FOUNDATIONONE®CDx

PATIENT
Yang, Chang-Chou

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
31 May 2022
ORDERED TEST #
ORD-1372378-01

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

PATIENT
DISEASE Brain glioblastoma (GBM)
NAME Yang, Chang-Chou
DATE OF BIRTH 31 August 1957
SEX Male
MEDICAL RECORD # 48192387

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

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S111-06019 B (PF22064)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 15 February 2022
SPECIMEN RECEIVED 23 May 2022

Biomarker Findings

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

Genomic Findings

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

EGFR P596L, amplification, EGFRvIII, EGFRvIII
PDGFRA amplification - equivocal[†]
CDK6 amplification - equivocal[†]
MDM2 amplification
CDKN2A/B CDKN2A loss, CDKN2B loss
MTAP loss
MUTYH splice site 892-2A>G
TERT promoter -124C>T
TET2 E1151*

1 Disease relevant genes with no reportable alterations: ***IDH1***

† See About the Test in appendix for details.
α The sensitivity for detecting MSI is reduced due to sample quality. Confirmatory testing using a validated orthogonal (alternative) method should be performed.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***EGFR* amplification** (p. 5), ***TERT* promoter -124C>T** (p. 10)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cetuximab** (p. 11), **Erlotinib** (p. 11), **Gefitinib** (p. 12), **Imatinib** (p. 12), **Panitumumab** (p. 13)
- 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: ***TERT* promoter -124C>T** (p. 10)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***MUTYH* splice site 892-2A>G** (p. 9)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***TET2* E1151*** (p. 10)

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

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
EGFR **-** P596L, amplification, EGFRvIII, EGFRvIII	none	Cetuximab
		Erlotinib
		Gefitinib
10 Trials *see p. 16*		Panitumumab
PDGFRA **-** amplification - equivocal	none	Imatinib
1 Trial *see p. 19*		
CDK6 **-** amplification - equivocal	none	none
10 Trials *see p. 14*		
MDM2 **-** amplification	none	none
6 Trials *see p. 18*		

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

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

MUTYH **-** splice site 892-2A>G ..... p. 9

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

TET2 **-** E1151* ..... p. 10

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.

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[10]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[10-12]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER

Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[16,26-27]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[28-29] or anti-PD-L1[30] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)[31]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[35].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[16,26-30].

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GENE
EGFR

ALTERATION
P596L, amplification, EGFRvIII, EGFRvIII

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
1787C>T

VARIANT ALLELE FREQUENCY (% VAF)
13.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In multiple glioblastoma (GBM) studies, the presence of EGFRvIII has not predicted clinical benefit from first-generation EGFR TKIs such as erlotinib[47-52] or gefitinib[50,53]. However, case reports have described patients with EGFRvIII-positive GBM responding to erlotinib[54-57]. In a retrospective study of patients with GBM treated with erlotinib or gefitinib, co-expression of EGFRvIII with PTEN protein was the strongest predictor of response (P<0.001)[58], suggesting that activity in this setting is dependent on PTEN status[59-60]. However, a prospective Phase 2 trial testing erlotinib monotherapy for patients with EGFRvIII and PTEN-positive recurrent glioblastoma reported minimal efficacy and was terminated[52]. The second-generation EGFR TKIs afatinib and dacomitinib have shown minimal efficacy for patients with EGFRvIII glioblastoma (GBM)[61-64]. A Phase 1/2 study of afatinib, temozolomide, or the combination for patients with GBM reported clinical benefit, including for patients with EGFRvIII; however, temozolomide alone and in combination exhibited better responses than afatinib monotherapy[61-62]. A Phase 2 trial of dacomitinib for patients with EGFR-amplified GBM reported a DCR of 26% (5/19) among patients with EGFR amplification and EGFRvIII; however, the trial failed to meet its primary endpoint of 6-month PFS[63]. A retrospective biomarker analysis of another Phase 2 study of dacomitinib for patients with GBM found no association between EGFRvIII and clinical benefit[64]. A patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFRvIII, experienced progression of the EGFRvIII-positive tumor during treatment with osimertinib[65]. Novel approaches that specifically target EGFRvIII in glioblastoma (GBM), such as the vaccine rindopepimut, are under investigation in both clinical and preclinical studies. A Phase 2 trial reported significant improvement in OS for patients with EGFRvIII-positive GBM with rindopepimut in combination with bevacizumab compared to bevacizumab alone (HR=0.53, p=0.01)[66]. However, a Phase 3 study of rindopepimut combined with temozolomide compared to temozolomide alone in newly diagnosed EGFRvIII-positive GBM patients was terminated after the interim analysis, due to a lack of clinical benefit as measured by OS (20 vs. 20 months)[67]. For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[68], gefitinib[69], afatinib[70], dacomitinib[71], and osimertinib[72]; however, the data for patients with other tumor types are limited[64,73-77]. A case study of a patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFR amplification and multiple missense mutations, reported a near-CR of the EGFR-amplified and -mutated tumor to osimertinib[65]. A case series of 11 patients with bithalamic gliomas with EGFR mutations suggested that treatment with EGFR inhibitors, including osimertinib, prolonged patient survival relative to other types of treatment; however, no patients attained PR or SD[76]. Another case series of 2 patients with osimertinib-treated bithalamic gliomas with EGFR exon 20 insertion mutations reported that one patient experienced no progression at 4 months of treatment and that another patient did not progress until after 6 months of treatment[78]. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy[61,63-64,79-80]; however, a small subset of patients has experienced clinical benefit[63-64,79]. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma[58,81-83]. There are conflicting data on the efficacy of anti-EGFR antibodies for the treatment of EGFR-amplified tumors. A meta-analysis of colorectal cancer patients treated with second-line or higher cetuximab or panitumumab observed an association between EGFR copy number gain and increased OS and PFS[84]. However, studies in head and neck squamous cell carcinoma and gastric cancer found either no association or a negative association between EGFR copy number gain and survival after treatment with first-line cetuximab or panitumumab in combination with chemotherapy[85-86]. The Phase 3 INTELLANCE trial of depatuxizumab mafodotin (ABT-414), an EGFR-targeted antibody-drug conjugate with a toxic payload, in patients with EGFR-amplified glioblastoma (GBM) was stopped for futility. Interim analysis demonstrated improved median PFS (mPFS) of ABT-414 monotherapy compared with placebo (HR=0.84); however, no OS benefit was observed (HR=1.01). Improved mPFS was also observed in patients harboring EGFRvIII (HR=0.73) but without an OS improvement (HR=0.95)[87]. The Phase 2 INTELLANCE trial demonstrated clinical benefit for EGFR-amplified GBM for the combination of ABT-414, temozolomide, and radiotherapy (HR=0.66, p=0.017), but there was no evidence of efficacy for ABT-414 monotherapy (HR=1.04, p=0.83)[88].

FREQUENCY & PROGNOSIS

Across several genomic studies of CNS tumors, EGFR amplification has been reported in 16.9% of anaplastic astrocytomas, and 39.7% of glioblastoma multiformes (GBMs)[89-92]. EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas in several genomic studies of CNS tumors[89-92]. In GBMs, Missense mutations in the EGFR extracellular domain have been found in 10-15% of cases and approximately half have a low-level amplification of the mutated allele[93-94]. In a study of IDH-wildtype GBM samples, EGFR alterations were detected in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event[95]. The EGFRvIII mutation has been variously reported in 6-46% of GBM samples[58,96-103]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[104-105]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[106]. The link between EGFRvIII status and prognosis is unclear, although some studies suggest that it may be linked to improved survival and response to chemotherapy[107].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[108]. Amplification of EGFR has been associated with increased expression of

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EGFR mRNA and protein in several cancer types[109-111]. A mutation of the EGFR gene, referred to as EGFRvIII, results from a gene rearrangement that deletes exons 2-7. This alteration causes an in-frame deletion of 801 base pairs encoding part of the extracellular ligand-binding domain[96]. This deletion has shown to result in ligand-independent (constitutive) phosphorylation and activation of EGFR, as well as consequent tumorigenesis[96,112]. EGFR mutations that have been characterized in biochemical assays to be activating, as observed here, are predicted to confer sensitivity to EGFR-targeted therapies[93,113-129].

POTENTIAL DIAGNOSTIC IMPLICATIONS

The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2021)[130].

GENE

PDGFRA

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence in solid tumors and hematologic cancers, PDGFRA activating alterations are associated with sensitivity to imatinib[131-168]. Sorafenib has shown clinical and preclinical activity against the FIP1L1-PDGFRA fusion in chronic eosinophilic leukemia (CEL) and mutations associated with clinical resistance to imatinib and sunitinib in both CEL and gastrointestinal stromal tumor (GIST)[169-174]. Complete responses to nilotinib have been reported in patients with CEL or hypereosinophilic syndrome with FIP1L1-PDGFRA or activating mutations[147,175-176]; preclinical evidence has reported efficacy of nilotinib in the context of PDGFRA mutations associated with GIST[177-178]. Patients with GIST harboring PDGFRA activating mutations have been reported to derive clinical benefit from treatment with sunitinib[179] or regorafenib[180-181]. Preclinical studies have reported sensitivity of activating PDGFRA mutations and FIP1L1-PDGFRA fusion to dasatinib[171,177]. PDGFRA D842 mutations were reported to be sensitive to avapritinib in clinical[182] and preclinical[182] studies of GIST, and demonstrated sensitivity to ripretinib for 1 patient[183].

FREQUENCY & PROGNOSIS

PDGFRA amplification has been suggested to be more common in higher grade astrocytomas than in lower grade astrocytomas; studies have reported PDGFRA amplification in 16.3% (27/166) of Grade 2 astrocytomas and in 23.6% (91/386) of Grade 3 and 4 astrocytomas analyzed[184-186]. PDGFRA amplification has been reported in 5.2-33% of glioblastoma cases[90,185,187-190]. A retrospective analysis of TCGA glioma samples reported elevated expression of ERBB3 correlated with PDGFRA expression and co-expression of these genes was an indicator of poor prognosis in a GBM patient cohort[191]. Amplification of PDGFRA has been associated with tumor grade and poor progression-free and overall survival in patients with glioblastoma[185,187,190]. In addition, PDGFRA amplification has been reported to occur in conjunction with IDH1 mutation in glioblastoma, and both alterations in the same tumor have been associated with poor patient prognosis[185]. Amplification of PDGFRA has also been strongly correlated with the presence of KDR and/or KIT amplification in glioblastomas, as well as with EGFR amplification[184,189,192-193].

FINDING SUMMARY

PDGFRA encodes platelet-derived growth factor receptor alpha (PDGFR-alpha), a tyrosine kinase receptor that, upon binding of cognate ligands (PDGFA or PDGFB), activates several signaling pathways, including PI3K and MAPK[194]. PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies[195]. Amplification of PDGFRA, frequently occurring with amplification of the genes KDR and KIT, has been associated with increased PDGFRA expression[102,196-198] and poor prognosis[185,196,199-200] in some subtypes of glioma.

GENE

CDK6

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Tumors with CDK6 activation may be sensitive to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[201-204]. Clinical benefit has been reported for patients with CDK6-amplified or mutated solid tumors in response to treatment with ribociclib[205-206] .

FREQUENCY & PROGNOSIS

In the Glioblastoma Multiforme (GBM) TCGA dataset, CDK6 mutation has not been found, while putative CDK6 amplification has been reported in 3% of cases[90,207]. CDK6 amplification has also been reported in GBM in the scientific literature[208-210]. Studies have reported higher expression of CDK6 in high-grade gliomas than in low-grade gliomas[211-213]. Elevated CDK6 expression in glioblastoma tumor margins was associated with reduced survival[214]. Knockdown or inhibition of CDK6 was associated with reduced proliferation of GBM cells and reduced growth of GBM xenografts[214-215].

FINDING SUMMARY

CDK6 encodes cyclin-dependent kinase 6, which regulates the cell cycle, differentiation, senescence, and apoptosis[216-218]. CDK6 and its functional homolog CDK4 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[219-220]. Amplification of the chromosomal region that includes CDK6 has been reported in multiple cancer types, and has been associated with overexpression of CDK6 protein[221-222].

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GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[223]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[224-225]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[226-227] . A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[228]. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[229-230] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[231]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[232]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[233-234] .

FREQUENCY & PROGNOSIS

In the Glioblastoma Multiforme (GBM) TCGA dataset, amplification of MDM2 has been found in 8% of cases[90]. A study has reported amplification of the 12q14-15 region, where MDM2 and CDK4 reside, in 5% (2/42) of GBMs[235]. Amplification of MDM2 has been associated with poor survival in patients with glioblastoma[235-236].

FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[237-239]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[240-241]. Overexpression or amplification of MDM2 is frequent in cancer[242]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[243] and 2/3 patients with MDM2 or MDM4 amplification[244] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[245]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[245].

GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[246-247], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[202,205-206,248-251]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[225,252], the clinical relevance of p14ARF as a predictive biomarker is not clear. Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[253-256]. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[201-202,205,249,257-258].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[91] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[90] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[259-260]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[102,187,261]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[262]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[95]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[263]. Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression[187,264]. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas[265-266].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[267-268]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[269-270]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[271-272]. One or more alterations observed here are predicted to result in p16INK4a loss of function[273-294]. One or more alterations seen here are predicted to result in p14ARF loss of function[277,294-297]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[298].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[299]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[300-301]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[302-304]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[305-307]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[308]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[309]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[308,310-311], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[312]; dual PRMT1 and PRMT5 inhibition may be more effective[313-315]. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells[316-326]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients[327].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[328-329]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[330], gastrointestinal stromal tumors[331], mantle cell lymphoma (MCL)[332], melanoma[333-334], gastric cancer[335], myxofibrosarcoma[336], nasopharyngeal carcinoma[337], ovarian carcinoma[328] and non-small cell lung cancer[338]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[339] or in astrocytoma[340]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[341], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[342]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[343-344], esophageal cancer[345-346], osteosarcoma[347], and CRC[348].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[349-350]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[330,351-352], thereby reducing intracellular arginine methylation[308,310,353] and altering cell signaling[352,354]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE
MUTYH

ALTERATION
splice site 892-2A>G

TRANSCRIPT ID
NM_001048171

CODING SEQUENCE EFFECT
892-2A>G

VARIANT ALLELE FREQUENCY (% VAF)
44.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2022)[355]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[356-357]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[358-360]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[361].

FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[362]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[356-357,363-365]. Numerous other MUTYH mutations have also been shown to result in loss of function[363-366].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH 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 MUTYH-associated polyposis (ClinVar, Mar 2022)[367]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[356,368-370]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[356]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[371-375]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[357]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
43.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[376]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[377]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[378].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[379-380], most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas[379-383]. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)[379,381]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[95]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[384]. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM[379,381,384-385]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v2.2021).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[386]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[387-389]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[390-392], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[390].

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v2.2021)[393]. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2021)[130].

GENE
TET2

ALTERATION
E1151*

TRANSCRIPT ID
NM_017628

CODING SEQUENCE EFFECT
3451G>T

VARIANT ALLELE FREQUENCY (% VAF)
48.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2022)[259-260]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2022).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[394-395]. Alterations such as seen here may disrupt TET2 function or expression[396-400].

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[401-406]. 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[401-402]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[407]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[405,408-409]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Cetuximab

Assay findings association

EGFR
P596L, amplification, EGFRvIII, EGFRvIII

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[84].

SUPPORTING DATA

A Phase 2 trial of cetuximab with bevacizumab (an anti-VEGF monoclonal antibody) in patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone[410]. However, another Phase 2 study demonstrated that in patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly better PFS and numerical (although not statistically significant) improvement in OS[103].

Erlotinib

Assay findings association

EGFR
P596L, amplification, EGFRvIII, EGFRvIII

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[68,411-413] . For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[414-418] . Responses to erlotinib have been reported for patients with EGFR rearrangements[419-423] .

SUPPORTING DATA

In the MyPathway Phase 2a basket study for advanced solid tumors, 1 of 9 patients with EGFR activation mutations responded to erlotinib monotherapy; the responding patient had urethral adenocarcinoma[424]. A patient with EGFR-mutated metastatic lacrimal gland adenoid cystic carcinoma experienced clinical benefit from erlotinib treatment that was ongoing at 14 months[425]. A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[58]. In a Phase 2 study of 65 patients with GBM or gliosarcoma, treatment with erlotinib, temozolomide, and radiotherapy resulted in longer progression-free survival relative to a historical control study utilizing a regimen of temozolomide and radiotherapy alone (19.3 months vs. 14.1 months)[426]. However, in a Phase 1/2 trial of erlotinib monotherapy in 11 patients with relapsed or refractory GBM or anaplastic astrocytoma, all patients showed disease progression and the drug showed significant toxicity[427]. In addition, a Phase 2 trial of patients with recurrent or progressive GBM treated with erlotinib and sorafenib did not meet its objective of a 30% increase in overall survival time compared with historical controls; sorafenib was found to increase erlotinib clearance[428].

Gefitinib

Assay findings association

EGFR
P596L, amplification, EGFRvIII, EGFRvIII

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[413,429-434] , and responses have been reported for patients with EGFR-rearranged NSCLC[421-422] . For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[414-418] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[414,435] .

SUPPORTING DATA

A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[58]. A Phase 2 clinical study of gefitinib in patients with high-grade glioma (including GBM, anaplastic astrocytoma, and oligodendroglioma) reported 18% (5/28) disease stabilization; efficacy was not correlated with EGFR expression[81]. However, a Phase 1/2 clinical trial of gefitinib combined with radiotherapy in 178 patients with GBM reported no overall survival benefit of added gefitinib, and EGFR expression was found to be of no prognostic value for patients treated with gefitinib plus radiotherapy[82]. A Phase 2 trial of preoperative gefitinib treatment in patients with recurrent GBM reported that although EGFR phosphorylation was decreased in treated patients as compared to the control group, measurement of 12 downstream molecules revealed no significant changes[83].

Imatinib

Assay findings association

PDGFRA
amplification - equivocal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

PDGFRA amplification may predict sensitivity to tyrosine kinase inhibitors such as imatinib; a patient with Merkel cell carcinoma expressing PDGFRA achieved a complete response to imatinib[141].

SUPPORTING DATA

In a clinical study where patients with recurrent glioblastoma were given imatinib, 2/24 patients achieved a PR, 10 patients reported SD, and median OS and PFS was observed to be 6.2 and 3 months, respectively[436]. However, other Phase 2 clinical trials of imatinib have reported no anti-tumor activity, with a study of 231 patients with glioblastoma reporting a radiographic response rate of only 3.4%[125,437] . In another Phase 2 study, imatinib plus hydroxyurea was shown to be well tolerated among patients with recurrent/progressive low-grade glioma, but had negligible antitumor activity[438].

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Panitumumab

Assay findings association

EGFR
P596L, amplification, EGFRvIII, EGFRvIII

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[84].

SUPPORTING DATA

A Phase 1 trial of EnGeneIC delivery vehicle (EDV) targeting EGFR with panitumumab in combination with doxorubicin for 14 patients with glioblastoma (GBM) reported no responses and 28% (4/14) SDs[439]. Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer[440-442] and has been investigated in a variety of other tumor types. For patients with head and neck squamous cell carcinoma (HNSCC), data are conflicting; some trials of panitumumab in various lines and with different chemotherapy combinations have shown modest benefit[443-445] and others have reported no benefit[446-448] . A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility[449]. Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)[450-451] ; biliary tract cancers, including cholangiocarcinoma[452-453] ; and renal cell carcinoma (RCC)[454].

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

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

GENE
CDK6

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

ALTERATION
amplification - equivocal

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)

NCT04594005

PHASE 1/2

CDK4/6 Tumor, Abemaciclib, Paclitaxel

TARGETS
CDK4, CDK6

LOCATIONS: Seoul (Korea, Republic of)

NCT04391595

PHASE NULL

LY3214996 Plus Abemaciclib in Recurrent Glioblastoma Patients

TARGETS
CDK4, CDK6, ERK1, ERK2

LOCATIONS: Arizona

NCT02933736

PHASE NULL

Ribociclib (LEE011) in Preoperative Glioma and Meningioma Patients

TARGETS
CDK6, CDK4

LOCATIONS: Arizona

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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)

NCT03158389

PHASE 1/2

NCT Neuro Master Match - N^2M^2 (NOA-20)

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

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

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

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

NCT02981940

PHASE 2

A Study of Abemaciclib in Recurrent Glioblastoma

TARGETS
CDK4, CDK6

LOCATIONS: Utah, California, Massachusetts

GENE
EGFR

ALTERATION
P596L, amplification, EGFRvIII, EGFRvIII

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

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)

NCT03783403

PHASE 1

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

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Seoul (Korea, Republic of), Heidelberg (Australia), Melbourne (Australia), Edmonton (Canada), Rouen (France), Oregon, Creteil (France), Nantes Cedex 01 (France), Borddeaux Cedex (France), Villejuif CEDEX (France)

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

NCT03618667

PHASE 2

GC1118 in Recurrent Glioblastoma Patients With High EGFR Amplification

TARGETS
EGFR

LOCATIONS: Seoul (Korea, Republic of)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

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

LOCATIONS: Utah

NCT04172597

PHASE 2

A Study of Poziotinib in Patients With EGFR or HER2 Activating Mutations in Advanced Malignancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: California

NCT02800486

PHASE 2

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

TARGETS
EGFR

LOCATIONS: New York

NCT02861898

PHASE 1/2

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

TARGETS
EGFR

LOCATIONS: New York

NCT04547777

PHASE 1

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

TARGETS
EGFRvIII, CD40

LOCATIONS: North Carolina

NCT02303678

PHASE 1

D2C7 for Adult Patients With Recurrent Malignant Glioma

TARGETS
EGFRvIII

LOCATIONS: North Carolina

GENE
MDM2

ALTERATION
amplification

RATIONALE
Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or amplification of MDM2 may increase sensitivity to these agents, but more data are required.

NCT04589845

PHASE 2

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

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

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing City (China), Beijing (China), Chengdu City (China)

NCT04785196

PHASE 1/2

APG-115 in Combination With PD-1 Inhibitor in Patients With Advanced Liposarcoma or Advanced Solid Tumors

TARGETS
PD-1, MDM2

LOCATIONS: Shanghai (China), Guangzhou (China)

NCT03449381

PHASE 1

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TARGETS
MDM2

LOCATIONS: Tokyo, Chuo-ku (Japan), Warsaw (Poland), Poznan (Poland), Berlin (Germany), Köln (Germany), Tübingen (Germany), Leuven (Belgium), Barcelona (Spain), Ottawa (Canada), Connecticut

NCT03158389

PHASE 1/2

NCT Neuro Master Match - N^2M^2 (NOA-20)

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

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

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Brisbane (Australia), South Brisbane (Australia), Bedford Park (Australia), Heidelberg (Australia), California, Arizona, Missouri, Arkansas, Ohio, Pennsylvania

NCT03725436

PHASE 1

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

TARGETS
MDM2, MDM4

LOCATIONS: Texas

GENE
PDGFRA

RATIONALE
PDGFRA amplification may predict sensitivity to imatinib and to anti-PDGFRA antibodies.

ALTERATION
amplification - equivocal

NCT01738139	**PHASE 1**
Ipilimumab and Imatinib Mesylate in Advanced Cancer	**TARGETS** KIT, ABL, CTLA-4

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.

ATM
Y171C

DAXX
E457del

EGFR
Y610C and rearrangement

MSH6
K1358fs*2

NOTCH1
A1325T

PTEN
Y16S

ROS1
S2255L

Electronically signed by Erik Williams, M.D. | 31 May 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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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*	*ETV1*
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)

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-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 6.3.0

The median exon coverage for this sample is 257x

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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Martinez R, et al. Oncology (2004) pmid: 15331927
7. Martinez R, et al. J. Cancer Res. Clin. Oncol. (2005) pmid: 15672285
8. Martinez R, et al. Cancer Genet. Cytogenet. (2007) pmid: 17498554
9. Szybka M, et al. Clin. Neuropathol. () pmid: 12908754
10. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
11. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
12. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
13. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
14. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
15. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
16. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
17. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
18. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
19. Cristescu R, et al. Science (2018) pmid: 30309915
20. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
21. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
22. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
23. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
24. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
25. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
26. Zhao J, et al. Nat. Med. (2019) pmid: 30742119
27. Touat M, et al. Nature (2020) pmid: 32322066
28. Bouffet E, et al. J. Clin. Oncol. (2016) pmid: 27001570
29. Johanns TM, et al. Cancer Discov (2016) pmid: 27683556
30. Lukas RV, et al. J. Neurooncol. (2018) pmid: 30073642
31. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
32. Patel RR, et al. Pediatr Blood Cancer (2020) pmid: 32386112
33. Johnson A, et al. Oncologist (2017) pmid: 28912153
34. Draaisma K, et al. Acta Neuropathol Commun (2015) pmid: 26699864
35. Wang L, et al. BMC Cancer (2020) pmid: 32164609
36. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
37. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
38. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
39. Rizvi NA, et al. Science (2015) pmid: 25765070
40. Johnson BE, et al. Science (2014) pmid: 24336570
41. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
42. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
43. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
44. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
45. Nature (2012) pmid: 22810696
46. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
47. van den Bent MJ, et al. J Clin Oncol (2009) pmid: 19204207
48. Haas-Kogan DA, et al. J Natl Cancer Inst (2005) pmid: 15956649
49. Brown PD, et al. J Clin Oncol (2008) pmid: 18955445
50. Preusser M, et al. J Neurooncol (2008) pmid: 18458820
51. Wen PY, et al. Neuro-oncology (2014) pmid: 24470557
52. Gallego O, et al. J Neurooncol (2014) pmid: 24352766
53. Uhm JH, et al. Int J Radiat Oncol Biol Phys (2011) pmid: 20510539
54. Doyle SP, et al. Oxf Med Case Reports (2018) pmid: 30410775
55. D'Alessandris QG, et al. Acta Neurochir (Wien) (2013) pmid: 23132371
56. Custodio A, et al. Clin Transl Oncol (2010) pmid: 20462843
57. D'Alessandris QG, et al. Acta Neurochir (Wien) (2018) pmid: 30306271
58. Mellinghoff IK, et al. N. Engl. J. Med. (2005) pmid: 16282176
59. Mellinghoff IK, et al. Clin Cancer Res (2007) pmid: 17255257
60. Arif SH, et al. Asian J Neurosurg () pmid: 29492119
61. Reardon DA, et al. Neuro-oncology (2015) pmid: 25140039
62. Alshami J, et al. Oncotarget (2015) pmid: 26423602
63. Sepúlveda-Sánchez JM, et al. Neuro-oncology (2017) pmid: 28575464
64. Chi AS, et al. JCO Precis Oncol (2020) pmid: 32923886
65. Makhlin I, et al. CNS Oncol (2019) pmid: 31769726
66. Reardon DA, et al. Clin Cancer Res (2020) pmid: 32034072
67. Weller M, et al. Lancet Oncol (2017) pmid: 28844499
68. Rosell R, et al. Lancet Oncol. (2012) pmid: 22285168
69. Douillard JY, et al. Br. J. Cancer (2014) pmid: 24263064
70. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
71. Mok TS, et al. J. Clin. Oncol. (2018) pmid: 29864379
72. Jänne PA, et al. N. Engl. J. Med. (2015) pmid: 25923549
73. Hong MH, et al. Cancer (2020) pmid: 32749686
74. Kim HS, et al. Oncotarget (2015) pmid: 26462025
75. Kim HS, et al. Clin. Cancer Res. (2015) pmid: 25424851
76. Mondal G, et al. Acta Neuropathol (2020) pmid: 32303840
77. Cavalieri S, et al. Eur. J. Cancer (2018) pmid: 29734047
78. Goyal A, et al. World Neurosurg (2021) pmid: 33940677
79. Tanaka S, et al. Sci Rep (2019) pmid: 30644426
80. Blumenthal DT, et al. J. Neurooncol. (2016) pmid: 27531351
81. Franceschi E, et al. Br. J. Cancer (2007) pmid: 17353924
82. Chakravarti A, et al. Int. J. Radiat. Oncol. Biol. Phys. (2013) pmid: 23182702
83. Hegi ME, et al. Mol. Cancer Ther. (2011) pmid: 21471286
84. Jiang Z, et al. PLoS ONE (2013) pmid: 23441167
85. Licitra L, et al. Ann. Oncol. (2011) pmid: 21048039
86. Smyth EC, et al. Gut (2021) pmid: 33199443
87. Lassman et al., 2019; Neuro-Oncology Abstract ACTR-21
88. Van Den Bent M, et al. Neuro Oncol (2020) pmid: 31747009
89. Jonsson P, et al. Clin. Cancer Res. (2019) pmid: 31263031
90. Brennan CW, et al. Cell (2013) pmid: 24120142
91. Ceccarelli M, et al. Cell (2016) pmid: 26824661
92. Thomas AA, et al. Neuro-oncology (2017) pmid: 28472509
93. Lee JC, et al. PLoS Med. (2006) pmid: 17177598
94. Vivanco I, et al. Cancer Discov (2012) pmid: 22588883
95. Yan et al. 2020; DOI:10.1200/PO.19.00385
96. Nishikawa R, et al. Proc. Natl. Acad. Sci. U.S.A. (1994) pmid: 8052651
97. Shinojima N, et al. Cancer Res. (2003) pmid: 14583498
98. Nishikawa R, et al. Brain Tumor Pathol (2004) pmid: 15700833
99. Viana-Pereira M, et al. Anticancer Res. () pmid: 18507036
100. Yoshimoto K, et al. Clin. Cancer Res. (2008) pmid: 18223223
101. Larysz D, et al. Folia Neuropathol (2011) pmid: 21455841
102. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
103. Lv S, et al. Int. J. Oncol. (2012) pmid: 22752145
104. Srividya MR, et al. J. Clin. Pathol. (2010) pmid: 20702468
105. Das P, et al. J Clin Neurosci (2011) pmid: 20888234
106. Smith JS, et al. J. Natl. Cancer Inst. (2001) pmid: 11504770
107. Montano N, et al. Neoplasia (2011) pmid: 22241957
108. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
109. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
110. Bhargava R, et al. Mod. Pathol. (2005) pmid: 15920544
111. Yang YL, et al. Chin. Med. J. (2012) pmid: 22490401
112. Nedergaard MK, et al. BioDrugs (2012) pmid: 22385404
113. Foster JM, et al. World J Surg Oncol (2010) pmid: 20942962
114. Cai CQ, et al. Oncogene (2008) pmid: 18193092
115. Stabile LP, et al. Cancer Res. (2005) pmid: 15735034
116. Zhang W, et al. J Thorac Oncol (2006) pmid: 17409930
117. Siegfried JM, et al. J Thorac Oncol (2012) pmid: 22258476
118. U M, et al. PLoS Comput. Biol. (2014) pmid: 24743239
119. Cho J, et al. Mol. Cancer (2014) pmid: 24894453
120. Hama T, et al. Oncologist (2009) pmid: 19726454
121. Tam IY, et al. Mol. Cancer Ther. (2009) pmid: 19671738
122. Kancha RK, et al. Clin. Cancer Res. (2009) pmid: 19147750
123. Chen YR, et al. Oncogene (2006) pmid: 16205628
124. Ymer SI, et al. Cancers (Basel) (2011) pmid: 24212795
125. Razis E, et al. Clin. Cancer Res. (2009) pmid: 19789313
126. Wang H, et al. Neoplasia (2011) pmid: 21532887
127. Kim N, et al. Int. J. Cancer (2019) pmid: 31290142
128. Sueangoen N, et al. Cell Biosci (2020) pmid: 32190291
129. Lundby A, et al. Cell (2019) pmid: 31585087
130. Louis DN, et al. Neuro Oncol (2021) pmid: 34185076
131. Arefi M, et al. Int. J. Hematol. (2012) pmid: 22806436
132. Baccarani M, et al. Haematologica (2007) pmid: 17666373
133. Cassier PA, et al. Clin. Cancer Res. (2012) pmid: 22718859
134. Chalmers ZR, et al. Blood Cancer J (2015) pmid: 25658984
135. Cools J, et al. N. Engl. J. Med. (2003) pmid: 12660384
136. Curtis CE, et al. Br. J. Haematol. (2007) pmid: 17555450
137. Debiec-Rychter M, et al. Eur. J. Cancer (2004) pmid: 15010069
138. Dileo P, et al. Int. J. Cancer (2011) pmid: 20473908
139. Fanta PT, et al. J. Clin. Oncol. (2015) pmid: 24638008
140. Florian S, et al. Leuk. Res. (2006) pmid: 16406018
141. Frenard C, et al. JAAD Case Rep (2016) pmid: 27051816
142. Griffin JH, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808148
143. Heinrich MC, et al. J. Clin. Oncol. (2003) pmid: 14645423
144. Helbig G, et al. Br. J. Haematol. (2009) pmid: 19120352
145. Helbig G, et al. Am. J. Hematol. (2014) pmid: 24009127
146. Hus M, et al. Leuk. Res. (2011) pmid: 21093052
147. Ikezoe T, et al. Leuk. Res. (2010) pmid: 20303172
148. Intermesoli T, et al. Br. J. Haematol. (2009) pmid:

19735261
149. Jain N, et al. Leuk. Res. (2009) pmid: 19013640
150. Jovanovic JV, et al. Blood (2007) pmid: 17299092
151. Kang HJ, et al. Acta Oncol (2012) pmid: 22150077
152. Klion AD, et al. Blood (2004) pmid: 14504092
153. Kobayashi M, et al. Respirology (2009) pmid: 19192229
154. Kocáková I, et al. Klin Onkol (2014) pmid: 24635438
155. Metzgeroth G, et al. Br. J. Haematol. (2008) pmid: 18950453
156. Murayama Y, et al. World J Gastrointest Oncol (2012) pmid: 22645636
157. Ogbogu PU, et al. J. Allergy Clin. Immunol. (2009) pmid: 19910029
158. Ohnishi H, et al. Br. J. Haematol. (2006) pmid: 16856885
159. Pardanani A, et al. Blood (2003) pmid: 12842979
160. Pardanani A, et al. Blood (2004) pmid: 15284118
161. Qu SQ, et al. Oncotarget (2016) pmid: 27120808
162. Score J, et al. Leukemia (2006) pmid: 16498388
163. Shah S, et al. J Hematol Oncol (2014) pmid: 24669761
164. Sugimoto Y, et al. Cancer Genet (2015) pmid: 26319757
165. Volz HC, et al. Int. J. Cardiol. (2011) pmid: 20609486
166. von Bubnoff N, et al. Leukemia (2005) pmid: 15618966
167. Walz C, et al. Genes Chromosomes Cancer (2006) pmid: 16845659
168. Yoo C, et al. Cancer Res Treat (2016) pmid: 26130666
169. Al-Riyami AZ, et al. Leuk. Lymphoma (2013) pmid: 23157309
170. Lierman E, et al. Blood (2006) pmid: 16645167
171. Lierman E, et al. Leukemia (2009) pmid: 19212337
172. Metzgeroth G, et al. Leukemia (2012) pmid: 21818111
173. Roubaud G, et al. Ann. Oncol. (2012) pmid: 22294526
174. von Bubnoff N, et al. Oncogene (2011) pmid: 20972453
175. Hochhaus A, et al. J. Cancer Res. Clin. Oncol. (2013) pmid: 24057647
176. Tabouret E, et al. Leuk. Res. (2011) pmid: 20832858
177. Dewaele B, et al. Clin. Cancer Res. (2008) pmid: 18794084
178. Weisberg E, et al. Gastroenterology (2006) pmid: 17087936
179. Brohl AS, et al. Clin Sarcoma Res (2015) pmid: 26396737
180. Grellety T, et al. Future Sci OA (2015) pmid: 28031906
181. Kollàr A, et al. Clin Sarcoma Res (2014) pmid: 25905001
182. Evans EK, et al. Sci Transl Med (2017) pmid: 29093181
183. Jaku et al., 2017; ASCO Abstract 2515
184. Holtkamp N, et al. Neuro-oncology (2007) pmid: 17504929
185. Phillips JJ, et al. Brain Pathol. (2013) pmid: 23438035
186. Motomura K, et al. J. Neuropathol. Exp. Neurol. (2013) pmid: 23242283
187. Sottoriva A, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23412337
188. Nobusawa S, et al. Neuropathology (2011) pmid: 21382095
189. Joensuu H, et al. J. Pathol. (2005) pmid: 16021678
190. Alentorn A, et al. Neuro-oncology (2012) pmid: 23074200
191. Song K, et al. Am J Cancer Res (2018) pmid: 29888103
192. Puputti M, et al. Mol. Cancer Res. (2006) pmid: 17189383
193. Szerlip NJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22323597
194. Andrae J, et al. Genes Dev. (2008) pmid: 18483217
195. Semin. Oncol. (2004) pmid: 15175998
196. Burford A, et al. PLoS ONE (2013) pmid: 23990986
197. Flavahan WA, et al. Nature (2016) pmid: 26700815
198. Roszik J, et al. Sci Rep (2016) pmid: 26787600
199. Koschmann C, et al. Oncotarget (2016) pmid: 27582545
200. Puget S, et al. PLoS ONE (2012) pmid: 22389665
201. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
202. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
203. Turner NC, et al. N. Engl. J. Med. (2015) pmid: 26030518
204. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
205. Peguero et al., 2016; ASCO Abstract 2528
206. Konecny et al., 2016; ASCO Abstract 5557
207. Nature (2008) pmid: 18772890
208. Bax DA, et al. Clin. Cancer Res. (2010) pmid: 20570930
209. Hodgson JG, et al. Neuro-oncology (2009) pmid: 19139420
210. Ruano Y, et al. Mol. Cancer (2006) pmid: 17002787
211. Costello JF, et al. Cancer Res. (1997) pmid: 9102208
212. Li B, et al. Oncol. Rep. (2012) pmid: 22736304
213. Lam PY, et al. Br J Neurosurg (2000) pmid: 10884881
214. Chen SM, et al. World J Surg Oncol (2013) pmid: 23594394
215. Michaud K, et al. Cancer Res. (2010) pmid: 20354191
216. Meyerson M, et al. Mol. Cell. Biol. (1994) pmid: 8114739
217. Grossel MJ, et al. J. Cell. Biochem. (2006) pmid: 16294322
218. Choi YJ, et al. Oncogene (2014) pmid: 23644662
219. Cell (1995) pmid: 7736585
220. Musgrove EA, et al. Nat. Rev. Cancer (2011) pmid: 21734724
221. Ismail A, et al. Clin. Cancer Res. (2011) pmid: 21593195
222. van Dekken H, et al. Cancer Genet. Cytogenet. (2009) pmid: 19167610
223. Cheok CF, et al. Nat Rev Clin Oncol (2011) pmid: 20975744
224. Ohnstad HO, et al. Cancer (2013) pmid: 23165797
225. Gamble LD, et al. Oncogene (2012) pmid: 21725357
226. Zhang et al., 2019; ASCO Abstract 3124
227. Rasco et al., 2019; ASCO Abstract 3126
228. Tolcher et al., 2021; ASCO Abstract 2506
229. Martinelli et al., 2016; EHA21 Abstract S504
230. Daver et al., 2018; ASH Abstract 767
231. Mascarenhas et al., 2019; ASH Abstract 134
232. Shustov et al., 2018; ASH Abstract 1623
233. Sallman et al., 2018; ASH Abstract 4066
234. Meric-Bernstam et al., 2017; ASCO Abstract 2505
235. Zheng S, et al. Genes Dev. (2013) pmid: 23796897
236. Fischer U, et al. Int. J. Cancer (2010) pmid: 19839052
237. Sdek P, et al. Mol. Cell (2005) pmid: 16337594
238. Brady M, et al. Mol. Cell. Biol. (2005) pmid: 15632057
239. Li M, et al. Mol. Cell (2004) pmid: 15053880
240. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
241. Cordon-Cardo C, et al. Cancer Res. (1994) pmid: 8306343
242. Beroukhim R, et al. Nature (2010) pmid: 20164920
243. Kato S, et al. Clin. Cancer Res. (2017) pmid: 28351930
244. Singavi et al., 2017; ESMO Abstract 1140PD
245. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
246. Elvin JA, et al. Oncologist (2017) pmid: 28283584
247. Gao J, et al. Curr Oncol (2015) pmid: 26715889
248. Gopalan et al., 2014; ASCO Abstract 8077
249. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
250. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
251. Johnson DB, et al. Oncologist (2014) pmid: 24797823
252. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
253. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
254. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
255. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
256. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
257. Shapiro et al., 2013; ASCO Abstract 2500
258. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
259. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
260. Gao J, et al. Sci Signal (2013) pmid: 23550210
261. Weber RG, et al. Oncogene (2007) pmid: 16909113
262. Nakamura M, et al. Brain Pathol. (2001) pmid: 11303791
263. Chakravarti A, et al. Clin. Cancer Res. (2001) pmid: 11489817
264. Feng J, et al. Cancer (2012) pmid: 21713760
265. Raabe EH, et al. Clin. Cancer Res. (2011) pmid: 21636552
266. Liu W, et al. J. Exp. Clin. Cancer Res. (2011) pmid: 21843312
267. Quelle DE, et al. Cell (1995) pmid: 8521522
268. Mutat. Res. (2005) pmid: 15878778
269. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
270. Oncogene (1999) pmid: 10498883
271. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
272. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
273. Ruas M, et al. Oncogene (1999) pmid: 10498896
274. Jones R, et al. Cancer Res. (2007) pmid: 17909018
275. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
276. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
277. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
278. Gombart AF, et al. Leukemia (1997) pmid: 9324288
279. Yang R, et al. Cancer Res. (1995) pmid: 7780957
280. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
281. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
282. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
283. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
284. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
285. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
286. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
287. Koh J, et al. Nature (1995) pmid: 7777061
288. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
289. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
290. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
291. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
292. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
293. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
294. Rutter JL, et al. Oncogene (2003) pmid: 12853981
295. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
296. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
297. Zhang Y, et al. Cell (1998) pmid: 9529249
298. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
299. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
300. Adv Exp Med Biol (2010) pmid: 20687502
301. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
302. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
303. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
304. Huerta C, et al. Acta Derm Venereol (2018) pmid:

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29405243
305. Kaufman DK, et al. Neurology (1993) pmid: 8414022
306. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
307. Chan AK, et al. Clin Neuropathol () pmid: 28699883
308. Marjon K, et al. Cell Rep (2016) pmid: 27068473
309. Heist et al., 2019; AACR-NCI-EORTC Abstract B116
310. Mavrakis KJ, et al. Science (2016) pmid: 26912361
311. Endoscopy (1989) pmid: 2691236
312. Guccione E, et al. Nat. Rev. Mol. Cell Biol. (2019) pmid: 31350521
313. Fedoriw A, et al. Cancer Cell (2019) pmid: 31257072
314. Srour N, et al. Cancer Cell (2019) pmid: 31287990
315. Gao G, et al. Nucleic Acids Res. (2019) pmid: 30916320
316. Hansen LJ, et al. Cancer Res. (2019) pmid: 31040154
317. Tang B, et al. Cancer Res. (2018) pmid: 29844120
318. Munshi PN, et al. Oncologist (2014) pmid: 24928612
319. de Oliveira SF, et al. PLoS ONE (2016) pmid: 26751376
320. Lubin M, et al. PLoS ONE (2009) pmid: 19478948
321. Tang B, et al. Cancer Biol. Ther. (2012) pmid: 22825330
322. Collins CC, et al. Mol. Cancer Ther. (2012) pmid: 22252602
323. Bertino JR, et al. Cancer Biol. Ther. (2011) pmid: 21301207
324. Coulthard SA, et al. Mol. Cancer Ther. (2011) pmid: 21282358
325. Miyazaki S, et al. Int. J. Oncol. (2007) pmid: 17912432
326. Efferth T, et al. Blood Cells Mol. Dis. () pmid: 11987241
327. Kindler HL, et al. Invest New Drugs (2009) pmid: 18618081
328. Wei R, et al. Sci Rep (2016) pmid: 27929028
329. Zhao M, et al. BMC Genomics (2016) pmid: 27556634
330. Kirovski G, et al. Am. J. Pathol. (2011) pmid: 21356366
331. Huang HY, et al. Clin. Cancer Res. (2009) pmid: 19887491
332. Marcé S, et al. Clin. Cancer Res. (2006) pmid: 16778103
333. Meyer S, et al. Exp. Dermatol. (2010) pmid: 20500769
334. Wild PJ, et al. Arch Dermatol (2006) pmid: 16618867
335. Kim J, et al. Genes Chromosomes Cancer (2011) pmid: 21412930
336. Li CF, et al. Oncotarget (2014) pmid: 25426549
337. He HL, et al. Medicine (Baltimore) (2015) pmid: 26656376
338. Su CY, et al. Eur J Surg Oncol (2014) pmid: 24969958
339. Mirebeau D, et al. Haematologica (2006) pmid: 16818274
340. Becker AP, et al. Pathobiology (2015) pmid: 26088413
341. Snezhkina AV, et al. Oxid Med Cell Longev (2016) pmid: 27433286
342. Bistulfi G, et al. Oncotarget (2016) pmid: 26910893
343. Antonopoulou K, et al. J. Invest. Dermatol. (2015) pmid: 25407435
344. Maccioni L, et al. BMC Cancer (2013) pmid: 23816148
345. Hyland PL, et al. Int J Epidemiol (2016) pmid: 26635288
346. Lin X, et al. Cancer Sci. (2017) pmid: 27960044
347. Zhi L, et al. J Cancer (2016) pmid: 27994653
348. Gu F, et al. Br. J. Cancer (2013) pmid: 23361049
349. Limm K, et al. PLoS ONE (2016) pmid: 27479139
350. Tang B, et al. G3 (Bethesda) (2014) pmid: 25387827
351. Limm K, et al. Eur. J. Cancer (2013) pmid: 23265702
352. Stevens AP, et al. J. Cell. Biochem. (2009) pmid: 19097084
353. Kryukov GV, et al. Science (2016) pmid: 26912360
354. Limm K, et al. Eur. J. Cancer (2014) pmid: 25087184
355. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
356. Hegde M, et al. Genet. Med. (2014) pmid: 24310308
357. Aretz S, et al. Eur. J. Hum. Genet. (2013) pmid: 22872101
358. Win AK, et al. Gastroenterology (2014) pmid: 24444654
359. Lubbe SJ, et al. J. Clin. Oncol. (2009) pmid: 19620482
360. Jones N, et al. Gastroenterology (2009) pmid: 19394335
361. Nielsen M, et al. J. Natl. Cancer Inst. (2010) pmid: 21044966
362. David SS, et al. Nature (2007) pmid: 17581577
363. Molatore S, et al. Hum. Mutat. (2010) pmid: 19953527
364. Kundu S, et al. DNA Repair (Amst.) (2009) pmid: 19836313
365. D'Agostino VG, et al. DNA Repair (Amst.) (2010) pmid: 20418187
366. Ali M, et al. Gastroenterology (2008) pmid: 18534194
367. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
368. Sampson JR, et al. Lancet (2003) pmid: 12853198
369. Sieber OM, et al. N. Engl. J. Med. (2003) pmid: 12606733
370. Al-Tassan N, et al. Nat. Genet. (2002) pmid: 11818965
371. Rennert G, et al. Cancer (2012) pmid: 21952991
372. Zhang Y, et al. Cancer Epidemiol. Biomarkers Prev. (2006) pmid: 16492928
373. von der Thüsen JH, et al. J. Clin. Oncol. (2011) pmid: 21189386
374. Casper M, et al. Fam. Cancer (2014) pmid: 24420788
375. Smith LM, et al. Pancreatology (2009) pmid: 20110747
376. Nat Rev Clin Oncol (2017) pmid: 27245281
377. Duperret EK, et al. Mol Ther (2018) pmid: 29249395
378. Chiappori AA, et al. Ann Oncol (2015) pmid: 25467017
379. Killela PJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23530248
380. Killela PJ, et al. Oncotarget (2014) pmid: 24722048
381. Nonoguchi N, et al. Acta Neuropathol. (2013) pmid: 23955565
382. Liu X, et al. Cell Cycle (2013) pmid: 23603989
383. Koelsche C, et al. Acta Neuropathol. (2013) pmid: 24154961
384. Arita H, et al. Acta Neuropathol. (2013) pmid: 23764841
385. Reitman ZJ, et al. Acta Neuropathol. (2013) pmid: 24217890
386. Shay JW, et al. Semin. Cancer Biol. (2011) pmid: 22015685
387. Shay JW, et al. Eur. J. Cancer (1997) pmid: 9282118
388. Kim NW, et al. Science (1994) pmid: 7605428
389. Hanahan D, et al. Cell (2000) pmid: 10647931
390. Horn S, et al. Science (2013) pmid: 23348503
391. Huang FW, et al. Science (2013) pmid: 23348506
392. Vinagre J, et al. Nat Commun (2013) pmid: 23887589
393. Weller M, et al. Nat Rev Clin Oncol (2021) pmid: 33293629
394. Ito S, et al. Nature (2010) pmid: 20639862
395. Guo JU, et al. Cell (2011) pmid: 21496894
396. Iyer LM, et al. Cell Cycle (2009) pmid: 19411852
397. Ko M, et al. Nature (2010) pmid: 21057493
398. Yang H, et al. Oncogene (2013) pmid: 22391558
399. Hu L, et al. Cell (2013) pmid: 24315485
400. Wang Y, et al. Mol. Cell (2015) pmid: 25601757
401. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
402. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
403. Xie M, et al. Nat. Med. (2014) pmid: 25326804
404. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
405. Severson EA, et al. Blood (2018) pmid: 29678827
406. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
407. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
408. Chabon JJ, et al. Nature (2020) pmid: 32269342
409. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
410. Hasselbalch B, et al. Neuro-oncology (2010) pmid: 20406901
411. Cappuzzo F, et al. Lancet Oncol. (2010) pmid: 20493771
412. Zhong WZ, et al. J. Clin. Oncol. (2019) pmid: 31194613
413. Petrelli F, et al. Clin Lung Cancer (2012) pmid: 22056888
414. Petty RD, et al. J. Clin. Oncol. (2017) pmid: 28537764
415. Philip PA, et al. J. Clin. Oncol. (2006) pmid: 16809731
416. Xie C, et al. Br J Cancer (2020) pmid: 32958820
417. Luo H, et al. JAMA Netw Open (2020) pmid: 33026449
418. Lee J, et al. Lancet Oncol. (2012) pmid: 22192731
419. Konduri K, et al. Cancer Discov (2016) pmid: 27102076
420. Zhu YC, et al. Lung Cancer (2018) pmid: 29290255
421. Wang J, et al. Int. J. Cancer (2019) pmid: 30255937
422. Baik CS, et al. J Thorac Oncol (2015) pmid: 26398831
423. Xu et al., 2018; ASCO Abstract e13538
424. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
425. Nie KK, et al. Chin Med J (Engl) (2018) pmid: 29998897
426. Prados MD, et al. J. Clin. Oncol. (2009) pmid: 19075262
427. Kesavabhotla K, et al. J. Exp. Ther. Oncol. (2012) pmid: 22946346
428. Peereboom DM, et al. Neuro-oncology (2013) pmid: 23328813
429. Han JY, et al. J. Clin. Oncol. (2012) pmid: 22370314
430. Maemondo M, et al. N. Engl. J. Med. (2010) pmid: 20573926
431. Mitsudomi T, et al. Lancet Oncol. (2010) pmid: 20022809
432. Mok TS, et al. N. Engl. J. Med. (2009) pmid: 19692680
433. Qi WX, et al. Curr Med Res Opin (2015) pmid: 25329826
434. Zhao H, et al. J Thorac Oncol (2015) pmid: 25546556
435. Dutton SJ, et al. Lancet Oncol. (2014) pmid: 24950987
436. Hassler MR, et al. Springerplus (2014) pmid: 25674429
437. Reardon DA, et al. Br. J. Cancer (2009) pmid: 19904263
438. Reardon DA, et al. Cancer (2012) pmid: 22371319
439. Whittle JR, et al. J Clin Neurosci (2015) pmid: 26279503
440. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
441. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896
442. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
443. Vermorken JB, et al. Lancet Oncol (2013) pmid: 23746666
444. Wirth LJ, et al. Ann. Oncol. (2010) pmid: 19892746
445. Siano M, et al. Oncologist (2017) pmid: 28592616
446. Mesía R, et al. Lancet Oncol (2015) pmid: 25596660
447. Giralt J, et al. Lancet Oncol (2015) pmid: 25596659
448. Siu LL, et al. JAMA Oncol (2016) pmid: 27930762
449. Waddell T, et al. Lancet Oncol. (2013) pmid: 23594787
450. Crawford J, et al. J Thorac Oncol (2013) pmid: 24389433
451. Schuette W, et al. Clin Lung Cancer (2015) pmid: 26094080
452. Leone F, et al. Cancer (2016) pmid: 26540314
453. Vogel A, et al. Eur J Cancer (2018) pmid: 29413685
454. Rowinsky EK, et al. J. Clin. Oncol. (2004) pmid: 15210739

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