FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Tsai, Meng Hsiu	Brain anaplastic astrocytoma	16 Feb 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1560720-01

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 anaplastic astrocytoma
NAME Tsai, Meng Hsiu
DATE OF BIRTH 08 April 1971
SEX Male
MEDICAL RECORD # 44743808

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

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S112-02216 A (PF23012)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 17 January 2023
SPECIMEN RECEIVED 07 February 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.

IDH1 R132H
MET amplification
CCND2 amplification - equivocal†
CDK6 amplification
ATRX E1702fs*22
EPHB4 amplification - equivocal†
FGF14 amplification
FGF23 amplification - equivocal†
FGF6 amplification - equivocal†
KDM5A amplification - equivocal†
MSH3 rearrangement intron 20
TP53 R273C

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***ATRX*** **E1702fs*22** (p. 6), ***IDH1*** **R132H** (p. 4)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cabozantinib** (p. 11), **Capmatinib** (p. 11), **Crizotinib** (p. 12), **Ivosidenib** (p. 12), **Olutasidenib** (p. 12), **Tepotinib** (p. 13)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***IDH1*** **R132H** (p. 4)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***IDH1*** **R132H** (p. 4)

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)**
***IDH1* -** R132H	none	Ivosidenib
10 Trials see p. 18		Olutasidenib
***MET* -** amplification	none	Cabozantinib
		Capmatinib
		Crizotinib
6 Trials see p. 20		Tepotinib
***CCND2* -** amplification - equivocal	none	none
8 Trials see p. 14		

Electronically signed by Erik Williams, M.D. | 16 February 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CDK6 **-** amplification	none	none
9 Trials see p. 16		

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

MSI-High has been reported in 3-8% of adult or pediatric astrocytomas and was generally not associated with Lynch syndrome[6-8]. Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[9-11]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[9], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[12]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[9], in GBMs with a previous lower grade astrocytoma[10], and in giant cell GBM compared to classic GBM[11].

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[13]. 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[13-15]. 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[16-18]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[13,15,17-18].

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[19-21], anti-PD-1 therapies[19-22], and combination nivolumab and ipilimumab[23-28]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[19,29-30]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[31-32] or anti-PD-L1[33] 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

Anaplastic astrocytoma harbors a median TMB of 1.8 mutations per megabase (muts/Mb), and 2% of cases have high TMB (>20 muts/Mb)[34]. 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[35-36]. Increased TMB has been reported to correlate with higher tumor grade in glioma[37] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[31], as well as with shorter OS of patients with diffuse glioma[38].

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[39-40] and cigarette smoke in lung cancer[41-42], treatment with temozolomide-based chemotherapy in glioma[43-44], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[45-49], and microsatellite instability (MSI)[45,48-49]. 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[19,29-33].

GENE
IDH1

ALTERATION
R132H

TRANSCRIPT ID
NM_005896.2

CODING SEQUENCE EFFECT
395G>A

VARIANT CHROMOSOMAL POSITION
chr2:209113112

VARIANT ALLELE FREQUENCY (% VAF)
48.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib[50] and olutasidenib[51]. A Phase 1B/2 basket study of the IDH1 inhibitor olutasidenib reported a DCR of 48% (12/25, 2 PR) in patients with glioma; patients with other solid tumors including intrahepatic cholangiocarcinoma and chondrosarcoma achieved SD[51]. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)[52]. Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors[53-56]. In a Phase 1 trial of the PD-L1 inhibitor atezolizumab for patients with glioblastoma (GBM), 2/3 patients with IDH1-mutated tumors experienced clinical benefit (1 PR, 1 long-term SD, 1 short-term SD), whereas none of the 8 patients with IDH1-wildtype GBM experienced benefit (8/8 PD); significantly longer PFS and a trend toward longer OS were observed for patients with IDH1-mutated tumors compared with the patients with IDH1-wildtype tumors[33]. A Phase 1 trial of the oral brain-penetrant mutated IDH1 selective inhibitor DS-1001 for patients with recurrent or progressive IDH1-mutated glioma reported 2 CRs and 4 PRs for 35 patients with enhancing tumors and 1 PR and 3 minor responses (MRs) for 12 patients with non-enhancing tumors[57]. Preclinical data indicate that IDH1-mutated glioma may be sensitive to the glutaminase inhibitor telaglenastat in combination with radiotherapy[58].

— Nontargeted Approaches —

IDH1/2 mutations are associated with improved survival outcomes for patients with glioma treated with radiation or alkylating chemotherapy (NCCN CNS Cancers Guidelines, v1.2022). Addition of procarbazine, lomustine, and vincristine (PCV) to radiotherapy significantly improved OS for patients with IDH-mutated (9.4 vs. 5.7 years, HR=0.59) but not IDH-non-mutated (1.3 versus 1.8 years, HR=1.14) anaplastic oligodendroglioma/oligoastrocytoma[59]. As adjuvant therapy after radiation for patients with IDH1/2-mutated anaplastic astrocytoma, temozolomide[60] or PCV[61] improved median PFS and median OS relative to radiotherapy or temozolomide alone, respectively.

FREQUENCY & PROGNOSIS

IDH1 mutation is characteristic of low-grade gliomas and secondary glioblastoma, and is relatively rare in primary glioblastoma[62-66]. In the TCGA datasets, IDH1 mutation has been found in 77% of lower grade glioma cases and in 5% of glioblastoma cases[67-68]. IDH1 mutations are highly prevalent in grade 2 and grade 3 astrocytoma, oligodendroglioma, and oligoastrocytoma, reported in 43-100% of grade 2 tumors and 45-93% of grade 3 tumors[69-72]. IDH1/2 mutations are a strong favorable prognostic marker for OS in Grade 2-3 glioma, particularly in combination with 1p/19q codeletion (NCCN CNS Cancers Guidelines, v1.2022). Several studies have found IDH1 mutations to be associated with improved prognosis and longer PFS and OS in patients with various types of glioma including anaplastic astrocytoma and GBM[66,73-79].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis[80]. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer[80-84]. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)[82-86], which promotes tumorigenesis[82,87-90].

POTENTIAL DIAGNOSTIC IMPLICATIONS

IDH mutation in the absence of TERT mutation is suggestive of astrocytoma (NCCN CNS Cancers Guidelines, v1.2022)[91]. IDH1/2 mutation is associated with Grade 2 and 3 astrocytomas and oligodendrogliomas, with the latter also harboring 1p19q deletion, and distinguishes secondary glioblastoma (GBM) from primary GBM (NCCN CNS Cancers Guidelines, v1.2022). ATRX mutations often co-occur with IDH1/2 mutations and may be indicative of Grade 2-3 astrocytoma or secondary glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v1.2022)[91-92].

GENE
MET

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. In a Phase 1b/2 trial for patients with MET-amplified recurrent glioblastoma, no responses were observed following treatment with capmatinib monotherapy (n=10) or capmatinib combined with buparlisib (n=33); patients in the combination therapy arm additionally harbored PTEN inactivating alterations[93]. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[94-97], gastroesophageal cancer[98], glioblastoma[99], and carcinoma of unknown primary[100]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified cholangiocarcinoma[101], as well as MET-amplified NSCLC, both as a monotherapy[102] and in combination with an EGFR TKI for patients with concurrent activating EGFR mutations[103-105]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[106] and NSCLC[107] as a monotherapy as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[108-110] . Savolitinib elicited responses for patients with MET-amplified gastric cancer either alone or in combination with docetaxel[111-112]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[113]. Patients with MET-amplified NSCLC[114] or MET-amplified gastric cancer[115] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[116]. The Phase 2 LUMINOSITY study of the MET antibody drug conjugate telisotuzumab vedotin (teliso-V) reported a 37% (19/52) ORR for patients with non-squamous EGFR-wildtype tumors; lower ORRs were observed for patients with squamous (11%, 3/27) or non-squamous EGFR-mutated (12%, 5/43) tumors[117]. A Phase 1 study showed that teliso-V plus osimertinib yielded an ORR of 56% (10/18) for patients with EGFR-mutated MET-overexpressing NSCLC who progressed on osimertinib, including ORRs of 56% (5/9) for patients with an EGFR L858R mutation and 67% (6/9) for those with an EGFR exon 19 deletion[118].

FREQUENCY & PROGNOSIS

In the glioblastoma multiforme (GBM) TCGA dataset, putative amplification of MET is reported in 2.5% of cases whereas MET mutation is reported in 0.4% of cases[68]. Lower level gain of MET has been reported in 47% and 44% of primary and secondary GBM, respectively, and in 38% of diffuse astrocytomas[119]. Multiple studies have reported MET expression to be associated with poor prognosis in patients with GBM[120-122]; however, one study reported improved overall survival in patients with GBM expressing MET relative to those negative for MET expression[123].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[124-125]. MET has been reported to be amplified in cancer[126], with amplification positively correlating with protein expression in some cancer types[127-131] and associating with therapeutic response to MET inhibitors in a variety of cancer types[94-96,98-100,132-133].

GENE
CCND2

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although preclinical studies suggest that cyclin D2 activates CDK4/6[134-135], it is unknown whether CCND2 amplification or activating mutation predicts response to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib. Clinical studies of CDK4/6 inhibitors have shown the most promise for estrogen receptor-positive breast cancer[136-137].

FREQUENCY & PROGNOSIS

In the TCGA dataset, CCND2 amplification was observed in 3% of glioblastoma cases[68] and 7% of lower grade glioma cases[67]. CCND2 amplification has been reported in 3% of primary malignant gliomas in one study, with amplification occurring in one anaplastic astrocytoma and two glioblastoma cases[138]. CCND2 mRNA expression has been reported to be increased in higher grade (3 and 4) astrocytoma tumors as compared to lower grade tumors[139]. Cyclin D2 has been reported to be the main cyclin expressed in glioblastoma stem cells (GSCs) but was barely detectable in differentiated glioblastoma cells[140]. Cyclin D2, in complex with CDK4/6, has been reported to be involved in the cell cycle progression of undifferentiated GSCs, but not differentiated GSCs, and to be involved in their tumorigenicity[140]. High CCND2 nuclear expression at the time of initial surgery for patients with glioblastoma was reported to significantly associate with early mortality in a multivariate analysis of 72 patients[141].

FINDING SUMMARY

CCND2 encodes the protein cyclin D2, which binds and regulates the cyclin-dependent kinases that control cell cycle progression, and is a downstream target of cancer signaling pathways including hedgehog and PI3K[142-143]. CCND2 has been reported to be amplified in cancer[126], and may be biologically relevant in this context[144-145].

GENE
CDK6

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Tumors with CDK6 activation may be sensitive to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[136,146-148]. Clinical benefit has been reported for patients with CDK6-amplified or mutated solid tumors in response to treatment with ribociclib[149-150] .

FREQUENCY & PROGNOSIS

CDK6 amplification was reported in 5% (2/37) of malignant astrocytomas but not in 13 low-grade astrocytomas in one study[151]. In the Glioblastoma Multiforme (GBM) TCGA dataset, CDK6 mutation has not been found, while putative CDK6 amplification has been reported in 3% of cases[68,152]. CDK6 amplification has also been reported in GBM in the scientific literature[153-155]. Studies have reported higher expression of CDK6 in high-grade gliomas than in low-grade gliomas[151,156-157]. Elevated CDK6 expression in glioblastoma tumor margins was associated with reduced survival[158].

Knockdown or inhibition of CDK6 was associated with reduced proliferation of GBM cells and reduced growth of GBM xenografts[158-159].

FINDING SUMMARY

CDK6 encodes cyclin-dependent kinase 6, which regulates the cell cycle, differentiation, senescence, and apoptosis[160-162]. CDK6 and its functional homolog CDK4 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[163-164]. Amplification of the chromosomal region that includes CDK6 has been reported in multiple cancer types, and has been associated with overexpression of CDK6 protein[165-166].

GENE
ATRX

ALTERATION
E1702fs*22

TRANSCRIPT ID
NM_000489.3

CODING SEQUENCE EFFECT
5104_5107delGAAA

VARIANT CHROMOSOMAL POSITION
chrX:76888721-76888725

VARIANT ALLELE FREQUENCY (% VAF)
82.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to directly address ATRX inactivation. Based on preclinical[167-168] and limited clinical data[169], ATRX alterations may confer sensitivity to combination strategies involving WEE1 inhibition. In a Phase 2 study evaluating the WEE1 inhibitor adavosertib plus irinotecan for the treatment of pediatric patients with neuroblastoma, prolonged SD was reported for 44% (4/9) of patients with ATRX-deficient tumors and responses were seen in two tumors that had evidence of ALT[169]. Preclinical evidence also suggests that ATRX deficiency may impart sensitivity to synthetic lethal approaches involving PARP inhibition and irinotecan[170], combined PARP and ATR inhibition[168], or double-strand break-induction with agents such as doxorubicin, irinotecan, and topotecan[171]; however, these approaches have not been demonstrated clinically.

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT[172]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[172-174], 12.6% of pheochromocytomas and paragangliomas[175], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[176-180]. ATRX loss in PNET[173,181] and melanoma[182] and mutation in other neuroendocrine tumors[175] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy[171]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[71,183-185] and has been proposed as a distinguishing biomarker[71,184-185]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[177-180]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation[71]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[186-187].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[188-189]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[172,187,190-191]. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function[192-194]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[188,195]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[196].

POTENTIAL DIAGNOSTIC IMPLICATIONS

ATRX mutations often co-occur with IDH1/2 mutations and may be indicative of Grade 2-3 astrocytoma or secondary glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v1.2022)[91-92].

GENE
EPHB4

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies available to target EPHB4 alterations in cancer. sEPHB4 is a soluble monomeric extracellular domain of EPHB4 that functions as an antagonist of EphrinB2-EPHB4 interaction[197], and fusion of sEPHB4 with human serum albumin (HSA) increases its stability[198]. Recombinant sEPHB4-HSA is under investigation in clinical trials. Preclinical studies have demonstrated that sEPHB4-HSA inhibits cell proliferation and xenograft tumor growth, including for cells expressing cancer-associated EPHB4 mutants or overexpressing wild-type EPHB4[197,199-203]. In addition, small-molecule inhibitors targeting multiple tyrosine kinases including EPHB4, such as JI-101 and XL647, have been under preclinical and clinical investigation[204-206].

FREQUENCY & PROGNOSIS

Increased EPHB4 mRNA and/or protein expression has been reported in a variety of cancer types, including head and neck squamous cell carcinoma (HNSCC)[207-210], gastric and esophageal[211-215], colorectal carcinoma (CRC)[216-222], breast[223-227], ovarian[227-229], endometrial[230-232], thyroid[233-235], lung[236-237], glioma[238-239], and other solid tumors[199,240-247]. In several of these studies, increased EPHB4 expression has been associated with clinicopathologic features, including disease stage[199,207,223,228-229,237,240,242], histological grade[213,223,230,239], and hormone receptor status[226,231]. High EPHB4 expression has been associated with inferior survival in multivariate analyses for patients with CRC treated with bevacizumab [hazard ratio (HR) = 5.95][221], HNSCC (HR = 2.95)[210], epithelial ovarian cancer (HR = 4.53)[227], or glioma (HR = 3.21)[239].

FINDING SUMMARY

EPHB4 encodes a member of the EPH family of receptor tyrosine kinases[248]. Ephrin signaling has been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration[249], and signaling between EPHB4 and its ligand EphrinB2 is particularly important for angiogenesis[250-251]. EPHB receptors, including EPHB4, have been shown to undergo dysregulation (amplification, mutation, under- or overexpression) in a number of different cancer types[252]. EPHB4 amplification has been reported in several solid tumor types[207-208,213,253-254] and was associated with advanced disease stage in head and neck squamous cell carcinoma (HNSCC)[207]. Activating missense mutations in or near the tyrosine kinase domain, including G723S, A742V, and P881S, have also been identified in lung cancer[203].

GENE
FGF14

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that address genomic alterations in FGF14.

FREQUENCY & PROGNOSIS

FGF14 mutations and amplification have each been found in 1-22% of samples for a variety of solid tumor types, whereas FGF14 deletion has been reported in 2% of prostate adenocarcinoma and 2% (1/48) diffuse large B-cell lymphoma cases (COSMIC, cBioPortal, 2023)[126,255-256]. The roles of FGF14 in cancer have not been extensively studied (PubMed, Jan 2023).

FINDING SUMMARY

FGF14 encodes an intracellular non-secretory fibroblast growth factor that plays roles in neural development[257-258]. Germline inactivating mutations in FGF14 cause a progressive autosomal dominant cerebellar ataxia[259-260]. FGF14 has been reported to be amplified in cancer[126] and may be biologically relevant in this context[144-145].

GENE
FGF23

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF23. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[261].

FREQUENCY & PROGNOSIS

FGF23 alterations have been reported with highest incidence in uterine carcinosarcoma (7.0%), ovarian carcinoma (6.5%), testicular germ cell cancer (5.4%), cutaneous melanoma (5.0%), low-grade glioma (4.9%), lung squamous cell carcinoma (4.5%), sarcoma (4.3%), colorectal adenocarcinoma (4.2%), lung adenocarcinoma (3.7%), and head and neck squamous cell carcinoma (3.4%) (cBioPortal, 2023)[126,255].

FINDING SUMMARY

FGF23 encodes a member of the fibroblast growth factor protein family that plays a central role in phosphate homeostasis[262]. Overexpression of FGF23 by tumor cells can cause hypophosphatemia through excessive renal phosphate clearance[263], while germline gain-of-function (protein stabilizing) mutations in FGF23 cause autosomal dominant hypophosphatemic rickets[264].

Electronically signed by Erik Williams, M.D. | 16 February 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

GENE
FGF6

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF6. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[261].

FREQUENCY & PROGNOSIS

Somatic alterations affecting FGF6 are infrequently documented, with the highest rates reported in penile cancer (4%), cutaneous melanoma (1-3%), stomach carcinoma (1-3%) and colorectal cancer (1%) (cBioPortal, COSMIC, 2023)[126,255-256]. Amplification of FGF6 has been frequently observed in testicular germ cell cancer (5%) and ovarian serous cystadenocarcinoma (5%), and in 2-6% of lower-grade gliomas, glioblastomas, sarcomas, breast invasive carcinomas, uterine carcinosarcomas, lung squamous cell carcinomas (SCC), head and neck SCC, pancreatic adenocarcinomas, and esophageal carcinomas (cBioPortal, 2023)[126,255]. FGF6 is co-localized with FGF23 and CCND2 at chromosomal locus 12p13 and has been reported to be co-amplified with these genes in 1.3% of patients with breast cancer[265]. FGF6 expression has been reported in 54% (14/26) of prostate cancer samples, which also frequently express FGFR4[266]. FGF6 expression has also been observed in 71% (12/17) of patients with childhood acute lymphoblastic leukemia[267].

FINDING SUMMARY

FGF6 (also known as HST-2) encodes a member of the fibroblast growth factor protein family and is hypothesized to play a role in muscle tissue regeneration[268] by signaling through FGFR4, and to a lesser extent FGFR1 and FGFR2[269]. FGF6 expression has been observed in several cancers[266-267,270] and was shown to be oncogenic in preclinical models[270-271]. FGF6 has been reported as amplified in cancer[126] and may be biologically relevant in this context[144-145].

GENE
KDM5A

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to directly address genomic alterations in KDM5A. However, multiple preclinical studies have identified potential targets in KDM5A amplified or activated cells that may respond to therapy. KDM5A-mediated chromatin remodeling induces CCND1 expression and represses CDKI expression[272-276]; therefore, KDM5A activation or amplification may sensitize cells to CDK4/CDK6 inhibitors. Drug-resistant cell populations, characterized by elevated KDM5A expression, responded to histone deacetylase (HDAC) inhibition[277], suggesting that HDAC inhibitors may be a potential therapeutic option. KDM5A also induces expression of VEGF and promotes angiogenesis, oncogenic transformation, and tumorigenesis, which can be inhibited by KDM5A knockdown[278-279], suggesting that tumors harboring KDM5A amplification may be sensitive to angiogenesis inhibitors, including kinase inhibitors that target the VEGF receptors, such as sunitinib, sorafenib, vandetanib, ponatinib, cabozantinib, regorafenib, pazopanib, and axitinib. However, these inhibitors have yet to be extensively tested in the context of KDM5A amplification or activation; therefore, it is not known if these therapeutic strategies are relevant.

FREQUENCY & PROGNOSIS

KDM5A amplification has been reported with the highest incidence in TCGA datasets in ovarian serous cystadenocarcinoma (7.2%), testicular germ cell cancer (5.8%), pancreatic adenocarcinoma (4.3%), and lung squamous cell carcinoma (3.9%) (cBioPortal, Jan 2023)[126,255]. Elevated levels of KDM5A expression have also been reported in a range of solid tumor types[273-274,276,278,280-281], and fusion of KDM5A to NUP98 has been documented in acute myeloid leukemia[282-283]. KDM5A expression is significantly correlated with HIF-1alpha and VEGF expression, as well as tumor size, angiogenesis, and poor patient prognosis in lung cancer[279].

FINDING SUMMARY

KDM5A encodes a lysine-specific histone demethylase that potentiates the expression of genes involved in cellular proliferation, senescence, angiogenesis, and migration[272-273,278,284-285]. KDM5A overexpression alters the transcriptional regulation of cell cycle genes, including CCND1, and a variety of cyclin-dependent kinase inhibitors (CDKIs), including CDKN1A, CDKN1B, and CDKN2A, and results in cell cycle progression[272-276,278]. Additionally, elevated KDM5A expression and associated chromatin remodeling has been implicated in resistance to various tyrosine kinase inhibitors in vitro, including erlotinib and gefitinib[277,280,286].

GENE
MSH3

ALTERATION
rearrangement intron 20

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted approaches to address MSH3 mutation or loss. However, preclinical studies in the context of MSH3-deficient cancer cells have demonstrated antitumor efficacy of DNA-PKcs inhibitors[287] and PARP inhibitors such as olaparib[288] and have shown increased chemosensitivity to cisplatin, oxaliplatin, and SN-38[288-289]. However, these remain to be tested clinically.

FREQUENCY & PROGNOSIS

MSH3 mutations have been reported with the highest incidence in endometrial (9.0%), stomach (3.6%), skin (3.4%), and CRC (1.9%) (cBioPortal, 2023)[126,255]. MSH3 loss has been reported with the highest incidence in ovarian serous cystadenocarcinoma (3.3%), prostate adenocarcinoma (2.6%), and esophageal adenocarcinoma (1.1%) (cBioPortal, 2023)[126,255]. MSH3 loss has been correlated with the late development and progression of a variety of sporadic cancers including lung, ovarian, bladder, breast, and colorectal tumors[290-295]. Consistent with this observation, studies have suggested that MSH3 loss increases chromosomal instability in p53-driven tumor models[296]. Certain germline polymorphisms in MSH3 have been associated with poor prognosis in CRC[295], HNSCC[297], non-small cell lung cancer (NSCLC)[298], and pancreatic cancer[299]. However, in one study of patients with MLH1-deficient CRC, MSH3 loss was associated with improved post-surgery outcome[300].

FINDING SUMMARY

MSH3 encodes a DNA mismatch repair protein. Two MutS homolog (MSH) complexes, MSH2-MSH6 (MutS-alpha) and MSH2-MSH3 (MutS-beta), are responsible for recognition of mismatched bases[296]. MSH3 and MutS-beta has also been shown to participate in double-strand break repair by homologous recombination[287,296]. MSH3 loss of function has been linked to the production of tetranucleotide microsatellite frameshift mutations termed EMAST (elevated microsatellite alterations at selected tetranucleotide repeats)[301-302]. The presence of EMAST has been recognized as a biomarker in multiple solid cancers with microsatellite instability (MSI)[303]. Inactivating MSH3 mutations found in cancer tend to be frameshift, missense, or allelic loss[295,300,304-305]. Certain germline polymorphisms in MSH3 have been reported to increase the risk of various cancers including colorectal (CRC)[306-310], breast[306,311], esophageal[312], prostate[306,313-314], gastric[305], and head and neck squamous cell carcinoma (HNSCC)[297]. Inactivating germline polymorphisms have been associated with hereditary colorectal adenomatous polyposis[315].

GENE
TP53

ALTERATION
R273C

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
817C>T

VARIANT CHROMOSOMAL POSITION
chr17:7577121

VARIANT ALLELE FREQUENCY (% VAF)
85.5%

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[316-319] or p53 gene therapy such as SGT53[320-324]. 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[325]. 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[326]. 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[327]. 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[328]. 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[111]. 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[329]. 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[330]. 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[324]. 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[331]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[332].

FREQUENCY & PROGNOSIS

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[333-338]. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)[339]. 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[340]. 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[341].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[342]. Alterations such as seen here may disrupt TP53 function or expression[343-347].

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)[348]. 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[349-351], including sarcomas[352-353]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[354] to 1:20,000[353]. 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[355]. 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[356-361]. 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[356-357]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[362]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[360,363-364]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Cabozantinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[365-366] , as well as by extensive preclinical data[367-373] .

SUPPORTING DATA

In a Phase 2 study, cabozantinib treatment achieved objective responses in 7 of 31 patients with glioblastoma (GBM) without prior antiangiogenic therapy and tumor shrinkage in 3 of 9 patients with prior antiangiogenic therapy, including bevacizumab[374]. In a preclinical study, cabozantinib treatment reduced GBM tumor growth in 3 xenograft mouse lines, and increased survival in two of these lines, while showed no effect on the overall survival in the third line; however, combination treatment with cabozantinib resulted in sensitization of these xenografts to TMZ treatment[375]. A Phase 1 ascending dose study of cabozantinib in patients with advanced solid tumors has reported early indications of drug response and prolonged stable disease, with no dose-limiting toxicities or serious adverse events[376]. Another Phase 1 study of cabozantinib in high-grade gliomas included 1 patient with anaplastic astrocytoma who had stable disease for >900 days[377]. A Phase 1 study examining the combination of cabozantinib and temozolomide for patients with high-grade gliomas reported that the combination was safe; however, dose reductions were common and 62% of patients experienced treatment-related grade 3/4 adverse events[378]. The combination of cabozantinib and crizotinib has been found to result in an increase in overall survival in a glioblastoma xenograft model[369]. Cabozantinib treatment has also been reported to result in decreased endothelial cell proliferation, increased apoptosis, and an inhibition of tumor growth in mouse models of breast, glioma, and lung tumors[367].

Capmatinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[107-110,379-380] , hepatocellular carcinoma[106], renal cell carcinoma[381], and gastric cancer[111], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

A Phase 1b/2 study of capmatinib with or without buparlisib did not result in CR or PR for patients with recurrent PTEN-deficient glioblastoma, and 30% (3/10) of patients treated with capmatinib monotherapy experienced SD[93].

Crizotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), adult and pediatric patients with ALK-positive inflammatory myofibroblastic tumor (IMT), and pediatric and young adult patients with ALK-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[94-96,382-383] , gastric cancer[132], gastroesophageal cancer[98], glioblastoma[99], and carcinoma of unknown primary[100], as well as in patients with MET-mutated cancers, including NSCLC[365,384-388] , renal cell carcinoma (RCC)[389], and histiocytic sarcoma[384]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[365,384,386-388,390] .

SUPPORTING DATA

Case reports describe 2 patients with glioblastoma who benefited from crizotinib: 1 patient with MET amplification experienced a rapid radiographic regression[99] and another patient with overexpression of MET and ALK showed prolonged SD[391]; another patient with MET amplification did not respond to crizotinib[391]. A Phase 1 study of crizotinib combined with temozolomide and radiotherapy reported a median PFS of 16.8 months and a median OS of 31.4 months for patients with glioblastoma[392]. A Phase 1 study of crizotinib in pediatric patients with solid tumors or lymphoma reported intratumoral hemorrhage in 2 patients with primary central nervous system (CNS) tumors, and patients with CNS lesions were subsequently excluded from the study[393].

Ivosidenib

Assay findings association

IDH1
R132H

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML) or previously treated locally advanced or metastatic cholangiocarcinoma. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML[394] and cholangiocarcinoma[395-396] and limited clinical data in myelodysplastic syndrome (MDS)[394] and glioma[50,397] , IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

In a Phase 1 study of ivosidenib for patients with IDH1-mutated advanced solid tumors, 1 patient achieved PR in the non-enhancing glioma population (ORR=2.9% [1/35]); for patients with non-enhancing glioma and enhancing glioma, SD rates were 85.7% (30/35) and 45.2% (14/31), respectively, and median PFS was 13.6 months and 1.4 months, respectively[50,397] .

Olutasidenib

Assay findings association

IDH1
R132H

AREAS OF THERAPEUTIC USE

Olutasidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical data in acute myeloid leukemia (AML)[398] and limited clinical data in both myelodysplastic syndrome (MDS)[399] and glioma[51], IDH1 R132 mutation may confer sensitivity to olutasidenib.

SUPPORTING DATA

The Phase 1b/2 trial investigating olutasidenib for patients with IDH1-mutated glioma reported a DCR of 48% (12/25, 2 PRs) and a median duration of disease control of 8.6 months; both PRs were observed for patients with enhancing high-grade glioma[51].

Tepotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[107-110,379-380] , hepatocellular carcinoma[106], renal cell carcinoma[381], and gastric cancer[111], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of tepotinib for the treatment of CNS tumors are limited (PubMed, Sep 2022). A case study reported a patient with MET amplified glioblastoma who experienced sustained CR after surgical resection and radiation treatment followed by temozolomide and 19 weeks of tepotinib[400]. Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[107] and MET exon 14-skipping alterations[401-402] . Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[109-110] . In advanced hepatocellular carcinoma, Phase 2 studies of tepotinib reported improved ORR and PFS for both treatment-naive and previously treated patients with MET protein overexpression[106,403-405] . In a Phase 1 study of advanced solid tumors, tepotinib monotherapy yielded an ORR of 1.3% and a DCR of 24%, with 2 confirmed PRs observed for patients with esophageal or lung cancer and 2 unconfirmed PRs for patients with colorectal or nasopharyngeal cancer[406]. In another Phase 1 study of solid tumors, tepotinib yielded a DCR of 17% (2/12), with 2 SD of ≥12 weeks observed in a patient with gastric cancer and another with urachal cancer[407].

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
CCND2

ALTERATION
amplification - equivocal

RATIONALE
CCND2 amplification or activation may predict sensitivity to CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT02933736

PHASE NULL

Ribociclib (LEE011) in Preoperative Glioma and Meningioma Patients

TARGETS
CDK6, CDK4

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)

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts, Arkansas, New York, Virginia, Texas, Florida

NCT03310879

PHASE 2

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

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT05159245

PHASE 2

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

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

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

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

GENE
CDK6

ALTERATION
amplification

RATIONALE
Tumors with CDK6 amplification may be sensitive to CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (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)

NCT02933736

PHASE NULL

Ribociclib (LEE011) in Preoperative Glioma and Meningioma Patients

TARGETS
CDK6, CDK4

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)

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts, Arkansas, New York, Virginia, Texas, Florida

NCT03310879

PHASE 2

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

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT05159245

PHASE 2

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

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

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

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

GENE
IDH1

ALTERATION
R132H

RATIONALE
IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP inhibitors in solid tumors. Preclinical data indicate that IDH1 mutations may predict sensitivity to glutaminase inhibitors.

NCT04521686

PHASE 1

Study of LY3410738 Administered to Patients With Advanced Solid Tumors With IDH1 Mutations

TARGETS
PD-L1, IDH2, IDH1

LOCATIONS: Taichung City (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Suita-shi (Japan), Nagaizumi (Japan), Yokohama (Japan), Chuo-ku (Japan), Kashiwa (Japan), Singapore (Singapore)

NCT05417594

PHASE 1/2

Study of AZD9574 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Advanced Solid Malignancies

TARGETS
PARP

LOCATIONS: Seoul (Korea, Republic of), Melbourne (Australia), Stockholm (Sweden), Sant Cugat del Valles (Spain), Pozuelo de Alarcon (Spain), A Coruña (Spain), Sevilla (Spain), Texas

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)

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)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

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

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

GENE
MET

ALTERATION
amplification

RATIONALE
Activating MET alterations may confer sensitivity to MET inhibitors.

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), North Adelaide (Australia), Bedford Park (Australia)

NCT04647838

PHASE 2

Tepotinib in Solid Tumors Harboring MET Alterations

TARGETS
MET

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

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

LOCATIONS: Villejuif (France), Nice (France), Lyon (France), Marseille (France), Toulouse (France), Bordeaux (France)

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)

NCT04693468

PHASE 1

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

TARGETS
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

LOCATIONS: Texas

NCT05038839

PHASE 1

Cabozantinib and Pamiparib for the Treatment of Advanced of Refractory Solid Tumors

TARGETS
MET, ROS1, RET, VEGFRs, PARP

LOCATIONS: Texas

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BRIP1
D566E

CDK4
R255C

FANCG
G294E

MLH1
R217C

MSH3
A62_P63insAAA

NOTCH2
L744V

RAD52
amplification

SETD2
P190L

SMO
amplification

ORDERED TEST # ORD-1560720-01

APPENDIX Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.6.0

The median exon coverage for this sample is 807x

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. Alonso M, et al. Cancer Res. (2001) pmid: 11280776
7. Rodríguez-Hernández I, et al. PLoS ONE (2013) pmid: 24073290
8. Vladimirova V, et al. Neuropathol. Appl. Neurobiol. (2008) pmid: 18053027
9. Martinez R, et al. Oncology (2004) pmid: 15331927
10. Martinez R, et al. J. Cancer Res. Clin. Oncol. (2005) pmid: 15672285
11. Martinez R, et al. Cancer Genet. Cytogenet. (2007) pmid: 17498554
12. Szybka M, et al. Clin. Neuropathol. () pmid: 12908754
13. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
14. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
15. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
16. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
17. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
18. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
19. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
20. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
21. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
22. Cristescu R, et al. Science (2018) pmid: 30309915
23. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
24. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
25. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
26. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
27. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
28. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
29. Zhao J, et al. Nat. Med. (2019) pmid: 30742119
30. Touat M, et al. Nature (2020) pmid: 32322066
31. Bouffet E, et al. J. Clin. Oncol. (2016) pmid: 27001570
32. Johanns TM, et al. Cancer Discov (2016) pmid: 27683556
33. Lukas RV, et al. J. Neurooncol. (2018) pmid: 30073642
34. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
35. Patel RR, et al. Pediatr Blood Cancer (2020) pmid: 32386112
36. Johnson A, et al. Oncologist (2017) pmid: 28912153
37. Draaisma K, et al. Acta Neuropathol Commun (2015) pmid: 26699864
38. Wang L, et al. BMC Cancer (2020) pmid: 32164609
39. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
40. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
41. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
42. Rizvi NA, et al. Science (2015) pmid: 25765070
43. Johnson BE, et al. Science (2014) pmid: 24336570
44. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
45. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
46. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
47. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
48. Nature (2012) pmid: 22810696
49. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
50. Fan B, et al. Invest New Drugs (2019) pmid: 31028664
51. de la Fuente MI, et al. Neuro Oncol (2022) pmid: 35639513
52. Mellinghoff et al., 2020; ASCO Abstract 2504
53. Philip B, et al. Cell Rep (2018) pmid: 29719265
54. Molenaar RJ, et al. Clin. Cancer Res. (2018) pmid: 29339439
55. Lu Y, et al. Cancer Res. (2017) pmid: 28202508
56. Sulkowski PL, et al. Sci Transl Med (2017) pmid: 28148839
57. Natsume A, et al. Neuro Oncol (2022) pmid: 35722822
58. McBrayer SK, et al. Cell (2018) pmid: 30220459
59. Cairncross JG, et al. J Clin Oncol (2014) pmid: 24516018
60. van den Bent MJ, et al. Lancet Oncol (2021) pmid: 34000245
61. Esteyrie V, et al. Oncologist (2021) pmid: 33524191
62. Chaumeil MM, et al. Nat Commun (2013) pmid: 24019001
63. Hartmann C, et al. Clin. Cancer Res. (2013) pmid: 23918605
64. Rossetto M, et al. Rev. Neurol. (Paris) (2011) pmid: 21885076
65. Shin JH, et al. J. Neurooncol. (2013) pmid: 24129546
66. Parsons DW, et al. Science (2008) pmid: 18772396
67. Cancer Genome Atlas Research Network, et al. N. Engl. J. Med. (2015) pmid: 26061751
68. Brennan CW, et al. Cell (2013) pmid: 24120142
69. Thota B, et al. Am. J. Clin. Pathol. (2012) pmid: 22904127
70. Killela PJ, et al. Oncotarget (2014) pmid: 24140581
71. Haberler C, et al. Clin. Neuropathol. () pmid: 24559763
72. Yan H, et al. N. Engl. J. Med. (2009) pmid: 19228619
73. Hartmann C, et al. Acta Neuropathol. (2010) pmid: 21088844
74. Sonoda Y, et al. Cancer Sci. (2009) pmid: 19765000
75. Ahmadi R, et al. J. Neurooncol. (2012) pmid: 22528790
76. Jiang H, et al. Neuro-oncology (2013) pmid: 23486687
77. Shibahara I, et al. Int. J. Clin. Oncol. (2012) pmid: 21971842
78. Juratli TA, et al. J. Neurooncol. (2012) pmid: 23015095
79. Weller M, et al. J. Clin. Oncol. (2009) pmid: 19805672
80. Reitman ZJ, et al. J. Natl. Cancer Inst. (2010) pmid: 20513808
81. Jin G, et al. PLoS ONE (2011) pmid: 21326614
82. Gross S, et al. J. Exp. Med. (2010) pmid: 20142433
83. Ward PS, et al. Cancer Cell (2010) pmid: 20171147
84. Leonardi R, et al. J. Biol. Chem. (2012) pmid: 22442146
85. Dang L, et al. Nature (2009) pmid: 19935646
86. Ward PS, et al. Oncogene (2012) pmid: 21996744
87. Figueroa ME, et al. Cancer Cell (2010) pmid: 21130701
88. Xu W, et al. Cancer Cell (2011) pmid: 21251613
89. Turcan S, et al. Nature (2012) pmid: 22343889
90. Duncan CG, et al. Genome Res. (2012) pmid: 22899282
91. Weller M, et al. Nat Rev Clin Oncol (2021) pmid: 33293629
92. Louis DN, et al. Acta Neuropathol (2016) pmid: 27157931
93. van den Bent M, et al. J. Neurooncol. (2020) pmid: 31776899
94. Ou SH, et al. J Thorac Oncol (2011) pmid: 21623265
95. Schwab R, et al. Lung Cancer (2014) pmid: 24192513
96. Le X, et al. Clin Lung Cancer (2015) pmid: 25922291
97. Schrock AB, et al. J Thorac Oncol (2017) pmid: 28315738
98. Lennerz JK, et al. J. Clin. Oncol. (2011) pmid: 22042947
99. Chi AS, et al. J. Clin. Oncol. (2012) pmid: 22162573
100. Palma NA, et al. Case Rep Oncol (2014) pmid: 25232318
101. Lefler DS, et al. Cancer Biol Ther (2022) pmid: 35129063
102. Wolf J, et al. N Engl J Med (2020) pmid: 32877583
103. Wu YL, et al. J. Clin. Oncol. (2018) pmid: 30156984
104. Gainor JF, et al. J Thorac Oncol (2020) pmid: 31864558
105. Gautschi O, et al. J Thorac Oncol (2020) pmid: 31864554
106. Faivre et al., 2021; ASCO GI Abstract 329
107. Le et al., 2021; ASCO Abstract 9021
108. Yang et al., 2019; AACR Abstract CT193
109. Park et al., 2019; ESMO Abstract 477O
110. Wu et al., 2019; IASLC Abstract MA09.09
111. Lee J, et al. Cancer Discov (2019) pmid: 31315834
112. Kim ST, et al. Transl Oncol (2019) pmid: 30695737
113. Kwak et al., 2015; ASCO GI Abstract 01
114. Spigel DR, et al. J. Clin. Oncol. (2013) pmid: 24101053
115. Catenacci DV, et al. Cancer Discov (2011) pmid: 22389872
116. Harding JJ, et al. Clin. Cancer Res. (2019) pmid: 31142504
117. Camidge et al., 2021; AACR Abstract CT179
118. Goldman et al., 2022; ASCO Abstract 9013
119. Pierscianek D, et al. Brain Pathol. (2013) pmid: 22672415
120. Abounader R, et al. Neuro-oncology (2005) pmid: 16212809
121. Liu W, et al. J Clin Neurosci (2011) pmid: 20832323
122. Olmez OF, et al. Clin Transl Oncol (2014) pmid: 23740136
123. Kwak Y, et al. Int J Clin Exp Pathol (2015) pmid: 26823824
124. J. Clin. Oncol. (2011) pmid: 22042966
125. Jung KH, et al. Arch. Pharm. Res. (2012) pmid: 22553051
126. Gao J, et al. Sci Signal (2013) pmid: 23550210
127. Ang CS, et al. Anticancer Res. (2013) pmid: 23898085
128. Abou-Bakr AA, et al. Gulf J Oncolog (2013) pmid: 23996864
129. Ho JC, et al. Semin Respir Crit Care Med (2013) pmid: 24258573
130. Dziadziuszko R, et al. J Thorac Oncol (2012) pmid: 22237262
131. Madoz-Gúrpide J, et al. J Transl Med (2015) pmid: 26319934
132. Ali SM, et al. Oncologist (2015) pmid: 25882375
133. Kwak EL, et al. Cancer Discov (2015) pmid: 26432108
134. Busk PK, et al. Exp. Cell Res. (2005) pmid: 15707582
135. Busk PK, et al. Cell Cycle () pmid: 12695654
136. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
137. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
138. Büschges R, et al. Brain Pathol. (1999) pmid: 10416984
139. Kheirollahi M, et al. Med. Oncol. (2011) pmid: 20077038
140. Koyama-Nasu R, et al. Oncogene (2013) pmid: 22964630
141. Bouchart C, et al. Cancer Med (2019) pmid: 31568682
142. Katoh Y, et al. Curr. Mol. Med. (2009) pmid: 19860666
143. White PC, et al. Oncogene (2006) pmid: 16301994
144. Zack TI, et al. Nat. Genet. (2013) pmid: 24071852
145. Beroukhim R, et al. Nature (2010) pmid: 20164920
146. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
147. Turner NC, et al. N. Engl. J. Med. (2015) pmid: 26030518
148. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
149. Peguero et al., 2016; ASCO Abstract 2528
150. Konecny et al., 2016; ASCO Abstract 5557

151. Costello JF, et al. Cancer Res. (1997) pmid: 9102208
152. Nature (2008) pmid: 18772890
153. Bax DA, et al. Clin. Cancer Res. (2010) pmid: 20570930
154. Hodgson JG, et al. Neuro-oncology (2009) pmid: 19139420
155. Ruano Y, et al. Mol. Cancer (2006) pmid: 17002787
156. Li B, et al. Oncol. Rep. (2012) pmid: 22736304
157. Lam PY, et al. Br J Neurosurg (2000) pmid: 10884881
158. Chen SM, et al. World J Surg Oncol (2013) pmid: 23594394
159. Michaud K, et al. Cancer Res. (2010) pmid: 20354191
160. Meyerson M, et al. Mol. Cell. Biol. (1994) pmid: 8114739
161. Grossel MJ, et al. J. Cell. Biochem. (2006) pmid: 16294322
162. Choi YJ, et al. Oncogene (2014) pmid: 23644662
163. Cell (1995) pmid: 7736585
164. Musgrove EA, et al. Nat. Rev. Cancer (2011) pmid: 21734724
165. Ismail A, et al. Clin. Cancer Res. (2011) pmid: 21593195
166. van Dekken H, et al. Cancer Genet. Cytogenet. (2009) pmid: 19167610
167. Liang J, et al. Cancer Res (2020) pmid: 31551363
168. Garbarino J, et al. Transl Oncol (2021) pmid: 34118569
169. Cole et al., 2021; AACR Abstract CT059
170. George SL, et al. EBioMedicine (2020) pmid: 32846370
171. Koschmann C, et al. Sci Transl Med (2016) pmid: 26936505
172. Heaphy CM, et al. Science (2011) pmid: 21719641
173. Singhi et al., 2015; USCAP Abstract 1797
174. Jiao Y, et al. Science (2011) pmid: 21252315
175. Fishbein L, et al. Nat Commun (2015) pmid: 25608029
176. Morosini et al., 2014; ASCO Abstract 11008
177. Cheung NK, et al. JAMA (2012) pmid: 22416102
178. Molenaar JJ, et al. Nature (2012) pmid: 22367537
179. Pugh TJ, et al. Nat. Genet. (2013) pmid: 23334666
180. Cheung NK, et al. Nat. Rev. Cancer (2013) pmid: 23702928
181. Marinoni I, et al. Gastroenterology (2014) pmid: 24148618
182. Qadeer ZA, et al. J. Invest. Dermatol. (2014) pmid: 24468746
183. Kannan K, et al. Oncotarget (2012) pmid: 23104868
184. Reuss DE, et al. Acta Neuropathol. (2015) pmid: 25427834
185. Sahm F, et al. Acta Neuropathol. (2014) pmid: 25143301
186. Singhi et al., 2015; USCAP Abstract 93
187. Liau JY, et al. Am. J. Surg. Pathol. (2015) pmid: 25229770
188. Clynes D, et al. Trends Biochem. Sci. (2013) pmid: 23916100
189. Ratnakumar K, et al. Epigenetics (2013) pmid: 23249563
190. Lovejoy CA, et al. PLoS Genet. (2012) pmid: 22829774
191. Bower K, et al. PLoS ONE (2012) pmid: 23185534
192. Nan X, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17296936
193. Garrick D, et al. Gene (2004) pmid: 14729260
194. Eustermann S, et al. Nat. Struct. Mol. Biol. (2011) pmid: 21666677
195. Flynn RL, et al. Science (2015) pmid: 25593184
196. Gibbons RJ, et al. Cell (1995) pmid: 7697714
197. Kertesz N, et al. Blood (2006) pmid: 16322467
198. Shi S, et al. J Pharm Sci (2012) pmid: 22411527
199. Li X, et al. PLoS ONE (2014) pmid: 25148033
200. Liu R, et al. BMC Cancer (2013) pmid: 23721559
201. Bhatia S, et al. Sci Rep (2016) pmid: 27941840
202. Scehnet JS, et al. Blood (2009) pmid: 18836096
203. Ferguson BD, et al. Sci Rep (2015) pmid: 26073592
204. Werner TL, et al. Invest New Drugs (2015) pmid: 26365907
205. Pietanza MC, et al. J Thorac Oncol (2012) pmid: 22011666
206. Pietanza MC, et al. J Thorac Oncol (2012) pmid: 22722787
207. Sinha UK, et al. Arch. Otolaryngol. Head Neck Surg. (2006) pmid: 17043250
208. Masood R, et al. Int. J. Cancer (2006) pmid: 16615113
209. Ferguson BD, et al. Growth Factors (2014) pmid: 25391996
210. Yavrouian EJ, et al. Arch. Otolaryngol. Head Neck Surg. (2008) pmid: 18794445
211. Liersch-Löhn B, et al. Int. J. Cancer (2016) pmid: 26414866
212. Hu F, et al. Tumour Biol. (2014) pmid: 24771266
213. Hasina R, et al. Cancer Res. (2013) pmid: 23100466
214. Li M, et al. Dig. Dis. Sci. (2011) pmid: 20686847
215. Yin J, et al. Anticancer Res. (2017) pmid: 28739744
216. Stephenson SA, et al. BMC Mol. Biol. (2001) pmid: 11801186
217. Liu W, et al. Cancer (2002) pmid: 11920461
218. McCall JL, et al. Mol. Cell. Biol. (2016) pmid: 27273865
219. Stremitzer S, et al. Mol. Cancer Ther. (2016) pmid: 27535973
220. Lv J, et al. Exp. Mol. Pathol. (2016) pmid: 27072105
221. Guijarro-Muñoz I, et al. Med. Oncol. (2013) pmid: 23579861
222. Kumar SR, et al. Cancer Res. (2009) pmid: 19366806
223. Wu Q, et al. Pathol. Oncol. Res. (2004) pmid: 15029258
224. Berclaz G, et al. Oncol. Rep. () pmid: 12168060
225. Brantley-Sieders DM, et al. PLoS ONE (2011) pmid: 21935409
226. Huang G, et al. Int J Clin Exp Pathol (2015) pmid: 26191333
227. Pradeep S, et al. Cancer Cell (2015) pmid: 26481148
228. Alam SM, et al. Br. J. Cancer (2008) pmid: 18231102
229. Kumar SR, et al. Br. J. Cancer (2007) pmid: 17353927
230. Takai N, et al. Oncol. Rep. () pmid: 11295082
231. Dong LD, et al. Oncol Lett (2017) pmid: 28454369
232. Berclaz G, et al. Ann. Oncol. (2003) pmid: 12562648
233. Sharma GK, et al. Head Neck (2015) pmid: 24634162
234. Giaginis C, et al. Pathol. Oncol. Res. (2016) pmid: 26220827
235. Xuqing W, et al. Tumour Biol. (2012) pmid: 22528941
236. Ferguson BD, et al. PLoS ONE (2013) pmid: 23844053
237. Zheng MF, et al. Mol Med Rep (2012) pmid: 22684742
238. Chen T, et al. Tumour Biol. (2013) pmid: 23138393
239. Tu Y, et al. Clin Transl Oncol (2012) pmid: 22374425
240. Li M, et al. Mol. Biol. Rep. (2013) pmid: 23079712
241. Xia G, et al. Cancer Res. (2005) pmid: 15930280
242. Alam SM, et al. Gynecol. Oncol. (2009) pmid: 19356789
243. Ozgür E, et al. Urol. Oncol. () pmid: 19272799
244. Pierscianek D, et al. Neuropathology (2017) pmid: 27388534
245. Pierscianek D, et al. Brain Tumor Pathol (2016) pmid: 26951238
246. Becerikli M, et al. Int. J. Cancer (2015) pmid: 25274141
247. Xia G, et al. Clin. Cancer Res. (2005) pmid: 15958611
248. Noren NK, et al. Cancer Res. (2007) pmid: 17483308
249. Cell (2008) pmid: 18394988
250. Salvucci O, et al. Adv. Cancer Res. (2012) pmid: 22588055
251. Pitulescu ME, et al. Genes Dev. (2010) pmid: 21078817
252. Nat. Rev. Cancer (2010) pmid: 20179713
253. Boberg DR, et al. Chem. Biol. Interact. (2013) pmid: 23063927
254. Cromer A, et al. Oncogene (2004) pmid: 14676830
255. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
256. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
257. Smallwood PM, et al. Proc. Natl. Acad. Sci. U.S.A. (1996) pmid: 8790420
258. Zhang X, et al. Sci China Life Sci (2012) pmid: 23233218
259. van Swieten JC, et al. Am. J. Hum. Genet. (2003) pmid: 12489043
260. Lancet Neurol (2010) pmid: 20723845
261. Dumbrava et al., 2018; doi/full/10.1200/PO.18.00100
262. Jonsson KB, et al. N. Engl. J. Med. (2003) pmid: 12711740
263. Shimada T, et al. Proc. Natl. Acad. Sci. U.S.A. (2001) pmid: 11344269
264. Yu X, et al. Cytokine Growth Factor Rev. (2005) pmid: 15863037
265. Parish A, et al. Cell Cycle (2015) pmid: 25950492
266. Ropiquet F, et al. Cancer Res. (2000) pmid: 10945637
267. Niini T, et al. Leukemia (2002) pmid: 12399964
268. Neuhaus P, et al. Mol. Cell. Biol. (2003) pmid: 12917328
269. Ornitz DM, et al. J. Biol. Chem. (1996) pmid: 8663044
270. Iida S, et al. Oncogene (1992) pmid: 1549352
271. Marics I, et al. Oncogene (1989) pmid: 2649847
272. Zeng J, et al. Gastroenterology (2010) pmid: 19850045
273. Teng YC, et al. Cancer Res. (2013) pmid: 23722541
274. Liang X, et al. PLoS ONE (2013) pmid: 23922798
275. Jiping Z, et al. J. Cell. Biochem. (2013) pmid: 23794145
276. Vieira FQ, et al. Endocr. Relat. Cancer (2014) pmid: 24200674
277. Sharma SV, et al. Cell (2010) pmid: 20371346
278. Li L, et al. Mol. Cancer (2014) pmid: 24716659
279. Qi L, et al. PLoS ONE (2014) pmid: 25162518
280. Hou J, et al. Am J Transl Res (2012) pmid: 22937203
281. Paolicchi E, et al. Crit. Rev. Oncol. Hematol. (2013) pmid: 23266085
282. van Zutven LJ, et al. Genes Chromosomes Cancer (2006) pmid: 16419055
283. Wang GG, et al. Nature (2009) pmid: 19430464
284. Chicas A, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22615382
285. Lin W, et al. Mol. Cancer Res. (2015) pmid: 25537453
286. Dannenberg JH, et al. Cell (2010) pmid: 20371339
287. Dietlein F, et al. Cancer Discov (2014) pmid: 24556366
288. Takahashi M, et al. J. Biol. Chem. (2011) pmid: 21285347
289. Park JM, et al. PLoS ONE (2013) pmid: 23724141
290. Edelmann W, et al. Cancer Res. (2000) pmid: 10706084
291. Plaschke J, et al. Int J Colorectal Dis (2012) pmid: 22249440
292. Benachenhou N, et al. Int. J. Cancer (1998) pmid: 9650548
293. Kawakami T, et al. Biochem. Biophys. Res. Commun. (2004) pmid: 15541380
294. Benachenhou N, et al. Br. J. Cancer (1999) pmid: 10098729
295. Plaschke J, et al. Cancer Res. (2004) pmid: 14871813
296. van Oers JM, et al. Oncogene (2014) pmid: 24013230
297. Nogueira GA, et al. Int. J. Cancer (2015) pmid: 25598504
298. Xu XL, et al. Genet. Mol. Res. (2015) pmid: 25966119
299. Dong X, et al. Oncologist (2011) pmid: 21212431
300. Laghi L, et al. Clin. Cancer Res. (2012) pmid: 22496206
301. Haugen AC, et al. Cancer Res. (2008) pmid: 18922920
302. Lee SY, et al. Gastroenterology (2010) pmid: 20708618
303. Watson MM, et al. Br. J. Cancer (2014) pmid: 24691426

304. Kim TM, et al. Cell (2013) pmid: 24209623
305. Ohmiya N, et al. Gene (2001) pmid: 11470537
306. Miao HK, et al. Int J Clin Exp Pathol (2015) pmid: 26617824
307. Morak M, et al. Fam. Cancer (2017) pmid: 28528517
308. Duraturo F, et al. Int. J. Cancer (2011) pmid: 21128252
309. Reeves SG, et al. Cancer Epidemiol (2012) pmid: 21974800
310. Berndt SI, et al. Int. J. Cancer (2007) pmid: 17205513
311. Yang X, et al. PLoS ONE (2015) pmid: 25927356
312. Vogelsang M, et al. PLoS ONE (2012) pmid: 22623965
313. Jafary F, et al. Asian Pac. J. Cancer Prev. (2012) pmid: 23464402
314. Hirata H, et al. J. Urol. (2008) pmid: 18355840
315. Adam R, et al. Am. J. Hum. Genet. (2016) pmid: 27476653
316. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
317. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
318. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
319. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
320. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
321. Xu L, et al. Mol. Med. (2001) pmid: 11713371
322. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
323. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
324. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
325. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
326. Moore et al., 2019; ASCO Abstract 5513
327. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
328. Oza et al., 2015; ASCO Abstract 5506
329. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
330. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
331. Gourley et al., 2016; ASCO Abstract 5571
332. Park H, et al. ESMO Open (2022) pmid: 36084396
333. Uno M, et al. Cancer Lett. (2005) pmid: 15914282
334. Uno M, et al. Int. J. Biol. Markers () pmid: 16711514
335. Lass U, et al. PLoS ONE (2012) pmid: 22844452
336. Faria MH, et al. APMIS (2012) pmid: 23009112
337. Milinkovic V, et al. PLoS ONE (2013) pmid: 24358143
338. Galatro TF, et al. PLoS ONE (2013) pmid: 23613880
339. Schmidt MC, et al. J. Neuropathol. Exp. Neurol. (2002) pmid: 11939587
340. Yan et al. 2020; DOI:10.1200/PO.19.00385
341. Nozaki M, et al. Neuro-oncology (1999) pmid: 11550308
342. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
343. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
344. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
345. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
346. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
347. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
348. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
349. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
350. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
351. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
352. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
353. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
354. Lalloo F, et al. Lancet (2003) pmid: 12672316
355. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
356. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
357. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
358. Xie M, et al. Nat. Med. (2014) pmid: 25326804
359. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
360. Severson EA, et al. Blood (2018) pmid: 29678827
361. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
362. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
363. Chabon JJ, et al. Nature (2020) pmid: 32269342
364. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
365. Paik PK, et al. Cancer Discov (2015) pmid: 25971939
366. Klempner SJ, et al. J Thorac Oncol (2017) pmid: 27693535
367. Yakes FM, et al. Mol. Cancer Ther. (2011) pmid: 21926191
368. Weber H, et al. J Biomol Screen (2014) pmid: 25260782
369. Navis AC, et al. PLoS ONE (2013) pmid: 23484006
370. Yeh I, et al. Nat Commun (2015) pmid: 26013381
371. Lee YH, et al. Cancers (Basel) (2014) pmid: 25534569
372. Torres KE, et al. Clin. Cancer Res. (2011) pmid: 21540237
373. Sameni M, et al. Clin. Cancer Res. (2016) pmid: 26432786
374. de Groot et al., 2009; ASCO Abstract 2047
375. deCarvalho et al., 2014; AACR Abstract 3795
376. Yamamoto et al., 2011; AACR-EORTC Abstract C26
377. Schiff et al., 2013; Neuro-Oncology Annual Meeting Abstract MR026
378. Schiff D, et al. Cancer (2016) pmid: 26588662
379. Schuler et al., 2016; ASCO Abstract 9067
380. Wu et al., 2018; WLCL Abstract P1.01-97
381. Gan HK, et al. Clin. Cancer Res. (2019) pmid: 30952639
382. Vassal et al., 2015; ASCO Abstract 2595
383. Li et al., 2015; ASCO Abstract 8090
384. Frampton GM, et al. Cancer Discov (2015) pmid: 25971938
385. Benderra MA, et al. J Thorac Oncol (2016) pmid: 26845121
386. Waqar SN, et al. J Thorac Oncol (2015) pmid: 25898962
387. Mendenhall MA, et al. J Thorac Oncol (2015) pmid: 25898965
388. Jenkins RW, et al. Clin Lung Cancer (2015) pmid: 25769807
389. Stein MN, et al. Eur. Urol. (2015) pmid: 25457019
390. Awad et al., 2017; ASCO Abstract 8511
391. Le Rhun E, et al. CNS Oncol (2015) pmid: 26498130
392. Martinez-Garcia et al., 2019; ESMO Abstract 3418
393. Mossé YP, et al. Lancet Oncol. (2013) pmid: 23598171
394. DiNardo CD, et al. N. Engl. J. Med. (2018) pmid: 29860938
395. Lowery MA, et al. Lancet Gastroenterol Hepatol (2019) pmid: 31300360
396. Abou-Alfa GK, et al. Lancet Oncol. (2020) pmid: 32416072
397. Mellinghoff IK, et al. J. Clin. Oncol. (2020) pmid: 32530764
398. Cortes et al., 2022; ASH Abstract 2757
399. Watts JM, et al. Lancet Haematol (2022) pmid: 36370742
400. Pham et al., 2021; DOI: 10.1093/neuonc/noab196.432
401. Paik PK, et al. N. Engl. J. Med. (2020) pmid: 32469185
402. Mazieres et al., 2020; ESMO Abstract 1283P
403. Ryoo et al., 2018; ESMO Abstract 186P
404. Ryoo et al., 2018; ESMO Abstract 621PD
405. Decaens et al., 2019; ESMO Abstract 698P
406. Falchook GS, et al. Clin. Cancer Res. (2020) pmid: 31822497
407. Shitara K, et al. Jpn. J. Clin. Oncol. (2020) pmid: 32328660