FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Tsai, Yung Chen	Brain glioblastoma (GBM)	06 Jun 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1640271-01

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 Tsai, Yung Chen
DATE OF BIRTH 16 May 1984
SEX Female
MEDICAL RECORD # 40079638

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

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S112-18119A (PF23069)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 25 April 2023
SPECIMEN RECEIVED 30 May 2023

Biomarker Findings

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

Genomic Findings

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

CD274 (PD-L1) amplification
PDCD1LG2 (PD-L2) amplification
NF1 R1276*, Y489*
H3-3A (H3F3A) K28M
JAK2 amplification
TP53 M1R

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

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***H3-3A (H3F3A)*** **K28M** (p. 6)
- Targeted therapies with potential clinical benefit **approved in this patient's tumor type**: **Dostarlimab** (p. 8), **Pembrolizumab** (p. 8)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***H3-3A (H3F3A)*** **K28M** (p. 6)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***H3-3A (H3F3A)*** **K28M** (p. 6)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

GENOMIC FINDINGS

***CD274 (PD-L1)* -** amplification

10 Trials see p. 15

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Dostarlimab	Atezolizumab
Pembrolizumab	Avelumab
	Cemiplimab
	Durvalumab
	Nivolumab
	Nivolumab + Ipilimumab
	Retifanlimab

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
PDCD1LG2 (PD-L2) **-** amplification	Dostarlimab	Atezolizumab
	Pembrolizumab	Avelumab
		Cemiplimab
		Durvalumab
		Nivolumab
10 Trials see p. 19		Retifanlimab
NF1 **-** R1276*, Y489*	none	Cobimetinib
		Selumetinib
10 Trials see p. 17		Trametinib

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[6-8]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[6], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[9]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[6], in GBMs with a previous lower grade astrocytoma[7], and in giant cell GBM compared to classic GBM[8].

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[10]. 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[10-12]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER

Tumor Mutational Burden

RESULT
0 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[16,26-27]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[28-29] or anti-PD-L1[30] 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)[31]. 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[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[35].

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[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. 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[16,26-30].

GENE
CD274 (PD-L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of strong clinical evidence, CD274 amplification and PD-L1 overexpression may predict sensitivity to antibodies targeting PD-L1 or PD-1. Patients with high tumor PD-L1 expression across multiple solid tumor types have exhibited improved clinical benefit with the PD-L1 antibodies atezolizumab[47-48], toripalimab[49-55], and durvalumab[56]. The PD-1 antibodies pembrolizumab, nivolumab (alone or in combination with ipilimumab), and tislelizumab have elicited significant clinical responses for patients with solid tumors[57-60] and for patients with Hodgkin lymphoma, a tumor type that harbors frequent PD-L1 copy number gains[61]. However, studies evaluating nivolumab for patients with urothelial carcinoma or tislelizumab plus sitravatinib for patients with non-small cell lung cancer (NSCLC) have shown no correlation between clinical benefit and PD-L1 expression levels[62-63] . A Phase 1 trial evaluating bintrafusp alfa, a fusion protein targeting TGF-beta and PD-L1, reported ORRs of 37% (10/27) and 86% (6/7) for patients with NSCLC characterized as PD-L1-positive or having high PD-L1 expression, respectively[64]. Preclinical studies have demonstrated that JAK2 amplification regulates PD-L1 expression[65-66]; therefore, JAK2 inhibitors such as ruxolitinib may also be relevant for patients with PD-L1 amplification.

FREQUENCY & PROGNOSIS

CD274 amplification has been observed in <1% of CNS tumors in a retrospective pan-tumor study[67]. However, PD-L1 protein expression has been detected in 61-88% of GBM[68-70] and in 86% (18/21) grade 3 gliomas[71]. Apart from membranous PD-L1 staining, one study observed diffuse/fibrillary PD-L1 expression in a high fraction of GBM specimens[69]. PD-L1 protein positivity did not correlate with patient outcomes[68-69], although membranous PD-L1 expression in at least 5% of tumor cells associated with shorter survival in the secondary analysis of one study[68], which is supported by a small dataset of 17 glioblastoma cases[72]. The prognostic role of high PD-L1 gene expression in glioma and GBM is not clear. Two studies have reported a significant correlation with shorter survival[68,73], whereas another study observed no association[69]. Preclinical data in murine GBM models suggest that anti-PD-1 blockade alone or combined with other therapies may be an effective therapeutic strategy against malignant gliomas[74-76].

FINDING SUMMARY

CD274 encodes the programmed cell death ligand 1 (PD-L1), also known as B7-H1, which is a cell surface molecule important for regulating the activity of T-cells through binding to various T-cell receptors. Although PD-L1 is a costimulatory molecule for naive T-cells, it can provide inhibitory signals to activated T-cells through interactions with the receptors PD-1 or CD80[77-78]. These signals can help PD-L1-expressing tumor cells evade immune detection by natural killer cells or T-cells[79-81]. CD274 amplification is associated with positive PD-L1 protein expression in solid tumors[67,82-83] and lymphomas[61,65].

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PDCD1LG2 amplification, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-1, PD-L1, or PD-L2 antibodies. The PD-1 antibodies pembrolizumab and nivolumab and the PD-L1 antibody atezolizumab have elicited significant clinical responses in several cancer types, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC)[47,84-93], and Hodgkin lymphoma, which harbors frequent PD-L1 and PD-L2 copy number gains[61]. Additionally, preclinical studies in lymphoma cell lines have demonstrated that JAK2 amplification regulates PD-L2 expression[65-66]; therefore, JAK2 inhibitors such as ruxolitinib may also be relevant for patients with PD-L2 amplification.

FREQUENCY & PROGNOSIS

PDCD1LG2 amplification was detected in fewer than 1% of caes in the TCGA Brain Lower Grade Glioma and Glioblastoma datasets, while putative homozygous PDCD1LG2 deletion was observed in 0.78% and 1.5% of cases, respectively (cBioPortal, Feb 2023)[94-95]. Preclinical data in murine models suggest that anti-PD-1 blockade alone or combined with other therapies may be an effective therapeutic strategy against malignant gliomas[74-76]. Analysis of the Chinese Glioma Genome Atlas (CGGA) and TCGA datasets found that PD-L2 expression was upregulated in higher grade and IDH wild-type glioma, and that PD-L2 expression was linked to unfavorable prognosis independent of other variables including age, grade, IDH status, and chromosome 1p/19q status[96]. However, another analysis found that PD-L2 expression was not an independent predictor of prognosis in GBM[97].

FINDING SUMMARY

PDCD1LG2 encodes the programmed cell death 1 ligand 2 (PD-L2), also known as CD273, PD-L2, and B7-DC, which is essential for T-cell proliferation and interferon production. PD-1 signaling, which can be stimulated by PD-L2, results in 'T-cell exhaustion', a temporary inhibition of activation and proliferation that can be reversed on removal of the PD-1 signal[77-78]. Amplification of PDCD1LG2 and the adjacent locus CD274, encoding PD-L1, has been reported in 29% of primary mediastinal B-cell lymphoma (PMBCL) cases, and PDCD1LG2 copy number gain has been reported to correlate with increased PD-L2 protein expression as determined by immunohistochemistry[98-99].

GENE
NF1

ALTERATION
R1276*, Y489*

HGVS VARIANT
NM_001042492.2:c.3826C>T (p.R1276*),
NM_001042492.2:c.1467T>A (p.Y489*)

VARIANT CHROMOSOMAL POSITION
chr17:29562746, chr17:29541543

VARIANT ALLELE FREQUENCY (% VAF)
51.2%, 27.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis type 1-associated neurofibroma and malignant peripheral nerve sheath tumors[100-104], central nervous system tumors including glioma and astrocytoma[105-108], limited clinical evidence for MEK inhibitors in non-small cell lung cancer (NSCLC)[108-109], and in combination with chemotherapy for biliary tract cancers[110], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. On the basis of limited clinical data[111-113] and preclinical data[114-115], loss or inactivation of NF1 may predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient malignant peripheral nerve sheath tumors (MPNST)[116].

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[40,117-119]. 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[120]. 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[121].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[122]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[123]. Alterations such as seen here may disrupt NF1 function or expression[123-132].

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, Apr 2023)[133]. 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[134-136]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[137-138], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE
H3-3A (H3F3A)

ALTERATION
K28M

HGVS VARIANT
NM_002107.4:c.83A>T (p.K28M)

VARIANT CHROMOSOMAL POSITION
chr1:226252135

VARIANT ALLELE FREQUENCY (% VAF)
34.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Prospective data from pooled clinical studies and preclinical evidence suggest that H3F3A K28M mutation predicts benefit from the investigational selective dopamine receptor D2 (DRD2) antagonist ONC201[139-140], which is supported by increased expression of the ONC201 target DRD2 in H3F3A K28M-mutant versus wild-type gliomas[140]. Among adult patients with recurrent H3F3A K28M-mutant gliomas, ONC201 achieved a DCR of 64% (7/11) and a 6-month PFS rate of 36% (5/14), with 3 patients experiencing complete and durable regressions of thalamic lesions[141]. Data from pooled ONC201 monotherapy trials showed that 31% (9/29) of patients with recurrent H3F3A K28M-mutated glioma remain progression free at 6.5 months median follow-up[142]. Although other H3F3A mutations have been reported[33], it is unclear whether these therapeutic strategies would be relevant in gliomas with H3F3A mutations other than K28M.

— Nontargeted Approaches —

Patients with pediatric H3 K27-altered diffuse midline glioma may benefit from radiotherapy, either as a single modality or combined with alkylating agents (NCCN Pediatric Central Nervous Systems Cancers, v2.2023).

FREQUENCY & PROGNOSIS

Recurrent mutations in the histone tail of H3F3A, at sites involved in critical post-translational modifications, have been reported at high frequency in pediatric and young adult brain tumors, including diffuse midline gliomas[143], diffuse hemispheric glioma[144], glioblastomas[145-147], aggressive pediatric gliomas[148], pilocytic astrocytomas[149], gangliogliomas[150], glial and glioneuronal tumors[151], as well as in low-grade gliomas undergoing transformation and secondary high-grade gliomas[152]. These mutations were commonly found concurrently with mutations in TP53 or in ATRX and DAXX, which form a complex required for H3.3 recruitment to DNA, and were mutually exclusive with IDH1 mutations, which indirectly affect methylation of critical H3.3 residues[146]. H3F3A K28M (also known as K27M) is a poor prognostic marker in glioma (NCCN CNS Cancers Guidelines, v2.2022). H3F3A G35 mutations are associated with disease onset during adolescence, whereas K28 mutations affect younger children and predict poorer IOS[147,153]. H3F3A K28M mutation has also been identified in 58% of adult midline gliomas, and is associated with shorter OS for patients with brainstem gliomas but not for patients with thalamic gliomas[154]. Mutations of H3F3A or H3F3B, the other gene encoding histone H3.3, have also been detected in giant cell tumor of bone and chondroblastoma, with low mutation frequencies in other tumors of cartilage and bone[155-157]. H3F3B K37M (commonly known as K36M) has been identified in head and neck squamous cell carcinoma, specifically in tumors of the oral cavity[158]. Overexpression of H3F3A is associated with poor survival in lung adenocarcinomas, and is thought to promote cancer cell invasion[159].

FINDING SUMMARY

H3F3A encodes the histone 3 variant H3.3. Histones form part of the nucleosome complex around which DNA is coiled in the cell. H3F3A mutations affecting different hotspot residues, such as G35 (commonly referred to as G34 in the literature) and K28 (commonly known as K27), form different subgroups based on methylation and gene expression differences, the region of the brain affected, and clinical parameters[153].

POTENTIAL DIAGNOSTIC IMPLICATIONS

H3F3A K27M mutation is characteristic of diffuse midline glioma, H3 K27M-altered (NCCN CNS Cancers Guidelines, v2.2022, NCCN Pediatric CNS Cancers Guidelines, v2.2023)[160-161].

GENE
JAK2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

While JAK2 inhibitors have shown clinical benefit in hematological malignancies, clinical utility in solid tumors has not been demonstrated.

FREQUENCY & PROGNOSIS

JAK2 alterations are very rare in glioma and glioblastoma (GBM); in the TCGA datasets JAK2 mutations were reported in 1% of cases analyzed (cBioPortal, Jun 2022)[94-95]. Several preclinical studies have demonstrated activity of JAK2/STAT3 inhibitors against GBM cells and mouse models, particularly in EGFR-mutant GBM[162-167]. Published data investigating the prognostic implications of JAK2 alterations in glioma and GBM are limited (PubMed, Jun 2022).

FINDING SUMMARY

JAK2 encodes Janus kinase 2, a tyrosine kinase that regulates signals triggered by cytokines and growth factors[168]. JAK2 is often mutated in hematopoietic and lymphoid cancers. Cell lines and primary lymphoid cancer cells from a small number of patients with JAK2 amplification exhibit overabundance of JAK2 mRNA, protein, and phosphorylated JAK2 targets and respond to JAK2 inhibitors such as ruxolitinib similarly to JAK2-rearranged (activated) cell lines and primary blood cells from patients[65,169].

GENE
TP53

ALTERATION
M1R

HGVS VARIANT
NM_001126117.1:c.2T>G (p.M1?)

VARIANT CHROMOSOMAL POSITION
chr17:7578532

VARIANT ALLELE FREQUENCY (% VAF)
61.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[170-173] or p53 gene therapy such as SGT53[174-178]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[179]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[180]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[181]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[182]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[183]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[184]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[185]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[178]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[186]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[187]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

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[119,188]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[189]. 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[190-195]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[196]. 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[189]. 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[197].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[198]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[199-201], including sarcomas[202-203]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[204] to 1:20,000[203]. 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[205]. 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[206-211]. 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[206-207]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[212]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[210,213-214]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Dostarlimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

Activation of PDCD1LG2 may lead to overexpression of PD-L2 and may confer sensitivity to PD-1 inhibitors such as dostarlimab. CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as dostarlimab based on clinical evidence in multiple solid tumor types[215-218] .

SUPPORTING DATA

Clinical data on the efficacy of dostarlimab for the treatment of CNS tumors are limited (PubMed, Jan 2023). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[215,217,219] . 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[217,220] .

Pembrolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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 (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or MMR-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive head and neck squamous cell cancer (HNSCC), cervical cancer, or esophageal cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with non-small cell lung cancer (NSCLC), melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, MSI-H or dMMR endometrial carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma; and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or gastroesophageal junction cancer, renal cell carcinoma, TNBC, urothelial carcinoma, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to pembrolizumab. Treatment with pembrolizumab has resulted in a lasting CR in a patient with CD274-amplified DLBCL[221] and in a lasting PR in a patient with CD274-amplified cancer of unknown primary[57]. PD-L1 expression is associated with significantly prolonged median OS for patients with EGFR/ALK wildtype advanced NSCLC treated with pembrolizumab compared with chemotherapy[222-224] . One trial in patients with melanoma observed an improved objective response rate (51% vs. 6%) and PFS (12 vs. 3 months) for PD-L1 positive compared to PD-L1 negative tumors[225]. Furthermore, PD-L1 expression correlated positively with expression of PD-1 (on lymphocytes) and PD-L2, as well as with objective response to the anti-PD-1 antibody nivolumab in various advanced solid tumors[226].

SUPPORTING DATA

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[227]. 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[228]. 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[229]. 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[230].

Atezolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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) as well as adult and pediatric patients 2 years and older with alveolar soft part sarcoma, 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, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangements, that lead to overexpression of PD-L1 may predict sensitivity to atezolizumab based on clinical evidence in multiple solid tumor types[47,231-232] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to anti-PD-L1 inhibitors such as atezolizumab. Although atezolizumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved OS and response to atezolizumab[47,231-232] .

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[30]. A patient with POLE L424V-mutated GBM enrolled in this study achieved an OS of ~18 months[30]. 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[233]. Atezolizumab has been studied primarily for treating non-small cell lung cancer (NSCLC)[47-48,234-237] and urothelial carcinoma[238-241] . A study of atezolizumab as monotherapy for patients with advanced solid tumors reported a median PFS of 18 weeks and an ORR of 21%, including confirmed responses in 26% (11/43) of melanomas, 13% (7/56) of renal cell carcinomas (RCC) and 17% (1/6) of colorectal cancers (CRCs)[48]. As a single-agent therapy in genomically unselected young patients (<30 years old) with relapsed or refractory cancers, atezolizumab elicited an ORR of 1.5% (1/67) for patients with solid tumors, with similar safety and pharmacokinetics as seen in adults[242]. A Phase 1a study of atezolizumab reported an ORR of 15% (9/62), a median PFS of 5.6 months, and a median OS of 28.9 months for patients with clear cell renal cell carcinoma (ccRCC)[243]. A Phase 1b study evaluated atezolizumab combined with nab-paclitaxel for patients with previously treated metastatic triple-negative breast cancer (mTNBC) and reported confirmed objective responses for 42% (10/24) of patients; no dose-limiting toxicities were observed[244]. A Phase 1b study that evaluated atezolizumab in combination with the MEK inhibitor cobimetinib for advanced solid tumors reported an ORR of 8.3% (7/84) for patients with CRC, 41% (9/22) for patients with melanoma, 18% (5/28) for patients with NSCLC, and 19% (3/16) for patients with other tumors (ovarian cancer, clear-cell sarcoma, and RCC); there was no association between BRAF or KRAS mutation status and response rate in any disease setting, and no dose-limiting toxicities were encountered[245-246] .

Avelumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as avelumab based on clinical evidence in multiple solid tumor types[47,231-232,247-250] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as avelumab. Although avelumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved OS and response to the similar PD-L1-blocking antibody atezolizumab[47,231-232] .

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[251]. 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[252]. 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[253].

Cemiplimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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 non-small cell lung cancer (NSCLC), cutaneous squamous cell carcinoma, or basal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s). In multiple cancer types, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as improved clinical benefit in response to anti-PD-1 immunotherapies[61,224-226,254-257] and may predict sensitivity to cemiplimab.

SUPPORTING DATA

A Phase 1/2 trial of cemiplimab in combination with the investigational immunotherapeutic agents INO-5401 and INO-9012 reported a 12-month OS of 84% for patients with glioblastoma multiforme (GBM) and unmethylated-MGMT status[258]. In the neoadjuvant setting, cemiplimab was also associated with clinical benefit for 1 patient with high-grade glioma following a third recurrence and subsequent resection in a case report[259]. 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[260]. 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[261-262] . 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[263].

Cobimetinib

Assay findings association

NF1
R1276*, Y489*

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor that is FDA approved to treat patients with histiocytic neoplasms. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[100-101,264-267] , malignant peripheral nerve sheath tumors[102-104] , and central nervous system tumors including glioma, glioblastoma multiforme (GBM), and astrocytoma[105-108,268-269] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

MEK inhibitors have shown efficacy in several studies of low-grade and high-grade central nervous system (CNS) tumors. A Phase 2 study of selumetinib monotherapy for patients with NF1-associated low-grade glioma reported an ORR of 40%, with 10 patients experiencing PRs[105]. An NCI-MATCH subprotocol of trametinib in NF1-mutated solid tumors reported 1 PR, 1 durable SD, and lack of benefit for 3 patients with glioblastoma multiforme (GBM)[108]. Additionally, case studies of trametinib monotherapy for NF1-associated brain tumors have reported PRs for 3 patients with low-grade glioma, 5 patients with astrocytoma, 1 patient with an optic pathway glioma, and 1 patient with a GBM[106-107,268-271] . A minor response was reported for 1 patient with glioma on cobimetinib[272]. A Phase 1/2 study evaluating the use of cobimetinib for pediatric and young adult patients with relapsed or refractory solid tumors reported an ORR of 9.4% (3/32) among patients with low-grade glioma[272]. A patient with anaplastic pleomorphic xanthoastrocytoma with leptomeningeal dissemination harboring an ATG7-RAF1 fusion exhibited a complete cytologic response and clinical benefit following treatment with cobimetinib[273].

Durvalumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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), small cell lung cancer (SCLC), and biliary tract cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as durvalumab based on clinical evidence in multiple solid tumor types[47,56,231-232,247-250,274-278] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as durvalumab. Although durvalumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved OS and response to the similar PD-L1-blocking antibody atezolizumab[47,231-232] .

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[279]. 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[280]. 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[281].

Nivolumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

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 as a monotherapy 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, colorectal cancer (CRC), classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma or squamous cell carcinoma (ESCC). It is also approved in combination with chemotherapy to treat ESCC, in combination with cabozantinib to treat RCC, and in combination with relatlimab to treat melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to nivolumab. In various advanced solid tumors, including melanoma, lung, kidney, prostate, and colorectal cancer, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as with objective response to nivolumab[226,256] .

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)[282]. Exploratory CheckMate-143 cohorts showed combination of nivolumab and radiotherapy, with or without temozolomide, to be well tolerated[283]; 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[284-285] . Biallelic mismatch repair deficiency (bMMRD)-associated GBMs harbor extraordinarily high mutational loads[28,286] , and three pediatric patients with bMMRD-associated GBM achieved clinically and radiologically significant responses to nivolumab monotherapy[28,287] . An adult with previously treated GBM experienced tumor shrinkage and disease stabilization for 2 years after pseudoprogression on nivolumab[288]. In a Phase 1 study, three patients with progressive GBM benefited from regimens combining nivolumab with surgery and the VEGFR2-targeting vaccine VXM01[289].

Nivolumab + Ipilimumab

Assay findings association

CD274 (PD-L1)
amplification

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, and ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. The combination is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), pleural mesothelioma, and esophageal squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence for PD-L1 overexpression across various solid tumor types, alterations that lead to activation of CD274 may predict sensitivity to combination nivolumab and ipilimumab[25,59,86,290-291] .

SUPPORTING DATA

The Phase 1 CheckMate 143 study for patients with recurrent glioblastoma reported ORRs of 0-10%, median PFS of 1.5-2.1 months, and median OS of 7.3-9.2 months following treatment with nivolumab and ipilimumab at different doses[292]. A retrospective study of pediatric patients with recurrent or refractory CNS tumors treated with nivolumab combined with ipilimumab reported objective responses in 30% (3/9) of the patients[293].

Retifanlimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Retifanlimab 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 Merkel cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of PDCD1LG2 may lead to overexpression of PD-L2 and may confer sensitivity to PD-1 inhibitors such as retifanlimab. CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as retifanlimab based on clinical evidence in multiple solid tumor types[215-218] .

SUPPORTING DATA

For patients with recurrent glioblastoma, a Phase 2 study of retifanlimab plus bevacizumab and hypofractionated radiotherapy showed an ORR of 58% (14/24), median PFS of 7.0 months, and median OS of 12.2 months[294]. In the same setting, another Phase 2 study of retifanlimab plus the GITR agonist INCAGN01876 and fractionated stereotactic radiotherapy reported no responses, a DCR of 56% (9/16), median PFS of 3.9 months, and median OS of 9.8 months[295].

Selumetinib

Assay findings association

NF1
R1276*, Y489*

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients with neurofibromatosis type 1 (NF1)-associated 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[100-101,264-267] , malignant peripheral nerve sheath tumors[102-104] , and central nervous system tumors including glioma, glioblastoma multiforme (GBM), and astrocytoma[105-108,268-269] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

MEK inhibitors have shown efficacy in several studies of low-grade and high-grade central nervous system (CNS) tumors. A Phase 2 study of selumetinib monotherapy for patients with NF1-associated low-grade glioma reported an ORR of 40%, with 10 patients experiencing PRs[105]. An NCI-MATCH subprotocol of trametinib in NF1-mutated solid tumors reported 1 PR, 1 durable SD, and lack of benefit for 3 patients with glioblastoma multiforme (GBM)[108]. Additionally, case studies of trametinib monotherapy for NF1-associated brain tumors have reported PRs for 3 patients with low-grade glioma, 5 patients with astrocytoma, 1 patient with an optic pathway glioma, and 1 patient with a GBM[106-107,268-271] . A minor response was reported for 1 patient with glioma on cobimetinib[272]. Selumetinib has demonstrated clinical activity in low-grade glioma. A Phase 2 study of selumetinib for patients with low-grade glioma (LGG) reported 8/25 PRs for patients with BRAF alterations and 10/25 PRs for those with NF1-associated LGG[105]; a Phase 1 study of selumetinib reported 5/25 PRs for patients with LGG[296]. A Phase 2 study of selumetinib for patients with tumors with activating alterations in the MAPK pathway evaluated 8 patients with high-grade glioma (HGG); 2 SDs and no objective responses were observed in this subset[297].

Trametinib

Assay findings association

NF1
R1276*, Y489*

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[100-101,264-267] , malignant peripheral nerve sheath tumors[102-104] , and central nervous system tumors including glioma, glioblastoma multiforme (GBM), and astrocytoma[105-108,268-269] , NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

MEK inhibitors have shown efficacy in several studies of low-grade and high-grade central nervous system (CNS) tumors. A Phase 2 study of selumetinib monotherapy for patients with NF1-associated low-grade glioma reported an ORR of 40%, with 10 patients experiencing PRs[105]. An NCI-MATCH subprotocol of trametinib in NF1-mutated solid tumors reported 1 PR, 1 durable SD, and lack of benefit for 3 patients with glioblastoma multiforme (GBM)[108]. Additionally, case studies of trametinib monotherapy for NF1-associated brain tumors have reported PRs for 3 patients with low-grade glioma, 5 patients with astrocytoma, 1 patient with an optic pathway glioma, and 1 patient with a GBM[106-107,268-271] . A minor response was reported for 1 patient with glioma on cobimetinib[272]. A study of 2 pediatric patients with optic astrocytomas harboring BRAF duplications reported clinical benefit in response to trametinib with reductions in tumor volume (56-66%) and treatment ongoing at 484 and 468 days[298]. A study of 5 patients with KIAA1549-BRAF-fusion-positive pilocytic astrocytoma reported 1 PR and 3 minor responses[270] and, similarly, a patient with low-grade glioma harboring this fusion benefited from trametinib[299]. A patient with pilocytic astrocytoma harboring an NFIA-RAF1 fusion who had progressed on multiple lines of prior treatment exhibited ongoing SD following treatment with trametinib[300]. 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[301], 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[302].

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

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

GENE

CD274 (PD-L1)

ALTERATION

amplification

RATIONALE

CD274 (PD-L1) amplification or rearrangements that disrupt the 3' untranslated region (UTR) may promote PD-1 signaling and inhibit the antitumor immune response. Antibodies that block the interaction of PD-L1 and PD-1 (alone, in combination with anti-CTLA-4, or bispecific PD-1/CTLA-4 antibodies) may therefore be beneficial to release the antitumor immune response. Furthermore, JAK2 inhibitors may be relevant, as they may reduce PD-L1 expression.

NCT04237649

PHASE NULL

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

TARGETS ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

NCT04047862

PHASE 1

Study of BGB-A1217 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Hefei (China), Guangdong (China), Changsha (China)

NCT05166577

PHASE 1/2

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

TARGETS HDAC, PD-1

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy), Meldola (Italy)

NCT03821935

PHASE 1

Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of ABBV-151 as a Single Agent and in Combination With ABBV-181 in Participants With Locally Advanced or Metastatic Solid Tumors

TARGETS PD-1, GARP

LOCATIONS: Taichung City (Taiwan), Taipei City (Taiwan), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), South Brisbane (Australia), Camperdown (Australia), Ramat Gan (Israel), Tel Aviv-Yafo (Israel), Haifa (Israel)

NCT04215978

PHASE 1

Safety and Preliminary Effectiveness of BGB-A445 in Combination With Tislelizumab in Participants With Advanced Solid Tumors

TARGETS
PD-1, OX40

LOCATIONS: Changhua (Taiwan), Taipei (Taiwan), Tianan (Taiwan), Hangzhou (China), Shanghai (China), Changsha (China), Wuhan (China), Linyi (China), Gyeonggi-do (Korea, Republic of), Gyeongju (Korea, Republic of)

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT03744468

PHASE 1/2

Study of BGB-A425 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIM-3

LOCATIONS: Busan (Korea, Republic of), Ulsan (Korea, Republic of), Cheongju (Korea, Republic of), Suwon (Korea, Republic of), Incheon (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang (Korea, Republic of), Perth (Australia), Hervey Bay (Australia)

NCT04892498

PHASE 2

Hypofractionated Radiotherapy Combined With PD-1 Inhibitor Sequential GM-CSF and IL-2 for the Treatment of Advanced Refractory Solid Tumors (PRaG2.0)

TARGETS
PD-1

LOCATIONS: Hangzhou (China), Suzhou (China), Wuxi (China), Hefei (China), Xuzhou (China)

NCT05142423

PHASE 1/2

A Study of AK109 Combined With AK104 in Patients With Advanced Solid Tumors

TARGETS
PD-1, CTLA-4, VEGFR2

LOCATIONS: Hangzhou (China)

GENE
NF1

ALTERATION
R1276*, Y489*

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

LOCATIONS: Shanghai (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

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), California, Texas

NCT05580770

PHASE 1/2

Mirdametinib + BGB-3245 in Advanced Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Waratah (Australia), Melbourne (Australia), California, Ohio, Massachusetts, Texas, Connecticut, Florida

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

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

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

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

RATIONALE
PDCD1LG2 (PD-L2) amplification may promote PD-1 signaling and inhibit the anti-tumor immune response. Antibodies that block the interaction of PD-L2 and PD-1 may therefore be beneficial to release the anti-tumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L2 expression.

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

NCT04047862

PHASE 1

Study of BGB-A1217 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Hefei (China), Guangdong (China), Changsha (China)

NCT05166577

PHASE 1/2

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

TARGETS
HDAC, PD-1

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy), Meldola (Italy)

NCT03821935

PHASE 1

Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of ABBV-151 as a Single Agent and in Combination With ABBV-181 in Participants With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-1, GARP

LOCATIONS: Taichung City (Taiwan), Taipei City (Taiwan), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), South Brisbane (Australia), Camperdown (Australia), Ramat Gan (Israel), Tel Aviv-Yafo (Israel), Haifa (Israel)

NCT04215978

PHASE 1

Safety and Preliminary Effectiveness of BGB-A445 in Combination With Tislelizumab in Participants With Advanced Solid Tumors

TARGETS
PD-1, OX40

LOCATIONS: Changhua (Taiwan), Taipei (Taiwan), Tianan (Taiwan), Hangzhou (China), Shanghai (China), Changsha (China), Wuhan (China), Linyi (China), Gyeonggi-do (Korea, Republic of), Gyeongju (Korea, Republic of)

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT03744468

PHASE 1/2

Study of BGB-A425 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIM-3

LOCATIONS: Busan (Korea, Republic of), Ulsan (Korea, Republic of), Cheongju (Korea, Republic of), Suwon (Korea, Republic of), Incheon (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang (Korea, Republic of), Perth (Australia), Hervey Bay (Australia)

NCT04892498

PHASE 2

Hypofractionated Radiotherapy Combined With PD-1 Inhibitor Sequential GM-CSF and IL-2 for the Treatment of Advanced Refractory Solid Tumors (PRaG2.0)

TARGETS
PD-1

LOCATIONS: Hangzhou (China), Suzhou (China), Wuxi (China), Hefei (China), Xuzhou (China)

NCT05142423

PHASE 1/2

A Study of AK109 Combined With AK104 in Patients With Advanced Solid Tumors

TARGETS
PD-1, CTLA-4, VEGFR2

LOCATIONS: Hangzhou (China)

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.

CDKN2A/B
amplification and amplification

FANCG
amplification

MTAP
amplification

PAX5
amplification

PIK3C2G
NM_004570.4:
c.3299_3306dup
(p.Y1103Vfs*15)
chr12:18691183

TEK
amplification

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 or WTX)*	
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*	*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*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
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	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (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*	*MRE11 (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*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*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*
PRKN (PARK2)	*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*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*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

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

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 PRINCIPLE

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

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

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

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

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. 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.
5. 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.
6. 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.
7. 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%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating 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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.9.0

The median exon coverage for this sample is 836x

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