FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chang, Hsiu Fen	Brain glioblastoma (GBM)	23 Jan 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1544963-01

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 Chang, Hsiu Fen
DATE OF BIRTH 18 September 1965
SEX Female
MEDICAL RECORD # 49182856

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 S111-54614 B (PF23008)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 27 December 2022
SPECIMEN RECEIVED 16 January 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

EGFR EGFRvIII, amplification
PIK3CA C420R - subclonal†
PTEN loss
FAS loss
GRM3 T758M - subclonal†
PPP2R1A R260C - subclonal†
RB1 Q736*
TERT promoter -146C>T
TP53 V272M

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

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***EGFR* amplification** (p. 4), ***TERT* promoter -146C>T** (p. 8)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cetuximab** (p. 10), **Osimertinib** (p. 10), **Panitumumab** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***TERT* promoter -146C>T** (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***EGFR* -** EGFRvIII, amplification	none	Cetuximab
		Osimertinib
8 Trials see p. 12		Panitumumab
***PIK3CA* -** C420R - subclonal	none	none
10 Trials see p. 14		
***PTEN* -** loss	none	none
10 Trials see p. 16		

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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.

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
4 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
EGFR

ALTERATION
EGFRvIII, amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In multiple glioblastoma (GBM) studies, the presence of EGFRvIII has not predicted clinical benefit from first-generation EGFR TKIs such as erlotinib[47-52] or gefitinib[50,53]. However, case reports have described patients with EGFRvIII-positive GBM responding to erlotinib[54-57]. In a retrospective study of patients with GBM treated with erlotinib or gefitinib, co-expression of EGFRvIII with PTEN protein was the strongest predictor of response (P<0.001)[58], suggesting that activity in this setting is dependent on PTEN status[59-60]. However, a prospective Phase 2 trial testing erlotinib monotherapy for patients with EGFRvIII and PTEN-positive recurrent glioblastoma reported minimal efficacy and was terminated[52]. The second-generation EGFR TKIs afatinib and dacomitinib have shown minimal efficacy for patients with EGFRvIII glioblastoma (GBM)[61-64]. A Phase 1/2 study of afatinib, temozolomide, or the combination for patients with GBM reported clinical benefit, including for patients with EGFRvIII; however, temozolomide alone and in combination exhibited better responses than afatinib monotherapy[61-62]. A Phase 2 trial of dacomitinib for patients with EGFR-amplified GBM reported a DCR of 26% (5/19) among patients with EGFR amplification and EGFRvIII; however, the trial failed to meet its primary endpoint of 6-month PFS[63]. A retrospective biomarker analysis of another Phase 2 study of dacomitinib for patients with GBM found no association between EGFRvIII and clinical benefit[64]. Patients with glioma and co-occurring EGFR amplification and EGFRvIII have reported responses to osimertinib[65]. However, a patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFRvIII, experienced progression of the EGFRvIII-positive tumor during treatment with osimertinib[66]. On the basis of preclinical data, osimertinib inhibits EGFRvIIII-driven tumor growth in vitro[67-68]. Novel approaches that specifically target EGFRvIII in glioblastoma (GBM), such as the vaccine rindopepimut, are under investigation in both clinical and preclinical studies. A Phase 2 trial reported significant improvement in OS for patients with EGFRvIII-positive GBM with rindopepimut in combination with bevacizumab compared to bevacizumab alone (HR=0.53, p=0.01)[69]. However, a Phase 3 study of rindopepimut combined with temozolomide compared to temozolomide alone in newly diagnosed EGFRvIII-positive GBM patients was terminated after the interim analysis, due to a lack of clinical benefit as measured by OS (20 vs. 20 months)[70]. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy[61,63-64,71-72]; however, a small subset of patients has experienced clinical benefit[63-64,71]. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma[58,73-75]. There are conflicting data on the efficacy of anti-EGFR antibodies for the treatment of EGFR-amplified tumors. A meta-analysis of colorectal cancer patients treated with second-line or higher cetuximab or panitumumab observed an association between EGFR copy number gain and increased OS and PFS[76]. However, studies in head and neck squamous cell carcinoma and gastric cancer found either no association or a negative association between EGFR copy number gain and survival after treatment with first-line cetuximab or panitumumab in combination with chemotherapy[77-78]. The Phase 3 INTELLANCE trial of depatuxizumab mafodotin (ABT-414), an EGFR-targeted antibody-drug conjugate with a toxic payload, in patients with EGFR-amplified glioblastoma (GBM) was stopped for futility. Interim analysis demonstrated improved median PFS (mPFS) of ABT-414 monotherapy compared with placebo (HR=0.84); however, no OS benefit was observed (HR=1.01). Improved mPFS was also observed in patients harboring EGFRvIII (HR=0.73) but without an OS improvement (HR=0.95)[79]. The Phase 2 INTELLANCE trial demonstrated clinical benefit for EGFR-amplified GBM for the combination of ABT-414, temozolomide, and radiotherapy (HR=0.66, p=0.017), but there was no evidence of efficacy for ABT-414 monotherapy (HR=1.04, p=0.83)[80].

FREQUENCY & PROGNOSIS

Across several genomic studies of CNS tumors, EGFR amplification has been reported in 16.9% of anaplastic astrocytomas, and 39.7% of glioblastoma multiformes (GBMs)[81-84]. EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas in several genomic studies of CNS tumors[81-84]. In GBMs, Missense mutations in the EGFR extracellular domain have been found in 10-15% of cases and approximately half have a low-level amplification of the mutated allele[85-86]. In a study of IDH-wildtype GBM samples, EGFR alterations were detected in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event[87]. The EGFRvIII mutation has been variously reported in 6-46% of GBM samples[58,88-95]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[96-97]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[98]. The link between EGFRvIII status and prognosis is unclear, although some studies suggest that it may be linked to improved survival and response to chemotherapy[99].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[100]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[101-103]. A mutation of the EGFR gene, referred to as EGFRvIII, results from a gene rearrangement that deletes exons 2-7. This alteration causes an in-frame deletion of 801 base pairs encoding part of the extracellular ligand-binding domain[88]. This deletion has shown to result in ligand-independent (constitutive) phosphorylation and activation of EGFR, as well as consequent tumorigenesis[88,104].

POTENTIAL DIAGNOSTIC IMPLICATIONS

The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v1.2022)[105].

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GENE
PIK3CA

ALTERATION
C420R - subclonal

TRANSCRIPT ID
NM_006218.2

CODING SEQUENCE EFFECT
1258T>C

VARIANT CHROMOSOMAL POSITION
chr3:178927980

VARIANT ALLELE FREQUENCY (% VAF)
2.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[106-113], AKT[114-115], or mTOR[116-123]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[113]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[112]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[110-111]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[124]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[125]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[126]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[127], but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)[107].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 9% of glioblastoma (GBM) samples analyzed in the TCGA dataset[82], and other studies report the incidence of PIK3CA mutations in primary GBMs as 5-18%[128-130]. One study detected PIK3CA mutation in 16% (36/232) of IDH-wildtype GBM samples analyzed[87]. PIK3CA mutations have been reported in 5-23% of high-grade gliomas (including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas)[128-132]. While another study did not observe PIK3CA mutations in low-grade astrocytomas or in anaplastic astrocytomas, it did report high ERK and AKT activity[130]. One study found that PIK3CA mutation in glioblastoma (GBM) was associated with shorter median PFS in both a discovery cohort (6.9 vs. 12.4 months, HR=2.89, p=0.01) and in the TCGA cohort (6.1 vs. 9 months, p=0.008), but was not consistently associated with median OS[133]. In a study of IDH-wildtype GBM, patients with alterations in PI3K class I genes (PIK3CA, PIK3R1, PIK3CG, and PIK3R2) had significantly longer OS (20.0 months altered vs. 16.9 months wildtype, HR=0.62, p=0.002) and PFS (11.0 months altered vs. 7.4 months wildtype, p=0.0043); patients with PIK3CA alterations experienced an improved OS but this association was not highly significant (20.0 months altered vs. 18.1 months wildtype, p=0.0407)[87].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[134-135]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[136-157].

GENE
PTEN

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[111,158-160]. Clinical studies in glioblastoma have not observed an association between PTEN deficiency and response to everolimus or temsirolimus[161-163]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[164-168], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[169], ovarian cancer[170], uterine leiomyosarcoma[171], and endometrial cancer[168] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[172-173].

FREQUENCY & PROGNOSIS

Studies in the literature have indicated that PTEN alterations (mutation or homozygous deletion) occur most frequently in glioblastoma (GBM), less frequently in anaplastic astrocytoma, and rarely in lower grade glioma subtypes including low grade astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma[98,174-180]. One study detected PTEN mutation in 42% (97/232) and loss in 10% (24/232) of IDH-wildtype GBM samples analyzed[87]. In the TCGA dataset, PTEN mutation was observed in 23% of GBM cases and PTEN deletion was reported in 7% of cases[82], while in the Lower Grade Glioma TCGA dataset, PTEN mutation was observed in 4% of cases and homozygous deletion observed in 1.2% of cases[181]. Decreased PTEN expression is associated with the higher grade GBM tumors[182]. Loss of PTEN correlated with significantly worse prognosis in all grades of gliomas[177,183].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[159]. Alterations such as seen here may disrupt PTEN function or expression[179,184-224].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[225-226]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[225,227]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[225]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
FAS

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although CD95 is of significant interest as a target for anti-cancer therapies[228-230], there are no targeted therapies available to address mutation of FAS in cancer.

FREQUENCY & PROGNOSIS

In the TCGA datasets, FAS mutation has most frequently been observed in diffuse large B-cell lymphoma (DLBCL)(6%), uterine corpus endometrioid carcinoma (6%), cervical squamous cell carcinoma (2%), and melanoma (2%); FAS putative homozygous deletion was most frequently observed in diffuse large B-cell lymphoma (DLBCL)(6%), prostate adenocarcinoma (6%), and sarcomas (3%) (cBioPortal, 2023)[231-232].

FINDING SUMMARY

FAS encodes the protein CD95, a cell surface receptor for the protein FAS ligand (FASL) and a key regulator of apoptosis during lymphocyte development. Heterozygous mutations in FAS underlie autoimmune lymphoproliferative syndrome (ALPS) and certain germline mutations in FAS are associated with an increased risk of lymphoma development[233-235].

GENE
GRM3

ALTERATION
T758M - subclonal

TRANSCRIPT ID
NM_000840.2

CODING SEQUENCE EFFECT
2273C>T

VARIANT CHROMOSOMAL POSITION
chr7:86469103

VARIANT ALLELE FREQUENCY (% VAF)
0.65%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited preclinical evidence, GRM3 mutations may be associated with sensitivity to MEK inhibitors. Activating mutations of GRM3 were reported to promote MAPK signaling and were sensitive to the MEK inhibitor selumetinib in one preclinical study[236]. In 1 study, high expression of GRM3 was associated with better survival and better prognosis for patients with microsatellite-stable (MSS) colorectal cancer (CRC) tumors treated with bevacizumab[237].

FREQUENCY & PROGNOSIS

GRM3 mutations have been most frequently reported in melanoma, with an incidence of 30% (6/20) in desmoplastic melanoma[238], and an incidence of 13-18% in cutaneous melanoma[236,239-240]. GRM3 mutation has also been reported at lower frequencies in other cancer types, including small cell lung cancer (10-13%)[241-242], lung squamous cell carcinoma (8%)[243], and gastric adenocarcinoma (5%)[244].

FINDING SUMMARY

GRM3 (metabotropic glutamate receptor-3, or mGluR3) encodes a G protein-coupled receptor. In preclinical studies of melanoma cells, activating GRM3 mutations (including G561E, S610L, E767K, E870K) result in increased MAPK signaling, proliferation, anchorage-independent growth and migration[236]. Certain germline polymorphisms of the GRM3 locus have been reported to affect motor and cognitive function as well as the risk of developing schizophrenia, autism spectrum disorder, bipolar disorder, and alcohol dependence[245-249].

GENE
PPP2R1A

ALTERATION
R260C - subclonal

TRANSCRIPT ID
NM_014225.5

CODING SEQUENCE EFFECT
778C>T

VARIANT CHROMOSOMAL POSITION
chr19:52716334

VARIANT ALLELE FREQUENCY (% VAF)
2.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to directly address genomic alterations in PPP2R1A. Activation of PP2A with forskolin or the sphingosine analogue FTY720 has be shown to be beneficial in the context of CML and ALL[250], and is being investigated in solid tumors of the lung, breast, and colon[251-253]. In addition, other agents have been shown to upregulate PP2A activity in the context of various tumors[254]. However, the efficacy of these compounds in the context of PPP2R1A mutations has not yet been evaluated (PubMed, Dec 2022).

FREQUENCY & PROGNOSIS

PPP2R1A mutations have been reported in several subtypes of ovarian and uterine carcinoma, most frequently in uterine serous carcinoma (up to 26%) (COSMIC, cBioPortal, 2023)[231-232,255]. In addition, concurrent mutations in PPP2R1A, PIK3CA, and TP53 have been reported in cases of uterine serous carcinoma, and were also found in associated serous endometrial intraepithelial carcinomas, suggesting the alterations arose early in the pre-invasive stage of the disease[256]. PPP2R1A mutations have been reported in 9/42 carcinosarcoma samples analyzed[257].

FINDING SUMMARY

PPP2R1A encodes a regulatory subunit of protein phosphatase 2 (PP2A), which is involved in regulation of the cell cycle transition from mitosis to interphase[258]. A spatially constrained pattern of somatic missense alterations in PPP2R1A, clustered around codons 179, 182, and 256, has been documented[256-257,259-261]. Although the functional consequences of these PPP2R1A alterations have not been clearly characterized, they are presumed to disrupt binding of the PP2A regulatory and catalytic subunits, dysregulating normal PP2A function and cell cycle progression[260].

GENE
RB1

ALTERATION
Q736*

TRANSCRIPT ID
NM_000321.2

CODING SEQUENCE EFFECT
2206C>T

VARIANT CHROMOSOMAL POSITION
chr13:49037966

VARIANT ALLELE FREQUENCY (% VAF)
46.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data[262] and strong preclinical data[263-266], RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer (SCLC). A clinical study evaluating the Aurora kinase A inhibitor alisertib for patients with prostate cancer did not find an association between RB1 deletion and clinical benefit[267]. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members[268] and activation of the NOTCH pathway[269].

FREQUENCY & PROGNOSIS

In the TCGA datasets, RB1 mutation or homozygous deletion was observed in 9% of glioblastomas[82] and 2.5% of lower grade glioma cases[181]. In one study, loss of RB1 transcript expression was observed in 10.6% of glioblastomas and occurred more frequently in the proneural subtype[270]. One study reports that mutation of RB1 is correlated with shorter survival in glioblastoma patients[271]. Several studies suggest that RB1, PTEN, and/or TP53 mutations are early events in the development of glioblastoma[272-274].

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[275-276]. Alterations such as seen here may disrupt RB1 function or expression[277-283].

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[284]. Germline mutations in RB1 account for approximately 40% of RB tumors[285] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[286-287]. In the appropriate clinical context, germline testing of RB1 is recommended.

GENE
TERT

ALTERATION
promoter -146C>T

TRANSCRIPT ID
NM_198253.2

CODING SEQUENCE EFFECT
-146C>T

VARIANT CHROMOSOMAL POSITION
chr5:1295250

VARIANT ALLELE FREQUENCY (% VAF)
35.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[288]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[289]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[290].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[291-292], most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas[291-295]. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)[291,293]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[87]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[296]. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM[291,293,296-297]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v1.2022).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[298]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[299-301]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[302-304], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[302].

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v1.2022)[305]. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v1.2022)[105].

Electronically signed by Erik Williams, M.D. | 23 January 2023
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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
TP53

ALTERATION
V272M

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
814G>A

VARIANT CHROMOSOMAL POSITION
chr17:7577124

VARIANT ALLELE FREQUENCY (% VAF)
61.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[306-309] or p53 gene therapy such as SGT53[310-314]. 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[315]. 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[316]. 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[317]. 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[318]. 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[319]. 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[320]. 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[321]. 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[314]. 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[322]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[323].

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[132,324]. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations[87]. 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[325-330]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[331]. 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[87]. 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[332].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[333]. Alterations such as seen here may disrupt TP53 function or expression[334-338].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[339]. 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[340-342], including sarcomas[343-344]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[345] to 1:20,000[344]. 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[346]. 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[347-352]. 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[347-348]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[353]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[351,354-355]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Cetuximab

Assay findings association

EGFR
EGFRvIII, amplification

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[76].

SUPPORTING DATA

A Phase 2 trial of cetuximab with the anti-VEGF monoclonal antibody bevacizumab for patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone[356]. However, another Phase 2 study demonstrated that for patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly longer PFS and numerical (although not statistically significant) improvement in OS[95]. In addition, a case report for an EGFR-amplified patient with GBM treated with cetuximab using intraarterial cerebral infusion (SIACI) in combination with chemotherapy reported a stable response without recurrence at 6 months[357].

Osimertinib

Assay findings association

EGFR
EGFRvIII, amplification

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 21 L858R mutations, or T790M mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[358-362] . On the basis of clinical responses to the third-generation TKI osimertinib for patients with EGFR-rearranged glioma, EGFRvIII and activating rearrangements may confer sensitivity to osimertinib[65,363] . However, a case study of a patient with multiple glioblastoma tumors reported that the tumor harboring EGFRvIII and EGFR amplification did not respond to osimertinib[66].

SUPPORTING DATA

Clinical benefit from osimertinib has been observed for cases of pediatric and adult patients with EGFR-altered glioma[65-66,363-365] . Osimertinib has been studied primarily for the treatment of EGFR-mutated NSCLC. A Phase 2 trial of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with untreated advanced non-small cell lung cancer (NSCLC) harboring EGFR del19 or L858R reported no difference in ORR (82% vs 86%) and median PFS (22.1 vs 20.2 months, HR 0.862 p=0.213)[366]. The Phase 2 BOOSTER study of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with advanced NSCLC with EGFR-sensitizing mutations (exon 19 del or L858R) and L790M at progression on prior EGFR TKI reported no difference in ORR (55% vs 55%), median OS (24.0 vs 24.3 months, HR 1.03 p=0.91), or median PFS (15.4 vs 12.3 months, HR 0.96 p=0.83), although improved PFS was observed for the combination in the subgroup of current or former smokers (16.5 vs 8.4, HR 0.52) while nonsmokers had no benefit (HR 1.47)[367]. The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated NSCLC reported ORRs of 42% (15/36), 44% (8/18), and 44% (10/23), respectively[368].

Panitumumab

Assay findings association

EGFR
EGFRvIII, amplification

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[76].

SUPPORTING DATA

A Phase 1 trial of EnGeneIC delivery vehicle (EDV) targeting EGFR with panitumumab in combination with doxorubicin for 14 patients with glioblastoma (GBM) reported no responses and 28% (4/14) SDs[369].

Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer[370-372] and has been investigated in a variety of other tumor types. For patients with head and neck squamous cell carcinoma (HNSCC), data are conflicting; some trials of panitumumab in various lines and with different chemotherapy combinations have shown modest benefit[373-375] and others have reported no benefit[376-378] . A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility[379].

Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)[380-381] ; biliary tract cancers, including cholangiocarcinoma[382-383] ; and renal cell carcinoma (RCC)[384].

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

EGFR

ALTERATION

EGFRvIII, amplification

RATIONALE

EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRPα, in Subjects With Advanced Solid and Hematologic Cancers

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Seoul (Korea, Republic of), Heidelberg (Australia), Melbourne (Australia), Manchester (United Kingdom), Edmonton (Canada), Rouen (France), Oregon, Marseille (France), Creteil (France), Nantes Cedex 01 (France)

NCT04946968

PHASE 2

Phase-2 Dacomitinib Study on Patients With EGFR-Driven Advanced Solid Tumours With Low EGFR-AS1 lncRNA Expr or Other Novel Emerging Biomarkers

TARGETS
ERBB4, EGFR, ERBB2

LOCATIONS: Singapore (Singapore)

NCT04616196

PHASE 1/2

Study of NKTR 255 in Combination With Cetuximab in Solid Tumors

TARGETS
EGFR

LOCATIONS: California, Montana, Arizona, Minnesota, Illinois, Michigan, Texas, New York

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

NCT02800486

PHASE 2

Super Selective Intra-arterial Repeated Infusion of Cetuximab (Erbitux) With Reirradiation for Treatment of Relapsed/Refractory GBM, AA, and AOA

TARGETS
EGFR

LOCATIONS: New York

NCT02861898

PHASE 1/2

Super-selective Intra-arterial Repeated Infusion of Cetuximab for the Treatment of Newly Diagnosed Glioblastoma

TARGETS
EGFR

LOCATIONS: New York

NCT04670679

PHASE 1

A Dose Escalation/Expansion Study of ERAS-601 in Patients With Advanced or Metastatic Solid Tumors

TARGETS
SHP2, EGFR

LOCATIONS: Perth (Australia), Melbourne (Australia), Nevada, California, Texas, Massachusetts, New York, Tennessee, Florida

NCT04547777

PHASE 1

Phase 1 Trial of D2C7-IT in Combination With 2141-V11 for Recurrent Malignant Glioma

TARGETS
EGFRvIII, CD40

LOCATIONS: North Carolina

GENE
PIK3CA

ALTERATION
C420R - subclonal

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha, RAFs, NRAS

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

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)

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, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

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

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (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)

NCT04317105

PHASE 1/2

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Texas, Virginia

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
PTEN

ALTERATION
loss

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

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04740190

PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

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), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT05035745

PHASE 1/2

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

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04614909

PHASE NULL

Phase 0/2 Study of Pamiparib in Newly Diagnosed and rGBM

TARGETS
PARP

LOCATIONS: Arizona

NCT05076513

PHASE NULL

Trial of Niraparib in Participants With Newly-diagnosed Glioblastoma and Recurrent Glioma

TARGETS
PARP

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)

NCT03212742

PHASE 1/2

Phase I/IIa Study of Concomitant Radiotherapy With Olaparib and Temozolomide in Unresectable High Grade Gliomas Patients

TARGETS
PARP

LOCATIONS: Paris (France), Lyon (France), Caen (France), Toulouse (France), Bordeaux (France)

NCT04317105

PHASE 1/2

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Texas, Virginia

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.

ABL1
T984M

CUL3
R688S

FGFR3
R238Q

NOTCH3
N1597K

PDCD1 (PD-1)
D212N

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. 2022. 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) 7.4.0

The median exon coverage for this sample is 842x

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Martinez R, et al. Oncology (2004) pmid: 15331927
7. Martinez R, et al. J. Cancer Res. Clin. Oncol. (2005) pmid: 15672285
8. Martinez R, et al. Cancer Genet. Cytogenet. (2007) pmid: 17498554
9. Szybka M, et al. Clin. Neuropathol. () pmid: 12908754
10. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
11. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
12. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
13. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
14. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
15. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
16. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
17. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
18. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
19. Cristescu R, et al. Science (2018) pmid: 30309915
20. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
21. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
22. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
23. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
24. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
25. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
26. Zhao J, et al. Nat. Med. (2019) pmid: 30742119
27. Touat M, et al. Nature (2020) pmid: 32322066
28. Bouffet E, et al. J. Clin. Oncol. (2016) pmid: 27001570
29. Johanns TM, et al. Cancer Discov (2016) pmid: 27683556
30. Lukas RV, et al. J. Neurooncol. (2018) pmid: 30073642
31. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
32. Patel RR, et al. Pediatr Blood Cancer (2020) pmid: 32386112
33. Johnson A, et al. Oncologist (2017) pmid: 28912153
34. Draaisma K, et al. Acta Neuropathol Commun (2015) pmid: 26699864
35. Wang L, et al. BMC Cancer (2020) pmid: 32164609
36. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
37. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
38. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
39. Rizvi NA, et al. Science (2015) pmid: 25765070
40. Johnson BE, et al. Science (2014) pmid: 24336570
41. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
42. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
43. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
44. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
45. Nature (2012) pmid: 22810696
46. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
47. van den Bent MJ, et al. J Clin Oncol (2009) pmid: 19204207
48. Haas-Kogan DA, et al. J Natl Cancer Inst (2005) pmid: 15956649
49. Brown PD, et al. J Clin Oncol (2008) pmid: 18955445
50. Preusser M, et al. J Neurooncol (2008) pmid: 18458820
51. Wen PY, et al. Neuro-oncology (2014) pmid: 24470557
52. Gallego O, et al. J Neurooncol (2014) pmid: 24352766
53. Uhm JH, et al. Int J Radiat Oncol Biol Phys (2011) pmid: 20510539
54. Doyle SP, et al. Oxf Med Case Reports (2018) pmid: 30410775
55. D'Alessandris QG, et al. Acta Neurochir (Wien) (2013) pmid: 23132371
56. Custodio A, et al. Clin Transl Oncol (2010) pmid: 20462843
57. D'Alessandris QG, et al. Acta Neurochir (Wien) (2018) pmid: 30306271
58. Mellinghoff IK, et al. N. Engl. J. Med. (2005) pmid: 16282176
59. Mellinghoff IK, et al. Clin Cancer Res (2007) pmid: 17255257
60. Arif SH, et al. Asian J Neurosurg () pmid: 29492119
61. Reardon DA, et al. Neuro-oncology (2015) pmid: 25140039
62. Alshami J, et al. Oncotarget (2015) pmid: 26423602
63. Sepúlveda-Sánchez JM, et al. Neuro-oncology (2017) pmid: 28575464
64. Chi AS, et al. JCO Precis Oncol (2020) pmid: 32923886
65. Cardona AF, et al. J Neurooncol (2021) pmid: 34498213
66. Makhlin I, et al. CNS Oncol (2019) pmid: 31769726
67. Chagoya G, et al. Oncotarget (2020) pmid: 32547705
68. Gao M, et al. Cancer Res (2021) pmid: 33910930
69. Reardon DA, et al. Clin Cancer Res (2020) pmid: 32034072
70. Weller M, et al. Lancet Oncol (2017) pmid: 28844499
71. Tanaka S, et al. Sci Rep (2019) pmid: 30644426
72. Blumenthal DT, et al. J. Neurooncol. (2016) pmid: 27531351
73. Franceschi E, et al. Br. J. Cancer (2007) pmid: 17353924
74. Chakravarti A, et al. Int. J. Radiat. Oncol. Biol. Phys. (2013) pmid: 23182702
75. Hegi ME, et al. Mol. Cancer Ther. (2011) pmid: 21471286
76. Jiang Z, et al. PLoS ONE (2013) pmid: 23441167
77. Licitra L, et al. Ann. Oncol. (2011) pmid: 21048039
78. Smyth EC, et al. Gut (2021) pmid: 33199443
79. Lassman et al., 2019; Neuro-Oncology Abstract ACTR-21
80. Van Den Bent M, et al. Neuro Oncol (2020) pmid: 31747009
81. Jonsson P, et al. Clin. Cancer Res. (2019) pmid: 31263031
82. Brennan CW, et al. Cell (2013) pmid: 24120142
83. Ceccarelli M, et al. Cell (2016) pmid: 26824661
84. Thomas AA, et al. Neuro-oncology (2017) pmid: 28472509
85. Lee JC, et al. PLoS Med. (2006) pmid: 17177598
86. Vivanco I, et al. Cancer Discov (2012) pmid: 22588883
87. Yan et al. 2020; DOI:10.1200/PO.19.00385
88. Nishikawa R, et al. Proc. Natl. Acad. Sci. U.S.A. (1994) pmid: 8052651
89. Shinojima N, et al. Cancer Res. (2003) pmid: 14583498
90. Nishikawa R, et al. Brain Tumor Pathol (2004) pmid: 15700833
91. Viana-Pereira M, et al. Anticancer Res. () pmid: 18507036
92. Yoshimoto K, et al. Clin. Cancer Res. (2008) pmid: 18223223
93. Larysz D, et al. Folia Neuropathol (2011) pmid: 21455841
94. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
95. Lv S, et al. Int. J. Oncol. (2012) pmid: 22752145
96. Srividya MR, et al. J. Clin. Pathol. (2010) pmid: 20702468
97. Das P, et al. J Clin Neurosci (2011) pmid: 20888234
98. Smith JS, et al. J. Natl. Cancer Inst. (2001) pmid: 11504770
99. Montano N, et al. Neoplasia (2011) pmid: 22241957
100. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
101. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
102. Bhargava R, et al. Mod. Pathol. (2005) pmid: 15920544
103. Yang YL, et al. Chin. Med. J. (2012) pmid: 22490401
104. Nedergaard MK, et al. BioDrugs (2012) pmid: 22385404
105. Louis DN, et al. Neuro Oncol (2021) pmid: 34185076
106. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
107. Juric D, et al. J. Clin. Oncol. (2018) pmid: 29401002
108. Gallant JN, et al. NPJ Precis Oncol (2019) pmid: 30793038
109. Delestre F, et al. Sci Transl Med (2021) pmid: 34613809
110. Morschhauser F, et al. Mol Cancer Ther (2020) pmid: 31619463
111. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
112. Santin AD, et al. Gynecol Oncol Rep (2020) pmid: 31934607
113. Damodaran S, et al. J Clin Oncol (2022) pmid: 35133871
114. André F, et al. N. Engl. J. Med. (2019) pmid: 31091374
115. Smyth LM, et al. NPJ Breast Cancer (2021) pmid: 33863913
116. Varnier R, et al. Eur J Cancer (2019) pmid: 31351267
117. Basse C, et al. JCO Precis Oncol (2018) pmid: 32914004
118. Sultova E, et al. Arch Gynecol Obstet (2021) pmid: 33277683
119. Mackay HJ, et al. Cancer (2014) pmid: 24166148
120. Myers AP, et al. Gynecol. Oncol. (2016) pmid: 27016228
121. Dhami J, et al. Cold Spring Harb Mol Case Stud (2018) pmid: 29588307
122. Harris EJ, et al. Front Oncol (2019) pmid: 30863722
123. Hanna GJ, et al. Clin Cancer Res (2018) pmid: 29301825
124. Krop et al., 2018; ASCO Abstract 101
125. Pascual J, et al. Cancer Discov (2021) pmid: 32958578
126. Dolly SO, et al. Clin. Cancer Res. (2016) pmid: 26787751
127. Canaud et al., 2021; ESMO Abstract LBA23
128. Gallia GL, et al. Mol. Cancer Res. (2006) pmid: 17050665
129. Broderick DK, et al. Cancer Res. (2004) pmid: 15289301
130. El-Habr EA, et al. Clin. Neuropathol. () pmid: 20569675
131. Derakhshandeh-Peykar P, et al. J. Neurogenet. (2011) pmid: 22026810
132. Nature (2008) pmid: 18772890
133. Tanaka S, et al. Acta Neuropathol Commun (2019) pmid: 31036078
134. Samuels Y, et al. Cancer Cell (2005) pmid: 15950905
135. Nat. Rev. Cancer (2009) pmid: 19629070
136. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15647370
137. Ikenoue T, et al. Cancer Res. (2005) pmid: 15930273
138. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17376864
139. Horn S, et al. Oncogene (2008) pmid: 18317450
140. Rudd ML, et al. Clin. Cancer Res. (2011) pmid: 21266528
141. Hon WC, et al. Oncogene (2012) pmid: 22120714
142. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22949682
143. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
144. Laurenti R, et al. Rev Saude Publica (1990) pmid: 2103068

145. Dan S, et al. Cancer Res. (2010) pmid: 20530683
146. Oda K, et al. Cancer Res. (2008) pmid: 18829572
147. Zhao L, et al. Oncogene (2008) pmid: 18794883
148. Lui VW, et al. Cancer Discov (2013) pmid: 23619167
149. Ross RL, et al. Oncogene (2013) pmid: 22430209
150. Rivière JB, et al. Nat. Genet. (2012) pmid: 22729224
151. Shibata T, et al. Cancer Lett. (2009) pmid: 19394761
152. Dogruluk T, et al. Cancer Res. (2015) pmid: 26627007
153. Croessmann S, et al. Clin. Cancer Res. (2018) pmid: 29284706
154. Ng PK, et al. Cancer Cell (2018) pmid: 29533785
155. Spangle JM, et al. (2020) pmid: 32929011
156. Chen L, et al. Nat Commun (2018) pmid: 29636477
157. Jin N, et al. J Clin Invest (2021) pmid: 34779417
158. Courtney KD, et al. J. Clin. Oncol. (2010) pmid: 20085938
159. Simpson L, et al. Exp. Cell Res. (2001) pmid: 11237521
160. Milella M, et al. Sci Rep (2017) pmid: 28220839
161. Galanis E, et al. J. Clin. Oncol. (2005) pmid: 15998902
162. Kreisl TN, et al. J. Neurooncol. (2009) pmid: 19018475
163. Mason WP, et al. Invest New Drugs (2012) pmid: 22160854
164. Mendes-Pereira AM, et al. EMBO Mol Med (2009) pmid: 20049735
165. Shen Y, et al. Clin. Cancer Res. (2013) pmid: 23881923
166. Chatterjee P, et al. PLoS ONE (2013) pmid: 23565244
167. McCormick A, et al. Int. J. Gynecol. Cancer (2016) pmid: 26905328
168. Forster MD, et al. Nat Rev Clin Oncol (2011) pmid: 21468130
169. Eikesdal HP, et al. Ann Oncol (2021) pmid: 33242536
170. Dougherty et al., 2014; ASCO Abstract 5536
171. Pan M, et al. Perm J (2021) pmid: 33970096
172. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
173. Romero I, et al. Gynecol Oncol (2020) pmid: 32988624
174. Zhou XP, et al. Int. J. Cancer (1999) pmid: 10096247
175. Rasheed BK, et al. Cancer Res. (1997) pmid: 9331072
176. Davies MP, et al. Br. J. Cancer (1999) pmid: 10188904
177. Lin H, et al. Clin. Cancer Res. (1998) pmid: 9796977
178. Schmidt EE, et al. J. Neuropathol. Exp. Neurol. (1999) pmid: 10560660
179. Kato H, et al. Clin. Cancer Res. (2000) pmid: 11051241
180. Furnari FB, et al. Genes Dev. (2007) pmid: 17974913
181. Cancer Genome Atlas Research Network, et al. N. Engl. J. Med. (2015) pmid: 26061751
182. Sano T, et al. Cancer Res. (1999) pmid: 10213484
183. Srividya MR, et al. Neuropathology (2011) pmid: 21134002
184. Campbell RB, et al. J. Biol. Chem. (2003) pmid: 12857747
185. Rodríguez-Escudero I, et al. Hum. Mol. Genet. (2011) pmid: 21828076
186. He X, et al. Cancer Res. (2013) pmid: 23475934
187. Han SY, et al. Cancer Res. (2000) pmid: 10866302
188. Myers MP, et al. Proc. Natl. Acad. Sci. U.S.A. (1998) pmid: 9811831
189. Pradella LM, et al. BMC Cancer (2014) pmid: 24498881
190. Kim JS, et al. Mol. Cell. Biol. (2011) pmid: 21536651
191. Denning G, et al. Oncogene (2007) pmid: 17213812
192. Hlobilkova A, et al. Anticancer Res. () pmid: 16619501
193. Redfern RE, et al. Protein Sci. (2010) pmid: 20718038
194. Shenoy S, et al. PLoS ONE (2012) pmid: 22505997
195. Wang Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19329485
196. Okumura K, et al. J. Biol. Chem. (2006) pmid: 16829519
197. Lee JO, et al. Cell (1999) pmid: 10555148
198. Maxwell GL, et al. Cancer Res. (1998) pmid: 9635567
199. Risinger JI, et al. Clin. Cancer Res. (1998) pmid: 9865913
200. Fenton TR, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22891331
201. Ngeow J, et al. J. Clin. Endocrinol. Metab. (2012) pmid: 23066114
202. Lobo GP, et al. Hum. Mol. Genet. (2009) pmid: 19457929
203. Liu J, et al. Oncogene (2014) pmid: 23995781
204. Maehama T, et al. Annu. Rev. Biochem. (2001) pmid: 11395408
205. De Vivo I, et al. J. Med. Genet. (2000) pmid: 10807691
206. Ramaswamy S, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10051603
207. Liu JL, et al. Mol. Cell. Biol. (2005) pmid: 15988030
208. Karoui M, et al. Br. J. Cancer (2004) pmid: 15026806
209. Gil A, et al. PLoS ONE (2015) pmid: 25875300
210. Furnari FB, et al. Cancer Res. (1998) pmid: 9823298
211. Spinelli L, et al. J. Med. Genet. (2015) pmid: 25527629
212. Mingo J, et al. Eur. J. Hum. Genet. (2018) pmid: 29706633
213. Wang Q, et al. J. Mol. Graph. Model. (2010) pmid: 20538496
214. Andrés-Pons A, et al. Cancer Res. (2007) pmid: 17942903
215. Butler MG, et al. J. Med. Genet. (2005) pmid: 15805158
216. Georgescu MM, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10468583
217. Staal FJ, et al. Br. J. Cancer (2002) pmid: 12085208
218. Nguyen HN, et al. Oncogene (2014) pmid: 24292679
219. Rahdar M, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19114656
220. Das S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808147
221. Wang X, et al. Biochem. J. (2008) pmid: 18498243
222. Valiente M, et al. J. Biol. Chem. (2005) pmid: 15951562
223. Nguyen HN, et al. Oncogene (2015) pmid: 25263454
224. Shan L, et al. Cell Discov (2020) pmid: 32704382
225. Blumenthal GM, et al. Eur. J. Hum. Genet. (2008) pmid: 18781191
226. Orloff MS, et al. Oncogene (2008) pmid: 18794875
227. Zbuk KM, et al. Nat. Rev. Cancer (2007) pmid: 17167516
228. Villa-Morales M, et al. Expert Opin. Ther. Targets (2012) pmid: 22239437
229. Abramson JS, et al. Blood (2005) pmid: 15855278
230. Debatin KM, et al. Oncogene (2004) pmid: 15077156
231. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
232. Gao J, et al. Sci Signal (2013) pmid: 23550210
233. Rao VK, et al. Blood (2011) pmid: 21885601
234. Straus SE, et al. Blood (2001) pmid: 11418480
235. Dowdell KC, et al. Blood (2010) pmid: 20360470
236. Prickett TD, et al. Nat. Genet. (2011) pmid: 21946352
237. Jayachandran et al., 2022; ASCO GI Abstract 177
238. Shain AH, et al. Nat. Genet. (2015) pmid: 26343386
239. Hodis E, et al. Cell (2012) pmid: 22817889
240. Krauthammer M, et al. Nat. Genet. (2012) pmid: 22842228
241. George J, et al. Nature (2015) pmid: 26168399
242. Rudin CM, et al. Nat. Genet. (2012) pmid: 22941189
243. Nature (2012) pmid: 22960745
244. Nature (2014) pmid: 25079317
245. Cherlyn SY, et al. Neurosci Biobehav Rev (2010) pmid: 20060416
246. Lencer R, et al. Eur Arch Psychiatry Clin Neurosci (2014) pmid: 24682224
247. Casey JP, et al. Hum. Genet. (2012) pmid: 21996756
248. O'Brien NL, et al. Psychiatr. Genet. (2014) pmid: 25046171
249. Wolen AR, et al. PLoS ONE (2012) pmid: 22511924
250. Perrotti D, et al. Lancet Oncol. (2013) pmid: 23639323
251. Cristóbal I, et al. Mol. Cancer Ther. (2014) pmid: 24448818
252. Saddoughi SA, et al. EMBO Mol Med (2013) pmid: 23180565
253. Baldacchino S, et al. EPMA J (2014) pmid: 24460909
254. Chen W, et al. Gastroenterol Res Pract (2013) pmid: 24307892
255. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
256. Kuhn E, et al. J. Natl. Cancer Inst. (2012) pmid: 22923510
257. McConechy MK, et al. J. Pathol. (2012) pmid: 22653804
258. Wurzenberger C, et al. Nat. Rev. Mol. Cell Biol. (2011) pmid: 21750572
259. Shih IeM, et al. Am. J. Pathol. (2011) pmid: 21435433
260. McConechy MK, et al. J. Pathol. (2011) pmid: 21381030
261. Zhao S, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23359684
262. Owonikoko et al., 2016; ESMO Abstract 14230
263. Hook KE, et al. Mol. Cancer Ther. (2012) pmid: 22222631
264. Gong X, et al. Cancer Discov (2019) pmid: 30373917
265. Oser MG, et al. Cancer Discov (2019) pmid: 30373918
266. Yang W, et al. Kaohsiung J Med Sci (2022) pmid: 34741392
267. Beltran H, et al. Clin. Cancer Res. (2019) pmid: 30232224
268. Allaman-Pillet N, et al. Ophthalmic Genet. () pmid: 21955141
269. Viatour P, et al. J. Exp. Med. (2011) pmid: 21875955
270. Goldhoff P, et al. J. Neuropathol. Exp. Neurol. (2012) pmid: 22157621
271. Bäcklund LM, et al. Clin. Cancer Res. (2003) pmid: 14519639
272. Chow LM, et al. Cancer Cell (2011) pmid: 21397855
273. Nobusawa S, et al. Brain Pathol. (2010) pmid: 20406234
274. Deighton RF, et al. Brain Pathol. (2010) pmid: 20175778
275. Burkhart DL, et al. Nat. Rev. Cancer (2008) pmid: 18650841
276. Knudsen ES, et al. Nat. Rev. Cancer (2008) pmid: 19143056
277. Berge EO, et al. Mol. Cancer (2010) pmid: 20594292
278. Giacinti C, et al. Oncogene (2006) pmid: 16936740
279. Otterson GA, et al. Proc. Natl. Acad. Sci. U.S.A. (1997) pmid: 9342358
280. Otterson GA, et al. Am. J. Hum. Genet. (1999) pmid: 10486322
281. Qin XQ, et al. Genes Dev. (1992) pmid: 1534305
282. Rubin SM, et al. Cell (2005) pmid: 16360038
283. Sun H, et al. Mol. Cell. Biol. (2006) pmid: 16449662
284. Chen Z, et al. Hum. Mutat. (2014) pmid: 24282159
285. Yun J, et al. Int J Ophthalmol (2011) pmid: 22553621
286. Houston SK, et al. Int Ophthalmol Clin (2011) pmid: 21139478
287. Ng AK, et al. Semin Radiat Oncol (2010) pmid: 19959033
288. Nat Rev Clin Oncol (2017) pmid: 27245281
289. Duperret EK, et al. Mol Ther (2018) pmid: 29249395
290. Chiappori AA, et al. Ann Oncol (2015) pmid: 25467017
291. Killela PJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23530248
292. Killela PJ, et al. Oncotarget (2014) pmid: 24722048
293. Nonoguchi N, et al. Acta Neuropathol. (2013) pmid: 23955565
294. Liu X, et al. Cell Cycle (2013) pmid: 23603989

295. Koelsche C, et al. Acta Neuropathol. (2013) pmid: 24154961
296. Arita H, et al. Acta Neuropathol. (2013) pmid: 23764841
297. Reitman ZJ, et al. Acta Neuropathol. (2013) pmid: 24217890
298. Shay JW, et al. Semin. Cancer Biol. (2011) pmid: 22015685
299. Shay JW, et al. Eur. J. Cancer (1997) pmid: 9282118
300. Kim NW, et al. Science (1994) pmid: 7605428
301. Hanahan D, et al. Cell (2000) pmid: 10647931
302. Horn S, et al. Science (2013) pmid: 23348503
303. Huang FW, et al. Science (2013) pmid: 23348506
304. Vinagre J, et al. Nat Commun (2013) pmid: 23887589
305. Weller M, et al. Nat Rev Clin Oncol (2021) pmid: 33293629
306. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
307. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
308. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
309. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
310. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
311. Xu L, et al. Mol. Med. (2001) pmid: 11713371
312. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
313. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
314. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
315. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
316. Moore et al., 2019; ASCO Abstract 5513
317. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
318. Oza et al., 2015; ASCO Abstract 5506
319. Lee J, et al. Cancer Discov (2019) pmid: 31315834
320. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
321. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
322. Gourley et al., 2016; ASCO Abstract 5571
323. Park H, et al. ESMO Open (2022) pmid: 36084396
324. Jha P, et al. Diagn. Mol. Pathol. (2011) pmid: 22089350
325. Uno M, et al. Cancer Lett. (2005) pmid: 15914282
326. Uno M, et al. Int. J. Biol. Markers () pmid: 16711514
327. Lass U, et al. PLoS ONE (2012) pmid: 22844452
328. Faria MH, et al. APMIS (2012) pmid: 23009112
329. Milinkovic V, et al. PLoS ONE (2013) pmid: 24358143
330. Galatro TF, et al. PLoS ONE (2013) pmid: 23613880
331. Schmidt MC, et al. J. Neuropathol. Exp. Neurol. (2002) pmid: 11939587
332. Nozaki M, et al. Neuro-oncology (1999) pmid: 11550308
333. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
334. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
335. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
336. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
337. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
338. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
339. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
340. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
341. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
342. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
343. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
344. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
345. Lalloo F, et al. Lancet (2003) pmid: 12672316
346. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
347. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
348. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
349. Xie M, et al. Nat. Med. (2014) pmid: 25326804
350. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
351. Severson EA, et al. Blood (2018) pmid: 29678827
352. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
353. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
354. Chabon JJ, et al. Nature (2020) pmid: 32269342
355. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
356. Hasselbalch B, et al. Neuro-oncology (2010) pmid: 20406901
357. Kulason KO, et al. J Exp Ther Oncol (2018) pmid: 29790314
358. Jänne PA, et al. N. Engl. J. Med. (2015) pmid: 25923549
359. Soria JC, et al. N. Engl. J. Med. (2018) pmid: 29151359
360. Alanazi A, et al. Lung Cancer Manag (2020) pmid: 33318755
361. Kim et al., 2021; DOI: 10.1200/PO.20.00296
362. Wang J, et al. Int. J. Cancer (2019) pmid: 30255937
363. Abousand et al., 2021; DOI: 10.26502/jcsct.5079114
364. Goyal A, et al. World Neurosurg (2021) pmid: 33940677
365. Mondal G, et al. Acta Neuropathol (2020) pmid: 32303840
366. Kenmotsu H, et al. J Thorac Oncol (2022) pmid: 35636696
367. Soo et al., 2021; ESMO Abstract VP3-2021
368. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298
369. Whittle JR, et al. J Clin Neurosci (2015) pmid: 26279503
370. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
371. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896
372. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
373. Vermorken JB, et al. Lancet Oncol (2013) pmid: 23746666
374. Wirth LJ, et al. Ann. Oncol. (2010) pmid: 19892746
375. Siano M, et al. Oncologist (2017) pmid: 28592616
376. Mesía R, et al. Lancet Oncol (2015) pmid: 25596660
377. Giralt J, et al. Lancet Oncol (2015) pmid: 25596659
378. Siu LL, et al. JAMA Oncol (2016) pmid: 27930762
379. Waddell T, et al. Lancet Oncol. (2013) pmid: 23594787
380. Crawford J, et al. J Thorac Oncol (2013) pmid: 24389433
381. Schuette W, et al. Clin Lung Cancer (2015) pmid: 26094080
382. Leone F, et al. Cancer (2016) pmid: 26540314
383. Vogel A, et al. Eur J Cancer (2018) pmid: 29413685
384. Rowinsky EK, et al. J. Clin. Oncol. (2004) pmid: 15210739