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 Tai, Ssu-Ling
DATE OF BIRTH 09 February 1983
SEX Female
MEDICAL RECORD # 47493958

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 S110-22215 C (PF21004)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 03 August 2021
SPECIMEN RECEIVED 23 August 2021

Biomarker Findings

Microsatellite status - MSI-High
Tumor Mutational Burden - 18 Muts/Mb

Genomic Findings

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

ATM R2993*
NF1 F1275fs*8, Y2285fs*5
PDGFRA N659S - subclonal†
MEN1 R521fs*43
PIK3R1 K448fs*32 - subclonal†
CBL R420Q
CDC73 K283fs*35
CDKN1A R32C
JAK1 P430fs*2 - subclonal†
NOTCH3 G2035fs*50 - subclonal†
P2RY8 R222H
SETD2 S2382fs*29
SMARCA4 R1077* - subclonal†
TP53 T125M, R248Q

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

† See About the Test in appendix for details.

15 Therapies with Clinical Benefit
0 Therapies with Lack of Response
47 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	Dostarlimab	Atezolizumab
	Pembrolizumab	Avelumab
		Cemiplimab
		Durvalumab
10 Trials *see p. 21*		Nivolumab
Tumor Mutational Burden - 18 Muts/Mb	none	none
2 Trials *see p. 23*		

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ATM **-** R2993*	none	Niraparib
		Olaparib
		Rucaparib
10 Trials *see p. 24*		Talazoparib
NF1 **-** F1275fs*8, Y2285fs*5	none	Selumetinib
10 Trials *see p. 28*		Trametinib
PDGFRA **-** N659S - subclonal	none	Imatinib
10 Trials *see p. 30*		Sorafenib
MEN1 **-** R521fs*43	none	none
10 Trials *see p. 26*		
PIK3R1 **-** K448fs*32 - subclonal	none	none
2 Trials *see p. 32*		

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

ATM **-** R2993* p. 5

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

CBL **-** R420Q p. 8

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain 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
MSI-High

POTENTIAL TREATMENT STRATEGIES

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] .

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]. This sample has a high level of MSI, equivalent to the clinical definition of an MSI-high (MSI-H) tumor: one with mutations in >30% of microsatellite markers[19-21]. MSI-H status indicates high-level deficiency in MMR and typically correlates with loss of expression of at least one, and often two, MMR family proteins[16,18,20-21].

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)[22]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[22-24] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[25-27]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
18 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[28-30], anti-PD-1 therapies[28-31], and combination nivolumab and ipilimumab[32-37]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[28,38-39]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[40-41] or anti-PD-L1[42] 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)[43]. 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[44-45]. Increased TMB has been reported to correlate with higher tumor grade in glioma[46] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[40], as well as with shorter OS of patients with diffuse glioma[47].

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[48-49] and cigarette smoke in lung cancer[11,50], treatment with temozolomide-based chemotherapy in glioma[51-52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[53-57], and microsatellite instability (MSI)[53,56-57]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents, for patients with glioma[28,38-42]. Although efficacy of immune checkpoint inhibitors has been observed for patients with other solid tumor types harboring TMB levels such as seen here[28-31,58], an association between TMB and clinical benefit has generally not been observed for patients with glioma[28,38-39], except for those with ultramutated glioma with POLE mutation[40-42].

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GENE
ATM

ALTERATION
R2993*

TRANSCRIPT ID
NM_000051

CODING SEQUENCE EFFECT
8977C>T

VARIANT ALLELE FREQUENCY (% VAF)
75.6%

POTENTIAL TREATMENT STRATEGIES

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[59]. Clinical data in prostate cancer[60-62], gastric cancer[63], colorectal cancer[64], breast cancer[64], papillary renal cell carcinoma[65], and cholangiocarcinoma[66] indicate that loss or inactivation of ATM may confer sensitivity to PARP inhibitors[67-74]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[75] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[76] harbored ATM inactivation or protein loss; studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[77-79] and hematologic malignancies[77,80] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[81].

FREQUENCY & PROGNOSIS

ATM mutations have been reported in 1% of glioblastoma cases[82-83]. An analysis of Grades 1-4 astrocytomas detected upregulation of ATM mRNA expression[84]. Higher expression of the ATM protein correlated with longer overall and progression-free survival in a study of 69 glioblastoma cases[85]. However, ATM gene and protein expression in glioblastoma cells has also been correlated with resistance to radiation therapy; glioma cells with lower ATM expression have been found to be more sensitive to radiation than cells with higher ATM expression[86-88]. In addition, one study reported that the ATM kinase inhibitor KU-60019 inhibited glioma cell growth and invasion and sensitized cells to radiation[88]. Preclinical studies have also shown that ATM kinase inactivation and ATM inhibitors such as LY294002 and KU-55933 increase the sensitivity of glioblastoma cells to cisplatin and temozolomide[89-91].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[92]. Loss of functional ATM promotes tumorigenesis[93]. Alterations such as seen here may disrupt ATM function or expression[94-96].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the ATM 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 ataxia-telangiectasia syndrome (ClinVar, Mar 2021)[97]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[98]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[99]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[92,99]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[99]. In the appropriate clinical context, germline testing of ATM 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[100-105]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[104,106-107]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
NF1

ALTERATION
F1275fs*8, Y2285fs*5

TRANSCRIPT ID
NM_001042492, NM_001042492

CODING SEQUENCE EFFECT
3822_3823delCT, 6852_6855delTTAC

VARIANT ALLELE FREQUENCY (% VAF)
38.3%, 38.3%

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[108-111], glioma or glioblastoma[111-115], non-small cell lung cancer[116], 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[117-119] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[120-121]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[122]. 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[123], 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[124].

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[51,82-83,125]. 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[126]. 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[127].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[128]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[129]. Alterations such as seen here may disrupt NF1 function or expression[129-138]. The consequences of alterations that may leave the GAP-related domain intact, such as seen here, are unclear; however, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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)[97]. 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[139-141]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[142-143], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE

PDGFRA

ALTERATION
N659S - subclonal

TRANSCRIPT ID
NM_006206

CODING SEQUENCE EFFECT
1976A>G

VARIANT ALLELE FREQUENCY (% VAF)
2.9%

POTENTIAL TREATMENT STRATEGIES

On the basis of extensive clinical evidence in solid tumors and hematologic cancers, PDGFRA activating alterations are associated with sensitivity to imatinib[144-181]. 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)[182-187]. Complete responses to nilotinib have been reported in patients with CEL or hypereosinophilic syndrome with FIP1L1-PDGFRA or activating mutations[160,188-189]; preclinical evidence has reported efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[190-191]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[192] or regorafenib[193-194]. Preclinical studies have reported sensitivity of activating PDGFRA mutations and FIP1L1-PDGFRA fusion to dasatinib[184,190]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[195] and preclinical[195] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[196].

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)[197]. PDGFRA mutations have been reported in 0-5% of lower grade glioma and glioblastoma samples[82-83,198-203], 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[204]. Amplification of PDGFRA has been associated with tumor grade and poor progression-free and overall survival in patients with glioblastoma[205-207]. 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[207].

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[208]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[209]. Many PDGFRA missense mutations, such as seen here, have been characterized as activating[126,210-213]. As a class, these mutations have also been shown in preclinical assays to confer sensitivity to targeted therapies, such as imatinib and crenolanib[210,212-215].

GENE

MEN1

ALTERATION
R521fs*43

TRANSCRIPT ID
NM_130801

CODING SEQUENCE EFFECT
1561delC

VARIANT ALLELE FREQUENCY (% VAF)
42.6%

POTENTIAL TREATMENT STRATEGIES

There are no therapies, either approved or in clinical trials, that directly target mutation or loss of MEN1. Preclinical studies in cells and transgenic mice have shown that tumor formation mediated by loss of MEN1 (a direct activator of p18INK4c) is associated with increased expression and activity of CDK4 and that CDK4 knockout abrogates formation of MEN1 loss-driven tumors[216-219]. Therefore, tumors with MEN1 loss or inactivation may be sensitive to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[220-223], although this has not been demonstrated clinically.

FREQUENCY & PROGNOSIS

MEN1 mutation has been observed in <1% of glioblastoma and lower grade glioma samples in the TCGA dataset[203]. However, biallelic inactivation of MEN1 was identified in a pediatric patient with grade 2 pilocytic astrocytoma[224]. One study found that high menin expression was correlated with shorter OS and larger tumor volume in glioma[225].

FINDING SUMMARY

MEN1 encodes menin, a tumor suppressor associated with a histone methyltransferase complex that regulates developmental gene expression via chromatin remodeling[226]. Alterations such as seen here may disrupt MEN1 function or expression[227-232].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MEN1 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 multiple endocrine neoplasia type 1 syndrome (ClinVar, Mar 2021)[97,233-238]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in MEN1 are associated with multiple endocrine neoplasia (MEN1) syndrome, an autosomal dominant hereditary cancer syndrome characterized most commonly by pancreatic endocrine tumors (in 40-70% of patients), pituitary adenomas (in 30-40% of patients), and parathyroid adenomas[239-240]. In addition, a small subset of breast cancers may be associated with germline MEN1 mutation[240-241]. Prevalence for this disorder in the general population is estimated to be 1:30,000[242], and in the appropriate clinical context, germline testing of MEN1 is recommended.

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GENE
PIK3R1

ALTERATION
K448fs*32 - subclonal

TRANSCRIPT ID
NM_181523

CODING SEQUENCE EFFECT
1344delA

VARIANT ALLELE FREQUENCY (% VAF)
1.2%

POTENTIAL TREATMENT STRATEGIES
On the basis of clinical[243-244] and preclinical[245-246] data, PIK3R1 alteration may predict sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. In patients with PIK3R1 mutation and no other alterations in the PI3K-AKT-mTOR pathway, 2 CRs have been achieved by patients with endometrial cancer treated with the pan-PI3K inhibitor pilaralisib[243], and 1 PR has been achieved by a patient with breast cancer treated with the PI3K-alpha inhibitor alpelisib in combination with ribociclib and letrozole[247]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[246,248-251] or AKT[252-253]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[254].

FREQUENCY & PROGNOSIS
One study detected PIK3R1 mutation in 10% (24/232) of IDH-wildtype glioblastoma (GBM) samples analyzed[255]. In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[53], glioblastoma (GBM; 11%)[82], uterine carcinosarcoma (11%)(cBioPortal, 2021)[256-257], and lower grade glioma (5%)[125]. PIK3R1 is often inactivated by in-frame insertions or deletions (indels), and the majority of this class of mutation (80%) was observed in endometrial carcinoma[258-260], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[258]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[261] and metastasis-free survival in breast cancer[262]. PIK3R1 expression is not associated with overall survival in neuroendocrine tumors[263].

FINDING SUMMARY
PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[264]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[265-268], promote tumorigenesis[245,252,265], and promote hyperplasia in the context of PTEN-deficiency[269]. Alterations such as seen here may disrupt PIK3R1 function or expression[246,253-254,259-260,270-278].

GENE
CBL

ALTERATION
R420Q

TRANSCRIPT ID
NM_005188

CODING SEQUENCE EFFECT
1259G>A

VARIANT ALLELE FREQUENCY (% VAF)
70.7%

POTENTIAL TREATMENT STRATEGIES
CBL inactivation may lead to the hyperactivation of various receptor tyrosine kinases (RTKs), including MET[279], PDGFRA[280], KIT[281], VEGFR2[282], and the TAM (TYRO3, AXL, MER) RTKs[283]. These RTKs are targets of the multikinase inhibitor sitravatinib[284], which has shown activity in CBL-mutated advanced solid tumors[285]. Among 8 patients with CBL inactivating alterations in a Phase 1b trial, sitravatinib produced 2 PRs (25% ORR), with 1 NSCLC and 1 melanoma responding for over 4 months, and 4 SD outcomes, with 3 prolonged SDs seen in a patient with NSCLC, a patient with esophageal cancer, and a patient with a pancreatic neuroendocrine tumor[285]. CBL has been shown to downregulate EGFR[286-290] and FLT3[291-293]. Preclinical models of myeloid malignancies have demonstrated that CBL inactivation confers sensitivity to the FLT3-targeting therapies sunitinib[291], midostaurin[293], and quizartinib[294], as well as to dasatinib[295], although clinical evidence for this approach in solid tumors is lacking.

FREQUENCY & PROGNOSIS
CBL mutation has been reported in <1% of lower grade glioma and glioblastoma samples[82,125]. High expression of c-Cbl has been reported to correlate with poor prognosis in glioma[296]. In preclinical studies, CBL has been shown to promote glioma cell invasion and glioblastoma tumor growth in mice[297-298].

FINDING SUMMARY
CBL encodes an E3 ubiquitin protein ligase that is involved in cell signaling and ubiquitination, targeting proteins such as EGFR, FGFR1, FGFR2, PDGFR-alpha, PDGFR-beta, FLT3, and SRC for degradation by the proteasome[299-303]. CBL alterations that result in loss or disruption of the tyrosine kinase binding domain, RING finger domain, and/or tail domain, as observed here, are predicted to be inactivating and to promote tumorigenesis[304-321].

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[100-105]. 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[100-101]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[322]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[104,106-107]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
CDC73

ALTERATION
K283fs*35

TRANSCRIPT ID
NM_024529

CODING SEQUENCE EFFECT
848_851delAACA

VARIANT ALLELE FREQUENCY (% VAF)
37.4%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in CDC73.

FREQUENCY & PROGNOSIS
Loss of parafibromin expression and to some extent CDC73 mutation has been correlated with higher incidence of metastasis, disease recurrence, and in some cases decreased overall survival in patients with PC[323-324]. CDC73 down-regulation has also been observed in oral squamous cell carcinomas (OSCC), and knockdown of CDC73 results in increased cell viability and proliferation in preclinical OSCC models[325-326].

FINDING SUMMARY
CDC73 encodes parafibromin, a component of the PAF protein complex[327]. PAF complexes with BCL9, PYGO, and beta-catenin to assemble a nuclear WNT signaling complex[328]. Parafibromin has been reported to inhibit MYC and CCND1[329-333], as well as cell proliferation[325-326,333-334]. It can also activate or inhibit beta-catenin signaling, depending on context[328,335-336]. Inactivating germline mutations in CDC73 are causal in hyperparathyroidism-jaw tumor syndrome[337], and frequent somatic mutation has been documented in parathyroid carcinoma (PC); however, CDC73 mutation is rare in benign parathyroid adenoma[338]. Heterozygous germline inactivation of CDC73 has additionally been suggested to be a predisposing factor for PC[339].

GENE
CDKN1A

ALTERATION
R32C

TRANSCRIPT ID
NM_000389

CODING SEQUENCE EFFECT
94C>T

VARIANT ALLELE FREQUENCY (% VAF)
8.9%

POTENTIAL TREATMENT STRATEGIES
There are currently no therapies that target alterations in CDKN1A. However, in one preclinical study, bladder cancer cell lines with concurrent inactivation of CDKN1A and TP53 were reported to have increased sensitivity to the combination of gemcitabine with a CHK1 inhibitor[340]. Although CDKN1A loss may result in increased CDK activity and several CDK inhibitors are currently in clinical development, the relevance of CDKN1A as a predictive biomarker for these therapies is not known.

FREQUENCY & PROGNOSIS
CDKN1A mutation is infrequently observed in most cancer types, occurring in 0.6% of cases in a pan-cancer analysis of the TCGA datasets[341]. However, CDKN1A mutations, most of which were predicted to be inactivating mutations, were observed frequently (14%) in bladder cancer[342-343], suggesting that CDKN1A may function as a tumor suppressor in this context.

FINDING SUMMARY
CDKN1A encodes the cell cycle regulator p21 (also known as WAF1 or CIP1) that negatively regulates cell cycle progression via inhibition of cyclin-dependent kinases (CDK1 and CDK2) and inhibition of DNA replication[344]. CDKN1A is a target gene of the tumor suppressor p53[345] that is a critical mediator of p53-dependent cell cycle arrest[346-347]. In addition to its tumor suppressive role, p21 has also been shown to have oncogenic functions[344].

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GENE
JAK1

ALTERATION
P430fs*2 - subclonal

TRANSCRIPT ID
NM_002227

CODING SEQUENCE EFFECT
1289delC

VARIANT ALLELE FREQUENCY (% VAF)
3.3%

POTENTIAL TREATMENT STRATEGIES
Inhibitors of the JAK-STAT pathway are under development. The JAK1/JAK2 inhibitor ruxolitinib is approved to treat myelofibrosis, and has shown efficacy in reducing symptoms in Phase 1 and 2 trials in patients with myeloproliferative disorders[348-350]. Other small molecule inhibitors of JAK1 are being investigated in preclinical studies in some types of solid tumors[351-352]. HSP90 inhibitors are also being investigated in preclinical studies to target components of the JAK-STAT pathway such as JAK1[353]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS
In the TCGA datasets, JAK1 mutation or amplification was observed in ~1% of glioblastoma cases[82] and was not observed in any lower grade gliomas[125]. A study of 96 glioma patients reported increased levels of JAK1 protein, and JAK1 phosphorylation was higher in glioma samples than in normal brain tissue[354]. High levels of JAK1 protein were correlated with poor prognosis in glioma patients[354].

FINDING SUMMARY
The JAK1 (Janus kinase 1) gene encodes a tyrosine kinase that regulates signals triggered by cytokines and growth factors[355]. Dysregulation of JAK-STAT signaling has been implicated in a variety of epithelial tumors[356]. However, JAK-STAT signaling is required for the antiviral and antiproliferative effects of interferons[357]. JAK1 alterations that result in the disruption or loss of the kinase domain (875-1153), as seen here, are predicted to be inactivating. JAK1 truncating mutations have been reported in approximately 8% of gynecological tumors in one study and characterized to be defective for interferon-gamma-induced tumor antigen presentation, suggesting that JAK1 truncating mutations could contribute to tumor immune evasion in gynecologic cancers[358]. On the basis of emerging clinical and preclinical data, inactivating mutations in JAK1 have been suggested to play a role in both primary and acquired resistance to anti-PD-1 immunotherapy, via the proposed mechanism of reduction in interferon-gamma-mediated PD-L1 activation[359-360].

GENE
NOTCH3

ALTERATION
G2035fs*50 - subclonal

TRANSCRIPT ID
NM_000435

CODING SEQUENCE EFFECT
6102delC

VARIANT ALLELE FREQUENCY (% VAF)
5.6%

POTENTIAL TREATMENT STRATEGIES
Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[361], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI)[362-364]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[365]. Phase 2 studies have evaluated the efficacy of tarextumab in combination with chemotherapy in metastatic pancreatic cancer or extensive-stage small cell lung cancer, though NOTCH3 expression was not found to be a predictor of OS or PFS in either study[366].

FREQUENCY & PROGNOSIS
NOTCH3 amplification and mutation have been observed in up to 1.0% and 4.9% of glioblastomas, respectively, and in up to 2.1% and 3.3% of lower grade gliomas, respectively (cBioPortal, Mar 2021)[82-83,125]. NOTCH3 amplification was associated with poorer survival in glioblastoma compared to non-amplified cases in one study (median survival 10 vs. 28 months)[367].

FINDING SUMMARY
NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[368-369]. Alterations that preserve the ANK repeat region and disrupt or remove the PEST domain have been reported to increase activity of NOTCH1 and NOTCH2[370-373]. Similar mutations in NOTCH3, such as observed here, have been reported in cancer[374] and are likely to also be activating.

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GENE
P2RY8

ALTERATION
R222H

TRANSCRIPT ID
NM_178129

CODING SEQUENCE EFFECT
665G>A

VARIANT ALLELE FREQUENCY (% VAF)
52.1%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in P2RY8.

FREQUENCY & PROGNOSIS
P2RY8 mutations have been reported in a variety of other hematologic malignancies and solid tumors at low incidence (COSMIC, 2021)[197]. P2RY8 mutations have been most frequently reported in germinal center DLBCL and Burkitt lymphoma in the literature[375-376] and are more common in transformed than in primary follicular lymphoma[377]. The P2RY8-CRLF2 fusion is a hallmark alteration in pediatric B-cell progenitor acute lymphoblastic leukemia, particularly in cases associated with Down syndrome (NCCN Pediatric ALL Guidelines, v2.2021)[378-379]. In another study, P2RY8 expression was observed to be downregulated in relapsed compared to initially diagnosed multiple myeloma[380].

FINDING SUMMARY
P2RY8 encodes a G-protein-coupled purinergic receptor (P2RY8); members of this family of receptors are activated by adenosine and uridine nucleotides[381]. Overexpression of P2RY8 has been shown to lead to cellular transformation[382]. P2RY8 has also been shown to suppress germinal center B-cell growth via a G-alpha dependent pathway[375]. The best characterized P2RY8 alterations are rearrangements leading to P2RY8-driven partner gene overexpression, with CRLF2 being the most frequently observed partner[379] and with a P2RY8-SOX5 fusion also having been characterized[383].

GENE
SETD2

ALTERATION
S2382fs*29

TRANSCRIPT ID
NM_014159

CODING SEQUENCE EFFECT
7143delC

VARIANT ALLELE FREQUENCY (% VAF)
39.1%

POTENTIAL TREATMENT STRATEGIES
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[384]. SETD2 has been associated with favorable prognosis in gastric cancer[385]. SETD2 has also been associated with poor prognosis in RCC and MDS[386], while data in other tumor types is limited (PubMed, Jun 2021).

FINDING SUMMARY
SETD2 encodes a histone lysine-36 methyltransferase[387] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[388]. 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[389]. SETD2 alterations such as observed here have been shown to be inactivating[390-395].

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GENE
SMARCA4

ALTERATION
R1077* - subclonal

TRANSCRIPT ID
NM_003072

CODING SEQUENCE EFFECT
3229C>T

VARIANT ALLELE FREQUENCY (% VAF)
3.4%

POTENTIAL TREATMENT STRATEGIES

Clinical[396] and preclinical[397-403] data suggest that patients with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) harboring SMARCA4 loss or inactivation may benefit from treatment with EZH2 inhibitors, including tazemetostat. In addition, preclinical data have demonstrated that SMARCA4-deficient non-small cell lung cancer (NSCLC) and SCCOHT patient-derived xenografts and cell lines are highly sensitive to CDK4/6 inhibition through a synthetic lethal mechanism of reduced cyclin D1 expression[404-405]. Notably, similar drug sensitivity was detected in SMARCA4-deficient lung and ovarian tumors, thereby suggesting that SMARCA4-deficient tumors are likely to be sensitive to CDK4/6 inhibition regardless of tissue of origin[404-405]. Downregulation of BRG1 and BRM was reported to enhance cellular sensitivity to cisplatin in lung and head and neck cancer cells[406]. In vitro studies have shown that SCCOHT cell lines are sensitive to treatment with epothilone B, methotrexate, and topotecan, compared to treatment with other chemotherapies such as platinum-containing compounds; similar sensitivity was not observed for treatment with ixabepilone, a compound closely related to epothilone B[407].

FREQUENCY & PROGNOSIS

In the TCGA datasets, SMARCA4 mutation was observed in 4.5% of lower grade glioma cases[125] and <1% of glioblastoma cases[82]. BRG1 expression has been reported to be increased in glioma tumors, compared to the surrounding normal tissue, and this study suggested that this increase may contribute to cell proliferation, migration, and/or invasion of glioma cells[408]. One study reported that certain germline polymorphisms in SMARCA4 are associated with increased risk of oligodendroglioma but not astrocytoma or glioblastoma[409].

FINDING SUMMARY

SMARCA4 encodes the protein BRG1, an ATP-dependent helicase that regulates gene transcription through chromatin remodeling[410]. SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[411]. Alterations such as seen here may disrupt SMARCA4 function or expression[412-416].

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GENE
TP53

ALTERATION
T125M, R248Q

TRANSCRIPT ID
NM_000546, NM_000546

CODING SEQUENCE EFFECT
374C>T, 743G>A

VARIANT ALLELE FREQUENCY (% VAF)
38.2%, 42.9%

POTENTIAL TREATMENT STRATEGIES

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[417-420], or p53 gene therapy and immunotherapeutics such as SGT-53[421-425] and ALT-801[426]. 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[427]. 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[428]. 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[429]. 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[430]. 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[431]. 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[432]. 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[425]. 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[433]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[434-436]. 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[437]. 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[80,438]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[439-440]. 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[83,441]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[255]. 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[442-447]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[448]. 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[255]. 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[449].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[450]. Alterations such as seen here may disrupt TP53 function or expression[451-455].

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)[97]. 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[456-458], including sarcomas[459-460]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[461] to 1:20,000[460]. 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[462]. 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[100-105]. 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[100-101]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[322]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[104,106-107]. 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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Dostarlimab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Dostarlimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor response. It is FDA approved to treat patients with mismatch repair deficient recurrent or advanced endometrial cancer or solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data showing efficacy of dostarlimab against various microsatellite instability-high (MSI-H) solid tumors[463-466] , MSI-H status may predict sensitivity to dostarlimab.

SUPPORTING DATA

Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[463,465,467] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[465,468] .

Pembrolizumab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with tumor mutational burden-high (TMB-High; ≥10 Muts/Mb), microsatellite instability-high (MSI-High), or mismatch repair deficient (dMMR) solid tumors, or PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin lymphoma, cervical cancer, gastric cancer, esophageal cancer, or gastroesophageal junction (GEJ) carcinoma. It is also approved in various treatment settings for patients with melanoma, NSCLC, small cell lung cancer, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, or cutaneous squamous cell carcinoma (CSCC). Combination treatments with pembrolizumab are approved for patients with NSCLC, renal cell carcinoma, endometrial carcinoma that is not MSI-High or dMMR, or triple-negative breast cancer (TNBC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of multiple prospective clinical studies showing efficacy of pembrolizumab against MSI-H or mismatch repair-deficient (dMMR) solid tumors[10,469-473] , MSI-H status may predict sensitivity to pembrolizumab.

SUPPORTING DATA

The Phase 2 KEYNOTE-158 study of pembrolizumab for patients with advanced, previously treated MSI-H/dMMR noncolorectal cancer reported an ORR of 0% (0/13) and median PFS of 1.1 months for patients with brain cancer[474]. A Phase 2 study of patients with bevacizumab-naïve, recurrent glioblastoma (GBM) reported that single-agent pembrolizumab had limited activity; similar median PFS (1.4 vs. 4.1 months) and OS (10.3 vs. 8.8 months) were reported for pembrolizumab monotherapy and pembrolizumab combined with bevacizumab, respectively[475]. Similar PFS (2.8 months) and OS (14.4 months) were reported for bevacizumab-naïve, recurrent PD-L1-positive GBM (≥1% in tumor or immune cells) treated with pembrolizumab monotherapy in the Phase 1b KEYNOTE-028 study[476]. Administration of pembrolizumab both before and after surgery in the treatment of recurrent GBM achieved lasting response (>34 months) for 13.3% (2/15) of patients in a single-arm study[477]. Combination of pembrolizumab with bevacizumab and stereotactic radiation in 23 adults with recurrent GBM or anaplastic astrocytoma elicited durable responses (CR or PR ≥6 months) in 53% of patients[478].

Atezolizumab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of emerging clinical data showing efficacy of atezolizumab alone or in combination with antiangiogenic therapy for patients with MSI-H colorectal cancer[3] or endometrial cancer[4], MSI-H status may predict sensitivity to atezolizumab.

SUPPORTING DATA

In a Phase 1a of atezolizumab for patients with glioblastoma (GBM) who had failed prior radiotherapy and/or temazolomide, an objective response rate (ORR) of 6% (1/16) was observed, with 1 patient achieving a partial response (PR) for 16 months and 3 others achieving stable disease (SD); of these 4 patients, all were microsatellite stable, 3 (including the patient with a PR) harbored IDH1 R132H mutations, and 2 experienced an overall survival (OS) of >16 months[42]. A patient with POLE L424V-mutated GBM enrolled in this study achieved an OS of ~18 months[42]. In a retrospective analysis of 17 solid tumor types (comprised of 47% NSCLC, 40% mUC, and 13% encompassing 15 other solid tumors, including GBM), a TMB of ≥16 muts/Mb associated with an improved ORR and duration of response to atezolizumab compared with chemotherapy alone[479].

Avelumab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as avelumab.

SUPPORTING DATA

A Phase 2 open-label study of avelumab monotherapy for the treatment of newly diagnosed glioblastoma after treatment with combined radiotherapy and temozolomide reported an ORR (iRANO) of 50.0% (2 CR, 1 PR, 1 SD) and median PFS of 11.9 months[480]. A Phase 2 study of avelumab with hypofractionated radiotherapy for the treatment of IDH-mutated glioblastoma after radiotherapy and temozolomide reported 1 out of 6 SD as best response, median PFS of 4.2 months, and median OS of 10.1 months[481]. A Phase 2 open-label study of axitinib combined with avelumab for the treatment of recurrent glioblastoma following surgery, radiotherapy, and temozolomide treatment reported an ORR (iRANO) of 41%, 6-month PFS of 18%, and median OS of 26 weeks[482].

Cemiplimab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with NSCLC with high PD-L1 expression (TPS ≥ 50%), cutaneous squamous cell carcinoma (CSCC), or basal cell carcinoma (BCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data showing efficacy of anti-PD-1 therapies against various MSI-high (MSI-H) solid tumors[7,9-10,469-472] , MSI-H status may predict sensitivity to cemiplimab.

SUPPORTING DATA

Clinical data on the efficacy of cemiplimab for the treatment of glioma are limited (PubMed, Jul 2021). Cemiplimab has been studied primarily in advanced cutaneous squamous cell carcinoma (CSCC), where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[483]. A Phase 2 trial of cemiplimab in patients with basal cell carcinoma (BCC) reported ORRs of 31% (5 CRs and 21 PRs) in patients with locally advanced BCC and 21% (6 PRs) in patients with metastatic BCC[484-485] . The Phase 3 EMPOWER-Lung 1 trial for advanced non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50% reported that cemiplimab is associated with improved PFS (8.2 vs. 5.7 months), OS (not reached vs. 14.2 months), and ORR (37% vs. 21%) compared with chemotherapy[486].

Durvalumab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with MSI-H colorectal cancer[3], endometrial cancer[4], or gastric/gastroesophageal junction cancer[5], MSI-H status may predict sensitivity to anti-PD-L1 therapies such as durvalumab.

SUPPORTING DATA

A Phase 2 study of durvalumab combined with standard radiotherapy followed by durvalumab monotherapy for patients with newly diagnosed unmethylated MGMT glioblastoma after resection reported a 12-month OS of 60.0% (24/40) and median OS of 15.1 months[487]. A Phase 2 study of durvalumab and 10 or 3 mg/kg bevacizumab (cohorts B2 and B3, respectively) for the treatment of bevacizumab-naive recurrent glioblastoma reported 9.1% (3/33) PRs in both cohorts and a 6-month PFS rate of 15.2% and 21.1%, respectively[488]. A Phase 2 study of durvalumab combined with bevacizumab for the treatment of bevacizumab-refractory recurrent glioblastoma reported 50.0% (11/22) of patients had PFS greater than 8 weeks and 36.4% (8/22) of patients had OS greater than 22 weeks[489].

Imatinib

Assay findings association

PDGFRA
N659S - subclonal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of strong clinical evidence, PDGFRA activating mutations[146,151-152,156,181], fusions[145,149,155,157,165,168,170,174,177,490], and expression[154] may predict sensitivity to imatinib.

SUPPORTING DATA

In a clinical study where patients with recurrent glioblastoma were given imatinib, 2/24 patients achieved a PR, 10 patients reported SD, and median OS and PFS was observed to be 6.2 and 3 months, respectively[491]. However, other Phase 2 clinical trials of imatinib have reported no anti-tumor activity, with a study of 231 patients with glioblastoma reporting a radiographic response rate of only 3.4%[492-493]. In another Phase 2 study, imatinib plus hydroxyurea was shown to be well tolerated among patients with recurrent/progressive low-grade glioma, but had negligible antitumor activity[494].

Niraparib

Assay findings association

ATM
R2993*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[60-62,495], colorectal cancer[64], breast cancer[64], gastric cancer[63], cholangiocarcinoma[66], and papillary renal cell carcinoma[65].

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of glioma are limited (PubMed, Apr 2021). Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[496]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[497]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[498].

Nivolumab

Assay findings association

Microsatellite status
MSI-High

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, hepatocellular carcinoma (HCC), classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma or squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data showing efficacy of nivolumab for patients with MSI-H CRC[7,9] , MSI-H status may predict sensitivity to nivolumab.

SUPPORTING DATA

The CheckMate 143 Phase 3 trial comparing nivolumab monotherapy to bevacizumab in recurrent glioblastoma (GBM) reported similar PFS (1.5 vs. 3.5 months) and median OS (9.8 vs. 10.0 months), although nivolumab elicited a numerically longer duration of response (11.1 vs. 5.3 months)[499]. Exploratory CheckMate-143 cohorts showed combination of nivolumab and radiotherapy, with or without temozolomide, to be well tolerated[500]; these regimens are being further evaluated in the CheckMate-548 (NCT02667587) study in newly diagnosed GBM. Retrospective studies in recurrent GBM or high-grade glioma reported stable disease rates of 56% (9/16) to 72% (36/50) for nivolumab alone or in combination with bevacizumab, with Grade 3/4 treatment-related AEs in 8% (4/50) to 13% (2/16) of patients[501-502] . Biallelic mismatch repair deficiency (bMMRD)-associated GBMs harbor extraordinarily high mutational loads[40,503] , and three pediatric patients with bMMRD-associated GBM achieved clinically and radiologically significant responses to nivolumab monotherapy[40,504] . An adult with previously treated GBM experienced tumor shrinkage and disease stabilization for 2 years after pseudoprogression on nivolumab[505]. In a Phase 1 study, three patients with progressive GBM benefited from regimens combining nivolumab with surgery and the VEGFR2-targeting vaccine VXM01[506].

Olaparib

Assay findings association

ATM
R2993*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[60-62,495] , colorectal cancer[64], breast cancer[64], gastric cancer[63], cholangiocarcinoma[66], and papillary renal cell carcinoma[65].

SUPPORTING DATA

A Phase 1 study of olaparib in combination with temozolomide for the treatment of patients with relapsed glioblastoma reported a 6-month PFS rate of 46% (6/13)[507]. An additional case study reported a durable response (>2 years) to combination olaparib and temozolomide in a pediatric patient with glioblastoma[508]. Olaparib has been studied primarily for the treatment of ovarian cancer, with response rates often significantly higher for patients with BRCA mutations than for those without[509-510] ; higher response rates have also been observed for patients with platinum-sensitive versus platinum-resistant cancer[510-513] . As maintenance therapy for patients with newly diagnosed or platinum-sensitive relapsed ovarian cancer, olaparib has demonstrated significantly improved median PFS and median OS compared with placebo in the Phase 3 SOLO-1 study[514] and in multiple later-phase studies[515-518] . Phase 3 studies of olaparib for patients with BRCA-mutated metastatic breast[519] or pancreatic cancer[520] or for patients with metastatic castration-resistant prostate cancer and BRCA or ATM alterations[521] have also reported significantly longer median PFS compared with chemotherapy, placebo, or hormone therapy. Additionally, olaparib has demonstrated clinical activity for patients with other solid tumors harboring BRCA mutations, including leiomyosarcoma[522], cholangiocarcinoma[523], and bladder cancer[524] in smaller studies. Olaparib in combination with the AKT inhibitor capivasertib has demonstrated clinical benefit for patients with solid tumors; a Phase 1 trial reported a 45% (25/56) DCR, including 14 PRs and 11 SDs, and 14 of those experiencing clinical benefit had germline BRCA1/2 mutated-solid tumors[525].

Rucaparib

Assay findings association

ATM
R2993*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[60-62,495] , colorectal cancer[64], breast cancer[64], gastric cancer[63], cholangiocarcinoma[66], and papillary renal cell carcinoma[65].

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of glioma are limited (PubMed, Apr 2021). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[526]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[428]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[527]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[528]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[529]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[530]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[531]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[532].

Selumetinib

Assay findings association

NF1
F1275fs*8, Y2285fs*5

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[108-111,533-537] , glioma[111-115,538] , and non-small cell lung cancer[116], 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 PR for patients with BRAF alterations and 10/25 PR for those with NF1-associated LGG[112] and a Phase 1 study for selumetinib reported 5/25 PR for LGG patients[539]. Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[109,533-534] and a Phase 1 study[108]. Phase 2 studies reported clinical responses in low-grade glioma[112,539] , melanoma[540-544] , lung[116,545-546] , and endometrial cancer[547]. Phase 1 studies for selumetinib in solid tumors resulted in 1/15 PR (CRC) and 5/15 SD reported from patients with tonsil SCC, NSCLC, and CRC[548], and achieved 2/39 PR (CRC) and 18/39 SD in combination with cyclosporin A[549]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[550], docetaxel or dacarbazine[551], AKT inhibitors[552], and cixutumumab (anti-IGF-1R antibody)[553] reported clinical responses in patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

Sorafenib

Assay findings association

PDGFRA
N659S - subclonal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical responses in patients with GIST, PDGFRA activating mutations may predict sensitivity to sorafenib[186,554].

SUPPORTING DATA

Phase 2 studies of sorafenib plus temozolomide report limited activity in patients with relapsed glioblastoma multiforme (GBM)[555]. A Phase 1/2 trial of temsirolimus in combination with sorafenib in patients with glioblastoma was terminated at the Phase 2 interim analysis after patients failed to meet the primary endpoint of 6 month progression-free survival[556]. A Phase 2 trial of sorafenib and erlotinib in glioblastoma also did not meet its primary endpoint, and erlotinib clearance was increased by the addition of sorafenib[557]. In a Phase 1 trial in patients with high-grade glioma, the combination of sorafenib with radiation therapy (RT) and temozolomide (TMZ) resulted in increased toxicity and did not result in significant improvement in clinical efficacy compared with RT and TMZ alone[558]. In a clinical study of sorafenib in pediatric patients with low-grade astrocytoma, one patient achieved a partial response (PR), one had stable disease (SD), and 9 patients had progressive disease; this study was terminated early due to unexpectedly high disease progression rates[559].

Talazoparib

Assay findings association

ATM
R2993*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[60-62,495] , colorectal cancer[64], breast cancer[64], gastric cancer[63], cholangiocarcinoma[66], and papillary renal cell carcinoma[65].

SUPPORTING DATA

Clinical data on the efficacy of talazoparib for the treatment of glioma are limited (PubMed, May 2021).

Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[560-561] . In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[64]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[562-565] .

Trametinib

Assay findings association

NF1
F1275fs*8, Y2285fs*5

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[108-111,533-537] , glioma[111-115,538] , and non-small cell lung cancer[116], 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[111,113-114,538] . 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[566-567] . 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[568]. 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[123], 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[124].

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

Electronically signed by Brennan Decker, M.D., Ph.D. | 31 August 2021
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

BIOMARKER

Microsatellite status

RATIONALE

High microsatellite instability (MSI) may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) and anti-PD-L1 immune checkpoint inhibitors.

RESULT

MSI-High

NCT04237649

PHASE NULL

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Missouri, Connecticut, Texas

NCT04181788

PHASE 1/2

Sasanlimab (PF-06801591, PD-1 Inhibitor) in Participants With Advanced Malignancies

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Kaohsiung (Taiwan), Shanghai (China), Nanjing (China), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Chongqing (China), Beijing (China), Chuo-ku (Japan), Kopeysk (Russian Federation)

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)

NCT02829723

PHASE 1/2

Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors

TARGETS
PD-1, CSF1R

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Nagoya (Japan), Koto ku (Japan), Singapore (Singapore), Tel Aviv (Israel), Zurich (Switzerland), Rozzano (Italy), Barcelona (Spain), Hospitalet de LLobregat (Spain)

NCT03797326

PHASE 2

Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants With Select Solid Tumors (MK-7902-005/E7080-G000-224/LEAP-005)

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia), Kazan (Russian Federation), Herston (Australia), Arkhangelsk (Russian Federation), Moscow (Russian Federation)

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

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

TARGETS
PD-L1, PD-1, CTLA-4

LOCATIONS: Taipei (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Amsterdam (Netherlands), Napoli (Italy), Roma (Italy), Villejuif Cedex (France), Barcelona (Spain)

NCT03565445

PHASE 1

A Study of ASP1948, Targeting an Immune Modulatory Receptor, in Subjects With Advanced Solid Tumors

TARGETS
PD-1, NRP1

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Tokyo (Japan), Chiba (Japan), Meldola (Italy), Modena (Italy), Newcastle upon Tyne (United Kingdom), Monza (Italy), Milano (Italy), Glasgow (United Kingdom)

NCT03799003

PHASE 1

A Study of ASP1951 in Subjects With Advanced Solid Tumors

TARGETS
PD-1, TNFRSF18

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Daegu (Korea, Republic of), Chungcheongbukdo (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Washington, California, Nevada

NCT03179436

PHASE 1/2

Safety, Pharmacokinetics (PK), and Efficacy of MK-1308 in Combination With Pembrolizumab in Advanced Solid Tumors (MK-1308-001)

TARGETS
CTLA-4, PD-1

LOCATIONS: Hangzhou (China), Chongqing (China), Beijing (China), Cairns (Australia), Brisbane (Australia), Kurralta Park (Australia), Waratah (Australia), Blacktown (Australia), Wollstonecraft (Australia), Melbourne (Australia)

NCT03059823

PHASE 1

A Phase 1 Study of MGA012 in Patients With Advanced Solid Tumors

TARGETS
PD-1

LOCATIONS: Xiamen (China), Guangzhou (China), Zhengzhou (China), Jinan (China), Xi'an (China), Beijing (China), Camperdown (Australia), Sumy (Ukraine), Ivano-frankivsk (Ukraine), Lublin (Poland)

BIOMARKER

Tumor Mutational Burden

RESULT

18 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

TARGETS

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

LOCATIONS: Villejuif (France)

NCT03335540

PHASE 1

An Adaptive Study to Match Patients With Solid Tumors to Various Immunotherapy Combinations Based Upon a Broad Biomarker Assessment

TARGETS

PD-1, LAG-3, CSF1R, CTLA-4, IDO1

LOCATIONS: Illinois, Pennsylvania, Maryland

GENE
ATM

ALTERATION
R2993*

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors.

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

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

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

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

NCT04740190

PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT04715620

PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
PARP

LOCATIONS: Tianjin (China)

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT03188965

PHASE 1

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

TARGETS
ATR

LOCATIONS: Sunto (Japan), Chuo-ku (Japan), Kashiwa (Japan), Singapore (Singapore), St. Gallen (Switzerland), Bellinzona (Switzerland), Newcastle Upon Tyne (United Kingdom), Genève (Switzerland), Sutton (United Kingdom), Edmonton (Canada)

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)

GENE
MEN1

ALTERATION
R521fs*43

RATIONALE
Based on limited clinical and preclinical evidence, tumors with MEN1 loss or inactivation may be sensitive to CDK4/6 inhibitors.

NCT03099174

PHASE 1

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

TARGETS
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

LOCATIONS: Seoul (Korea, Republic of), Goyang (Korea, Republic of), Aichi, Nagoya (Japan), Kanagawa, Isehara (Japan), Tokyo, Chuo-ku (Japan), Tokyo, Koto-ku (Japan), Chiba, Kashiwa (Japan), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04391595

PHASE NULL

LY3214996 Plus Abemaciclib in Recurrent Glioblastoma Patients

TARGETS
CDK4, CDK6, ERK1, ERK2

LOCATIONS: Arizona

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)

NCT02981940

PHASE 2

A Study of Abemaciclib in Recurrent Glioblastoma

TARGETS
CDK4, CDK6

LOCATIONS: Utah, California, Massachusetts

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)

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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

NCT03220646

PHASE 2

The Purpose of This Study is to Test Any Good and Bad Effects of a Study Drug Called Abemaciclib (LY2835219) in Patients With Recurrent Brain Tumors.

TARGETS
CDK4, CDK6

LOCATIONS: Connecticut, New Jersey, New York, Pennsylvania

NCT03434262

PHASE 1

SJDAWN: St. Jude Children's Research Hospital Phase 1 Study Evaluating Molecularly-Driven Doublet Therapies for Children and Young Adults With Recurrent Brain Tumors

TARGETS
CDK6, CDK4, MEK, SMO

LOCATIONS: Tennessee

GENE
NF1

ALTERATION
F1275fs*8, Y2285fs*5

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

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)

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

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

GENE
PDGFRA

RATIONALE
PDGFRA activating mutations may predict sensitivity to certain PDGFRA-targeted therapies.

ALTERATION
N659S - subclonal

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)

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

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)

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)

NCT03352427

PHASE 2

Study of Dasatinib in Combination With Everolimus for Children and Young Adults With Gliomas Harboring PDGFR/FGFR Alterations

TARGETS
mTOR, ABL, DDR2, KIT, SRC

LOCATIONS: Michigan

NCT02379416

PHASE 1

Combination Nilotinib and Paclitaxel in Adults With Relapsed Solid Tumors

TARGETS
ABL, KIT

LOCATIONS: Maryland

NCT04771520

PHASE 2

Avapritinib for the Treatment of CKIT or PDGFRA Mutation-Positive Locally Advanced or Metastatic Malignant Solid Tumors

TARGETS
KIT, PDGFRA

LOCATIONS: Texas

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
PIK3R1

ALTERATION
K448fs*32 - subclonal

RATIONALE
On the basis of clinical and strong preclinical data, PIK3R1 loss or inactivation may indicate sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors.

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03502733

PHASE 1

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

TARGETS
PI3K, PD-1

LOCATIONS: Maryland, Texas

Electronically signed by Brennan Decker, M.D., Ph.D. | 31 August 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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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.

ARID1A
A1522T

ASXL1
G653R

C11ORF30 (EMSY)
R36Q

CDK8
R237Q

CREBBP
P107L

FANCL
C12Y

GNAS
R16C

GSK3B
R367Q

IGF1R
S965N

IKBKE
R80Q

KIT
R686H

MERTK
P494L

MSH3
A58V

NOTCH3
D2171N

PARP1
I836M

PARP2
C165Y

POLD1
D987fs*58

PRDM1
E80V

QKI
M56L

RAD51B
R181W

SETD2
F1589L and N1522D

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APPENDIX Genes Assayed in FoundationOne®CDx

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)

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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 Alterations and Therapies

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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.

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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

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entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. 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 4.2.0

The median exon coverage for this sample is 982x

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