
264. Mingo J, et al. Eur. J. Hum. Genet. (2018) pmid: 29706633
265. Wang Q, et al. J. Mol. Graph. Model. (2010) pmid: 20538496
266. Andrés-Pons A, et al. Cancer Res. (2007) pmid: 17942903
267. Butler MG, et al. J. Med. Genet. (2005) pmid: 15805158
268. Georgescu MM, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10468583
269. Staal FJ, et al. Br. J. Cancer (2002) pmid: 12085208
270. Nguyen HN, et al. Oncogene (2014) pmid: 24292679
271. Rahdar M, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19114656
272. Das S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808147
273. Wang X, et al. Biochem. J. (2008) pmid: 18498243
274. Valiente M, et al. J. Biol. Chem. (2005) pmid: 15951562
275. Nguyen HN, et al. Oncogene (2015) pmid: 25263454
276. Blumenthal GM, et al. Eur. J. Hum. Genet. (2008) pmid: 18781191
277. Orloff MS, et al. Oncogene (2008) pmid: 18794875
278. Zbuk KM, et al. Nat. Rev. Cancer (2007) pmid: 17167516
279. Hao HX, et al. Nature (2012) pmid: 22575959
280. Koo BK, et al. Nature (2012) pmid: 22895187
281. Jiang X, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23847203
282. Koo BK, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 26023187
283. Tsukiyama T, et al. Mol. Cell. Biol. (2015) pmid: 25825523
284. Kinde I, et al. Sci Transl Med (2013) pmid: 23303603
285. Giannakis M, et al. Nat. Genet. (2014) pmid: 25344691
286. Madan B, et al. Mol. Cancer Ther. (2015) pmid: 25901018
287. Ryland GL, et al. J. Pathol. (2013) pmid: 23096461
288. Ong CK, et al. Nat. Genet. (2012) pmid: 22561520
289. Wang K, et al. Nat. Genet. (2014) pmid: 24816253
290. Nature (2014) pmid: 25079317
291. Sugiura T, et al. Exp. Cell Res. (2008) pmid: 18313049
292. Yagyu R, et al. Int. J. Oncol. (2004) pmid: 15492824
293. Shinada K, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21108931
294. Tee AR, et al. Curr. Biol. (2003) pmid: 12906785
295. Mallela K, et al. Mol Cell Biochem (2021) pmid: 33575875
296. Kwiatkowski DJ, et al. Eur J Hum Genet (2015) pmid: 25782670
297. Wang T, et al. Cancer Biol Ther (2020) pmid: 31597506
298. Guo G, et al. Front Oncol (2020) pmid: 33575217
299. Espinosa M, et al. BMC Cancer (2018) pmid: 29764404

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300. Chuang CK, et al. Int Urol Nephrol (2017) pmid: 28547571
301. Adib E, et al. Clin Cancer Res (2021) pmid: 33727259
302. Nassar AH, et al. Mol Cancer Ther (2020) pmid: 31653662
303. De S, et al. Gegenbaurs Morphol Jahrb (1986) pmid: 3032730
304. Wagner AJ, et al. J. Clin. Oncol. (2010) pmid: 20048174
305. Dickson MA, et al. Int. J. Cancer (2013) pmid: 22927055
306. Wagle N, et al. N. Engl. J. Med. (2014) pmid: 25295501
307. Tannir NM, et al. Eur. Urol. (2016) pmid: 26626617
308. Maroto P, et al. J Natl Compr Canc Netw (2018) pmid: 29632054
309. Zureick AH, et al. BMJ Case Rep (2019) pmid: 31154346
310. Hu W, et al. Front Oncol (2020) pmid: 33344249
311. Perini GF, et al. Blood Cancer J (2016) pmid: 27176796
312. Voss MH, et al. Clin. Cancer Res. (2018) pmid: 30327302
313. Parry L, et al. Hum. Genet. (2000) pmid: 11129334
314. Lau N, et al. Int. J. Oncol. (2003) pmid: 12469204
315. Rosner M, et al. Leuk. Res. (2009) pmid: 19286253
316. Riemenschneider MJ, et al. Cancer Res. (2006) pmid: 16740698
317. Inoki K, et al. Genes Dev. (2003) pmid: 12869586
318. Ann. N. Y. Acad. Sci. (1991) pmid: 2039135
319. Kandt RS, et al. Nat. Genet. (1992) pmid: 1303246
320. Cell (1993) pmid: 8269512
321. Curatolo P, et al. Lancet (2008) pmid: 18722871
322. Gruber et al., 2019; ASCO Abstract 3006
323. Peasland A, et al. Br. J. Cancer (2011) pmid: 21730979
324. McCabe N, et al. Cancer Res. (2006) pmid: 16912188
325. Jardim MJ, et al. Mol. Biol. Cell (2009) pmid: 19570909
326. Harefuah (1991) pmid: 1937255
327. Sangster-Guity N, et al. Oncogene (2011) pmid: 21258400
328. Wang H, et al. Life Sci. (2010) pmid: 19969004
329. Levin VA, et al. Proteome Sci (2012) pmid: 22276931
330. Ha K, et al. Mol. Cancer Ther. (2011) pmid: 21566061
331. Liang Y, et al. World J Surg (2009) pmid: 19034564
332. Mordes DA, et al. Genes Dev. (2008) pmid: 18519640
333. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
334. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
335. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
336. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
337. Elvin JA, et al. Oncologist (2017) pmid: 28283584
338. Gao J, et al. Curr Oncol (2015) pmid: 26715889
339. Gopalan et al., 2014; ASCO Abstract 8077
340. Peguero et al., 2016; ASCO Abstract 2528
341. Konecny et al., 2016; ASCO Abstract 5557
342. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
343. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
344. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
345. Johnson DB, et al. Oncologist (2014) pmid: 24797823
346. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
347. Gamble LD, et al. Oncogene (2012) pmid: 21725357
348. Ceccarelli M, et al. Cell (2016) pmid: 26824661
349. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
350. Gao J, et al. Sci Signal (2013) pmid: 23550210
351. Weber RG, et al. Oncogene (2007) pmid: 16909113
352. Nakamura M, et al. Brain Pathol. (2001) pmid: 11303791
353. Chakravarti A, et al. Clin. Cancer Res. (2001) pmid: 11489817
354. Feng J, et al. Cancer (2012) pmid: 21713760
355. Raabe EH, et al. Clin. Cancer Res. (2011) pmid: 21636552
356. Liu W, et al. J. Exp. Clin. Cancer Res. (2011) pmid: 21843312
357. Quelle DE, et al. Cell (1995) pmid: 8521522
358. Mutat. Res. (2005) pmid: 15878778
359. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
360. Oncogene (1999) pmid: 10498883
361. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
362. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
363. Ruas M, et al. Oncogene (1999) pmid: 10498896
364. Jones R, et al. Cancer Res. (2007) pmid: 17909018
365. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
366. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
367. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
368. Gombart AF, et al. Leukemia (1997) pmid: 9324288
369. Yang R, et al. Cancer Res. (1995) pmid: 7780957
370. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
371. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
372. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
373. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
374. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
375. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
376. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
377. Koh J, et al. Nature (1995) pmid: 7777061
378. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
379. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
380. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
381. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
382. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
383. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
384. Rutter JL, et al. Oncogene (2003) pmid: 12853981
385. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
386. Adv Exp Med Biol (2010) pmid: 20687502
387. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
388. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
389. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
390. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
391. Kaufman DK, et al. Neurology (1993) pmid: 8414022
392. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
393. Chan AK, et al. Clin Neuropathol () pmid: 28699883
394. Ceccaldi R, et al. Cancer Res. (2015) pmid: 25634215
395. Mohni KN, et al. PLoS ONE (2015) pmid: 25965342
396. Zhang YW, et al. Nucleic Acids Res. (2011) pmid: 21227924
397. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
398. Planchard D, et al. Ann. Oncol. (2009) pmid: 19297315
399. Simon GR, et al. Chest (2005) pmid: 15764785
400. Olaussen KA, et al. N. Engl. J. Med. (2006) pmid: 16957145
401. Jun HJ, et al. Br. J. Cancer (2008) pmid: 18594541
402. Bellmunt J, et al. Ann. Oncol. (2007) pmid: 17229776
403. Ferry KV, et al. Biochem. Pharmacol. (2000) pmid: 11008124
404. McNeil EM, et al. Nucleic Acids Res. (2012) pmid: 22941649
405. EMBO J. (2017) pmid: 28659377
406. Manandhar M, et al. Gene (2015) pmid: 26074087
407. Liu KW, et al. J. Clin. Invest. (2011) pmid: 21393858
408. Feng H, et al. Oncogene (2012) pmid: 21996738
409. Wang S, et al. J. Biol. Chem. (2009) pmid: 19008228
410. Zhou XD, et al. Cell Death Differ. (2008) pmid: 18421299
411. Voruz S, et al. Haematologica (2018) pmid: 29097496
412. Tasian SK, et al. Leukemia (2019) pmid: 29884903
413. Krenz M, et al. Circ. Res. (2005) pmid: 16166557
414. Nakamura T, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19706403
415. Sturla LM, et al. Br. J. Cancer (2011) pmid: 21934682
416. Jones DT, et al. Nat. Genet. (2013) pmid: 23817572
417. Schuettpelz LG, et al. Pediatr Blood Cancer (2009) pmid: 19621452
418. Ferguson SD, et al. Oncotarget (2016) pmid: 27579614
419. Tartaglia M, et al. Nat. Genet. (2003) pmid: 12717436
420. Bard-Chapeau EA, et al. Cancer Cell (2011) pmid: 21575863
421. Grossmann KS, et al. Adv. Cancer Res. (2010) pmid: 20399956
422. Sarkisian KA, et al. Vopr. Virusol. () pmid: 9791886
423. Chan RJ, et al. Blood (2007) pmid: 17053061
424. Chan RJ, et al. Blood (2005) pmid: 15644411
425. Tartaglia M, et al. Am. J. Hum. Genet. (2006) pmid: 16358218
426. Niihori T, et al. J. Hum. Genet. (2005) pmid: 15834506
427. Bentires-Alj M, et al. Cancer Res. (2004) pmid: 15604238
428. O'Reilly AM, et al. Mol. Cell. Biol. (2000) pmid: 10594032
429. Eminaga S, et al. J. Biol. Chem. (2008) pmid: 18378677
430. Martinelli S, et al. J. Biol. Chem. (2012) pmid: 22711529
431. Edwards JJ, et al. Am. J. Med. Genet. A (2014) pmid: 24891296
432. Yu ZH, et al. Biochemistry (2014) pmid: 24935154
433. Martinelli S, et al. Hum. Mol. Genet. (2008) pmid: 18372317
434. LaRochelle JR, et al. Biochemistry (2016) pmid: 27030275
435. LaRochelle JR, et al. Nat Commun (2018) pmid: 30375388
436. Mohi MG, et al. Cancer Cell (2005) pmid: 15710330
437. Schubbert S, et al. Blood (2005) pmid: 15761018
438. Chan G, et al. Blood (2009) pmid: 19179468
439. Xu D, et al. Blood (2010) pmid: 20651068
440. Brasil AS, et al. Genet Test Mol Biomarkers (2010) pmid: 20578946
441. Horm. Res. (2009) pmid: 20029231
442. Chen Y, et al. Genes Chromosomes Cancer (2006) pmid: 16518851
443. Pierpont EI, et al. Genes Brain Behav. (2009) pmid: 19077116
444. Mathur D, et al. Fetal Pediatr Pathol (2014) pmid: 24754368
445. Varela I, et al. Nature (2011) pmid: 21248752
446. Chen Z, et al. Biochem Biophys Res Commun (2018) pmid: 29522714
447. Chen BY, et al. Blood (2020) pmid: 32202636
448. Sun XJ, et al. J. Biol. Chem. (2005) pmid: 16118227
449. Faber PW, et al. Hum. Mol. Genet. (1998) pmid: 9700202
450. Al Sarakbi W, et al. BMC Cancer (2009) pmid: 19698110
451. Parker H, et al. Leukemia (2016) pmid: 27282254
452. Zhang J, et al. Nature (2012) pmid: 22237106
453. McKinney M, et al. Cancer Discov (2017) pmid:

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28122867
454. Moffitt AB, et al. J. Exp. Med. (2017) pmid: 28424246
455. Zhu X, et al. Nat. Genet. (2014) pmid: 24509477
456. Lu C, et al. Science (2016) pmid: 27174990
457. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
458. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
459. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
460. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
461. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
462. Xu L, et al. Mol. Med. (2001) pmid: 11713371
463. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
464. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
465. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
466. Hajdenberg et al., 2012; ASCO Abstract e15010
467. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
468. Moore et al., 2019; ASCO Abstract 5513
469. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
470. Lee J, et al. Cancer Discov (2019) pmid: 31315834
471. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
472. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
473. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
474. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
475. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
476. Gourley et al., 2016; ASCO Abstract 5571
477. Kwok M, et al. Blood (2016) pmid: 26563132
478. Boudny M, et al. Haematologica (2019) pmid: 30975914
479. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
480. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
481. Jha P, et al. Diagn. Mol. Pathol. (2011) pmid: 22089350
482. Uno M, et al. Cancer Lett. (2005) pmid: 15914282
483. Uno M, et al. Int. J. Biol. Markers () pmid: 16711514
484. Lass U, et al. PLoS ONE (2012) pmid: 22844452
485. Faria MH, et al. APMIS (2012) pmid: 23009112
486. Milinkovic V, et al. PLoS ONE (2013) pmid: 24358143
487. Galatro TF, et al. PLoS ONE (2013) pmid: 23613880
488. Schmidt MC, et al. J. Neuropathol. Exp. Neurol. (2002) pmid: 11939587
489. Nozaki M, et al. Neuro-oncology (1999) pmid: 11550308
490. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
491. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
492. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
493. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
494. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
495. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
496. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
497. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
498. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
499. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
500. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
501. Lalloo F, et al. Lancet (2003) pmid: 12672316
502. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
503. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
504. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
505. Xie M, et al. Nat. Med. (2014) pmid: 25326804
506. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
507. Severson EA, et al. Blood (2018) pmid: 29678827
508. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
509. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
510. Chabon JJ, et al. Nature (2020) pmid: 32269342
511. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
512. Glassberg et al., 2020; ASPHO Abstract 2015
513. Coyne et al., 2020; ASCO Abstract 3612
514. McCowage et al., 2018; ASCO Abstract 10504
515. Mueller et al., 2020; SNO Abstract NFB-17
516. Waldner et al., 2020; DOI: 10.1055/s-0040-1715638
517. Romo et al., 2019; SNO Abstract RARE-54
518. Banerjee A, et al. Neuro-oncology (2017) pmid: 28339824
519. Allen et al., 2021; ASCO Abstract 10008
520. Gupta A, et al. Ann. Oncol. (2014) pmid: 24567366
521. Robert C, et al. Lancet Oncol. (2013) pmid: 23735514
522. Kirkwood JM, et al. Clin. Cancer Res. (2012) pmid: 22048237
523. Banerji U, et al. Clin. Cancer Res. (2010) pmid: 20179232
524. Boers-Sonderen MJ, et al. Anticancer Drugs (2012) pmid: 22293660
525. Lopez-Chavez A, et al. J. Clin. Oncol. (2015) pmid: 25667274
526. Hainsworth JD, et al. J Thorac Oncol (2010) pmid: 20802351
527. Coleman RL, et al. Gynecol. Oncol. (2015) pmid: 25887099
528. Deming DA, et al. Invest New Drugs (2016) pmid: 26666244
529. Krishnamurthy A, et al. Cancer Res. (2018) pmid: 30042150
530. Infante JR, et al. Invest New Drugs (2017) pmid: 28424891
531. LoRusso PM, et al. BMC Cancer (2017) pmid: 28264648
532. Tolcher AW, et al. Clin. Cancer Res. (2015) pmid: 25516890
533. Wilky BA, et al. Br. J. Cancer (2015) pmid: 25268371
534. Miller et al., 2016; ISPNO Abstract LG-01
535. Miller C, et al. J Neurosurg Pediatr (2017) pmid: 28009226
536. Yde CW, et al. Cancer Genet (2016) pmid: 27810072

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