FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Li, Hsiao-Shu	Brain glioblastoma (GBM)	19 Apr 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1341405-01

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 Li, Hsiao-Shu
DATE OF BIRTH 23 October 1968
SEX Female
MEDICAL RECORD # 48358129

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 S111-12417A (PF22048)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 25 March 2022
SPECIMEN RECEIVED 11 April 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

EGFR amplification, EGFRvIII
BARD1 A25fs*41
HGF amplification - equivocal†
MDM4 amplification
CDKN2A/B CDKN2B loss, CDKN2A loss
MTAP loss
PIK3C2B amplification
TERT promoter -124C>T

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

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***EGFR* amplification** (p. 4), ***TERT* promoter -124C>T** (p. 8)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cetuximab** (p. 9), **Panitumumab** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***TERT* promoter -124C>T** (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***EGFR* -** amplification, EGFRvIII	none	Cetuximab
7 Trials *see p. 12*		Panitumumab
***BARD1* -** A25fs*41	none	none
10 Trials *see p. 10*		
***HGF* -** amplification - equivocal	none	none
2 Trials *see p. 14*		
***MDM4* -** amplification	none	none
1 Trial *see p. 15*		

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

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

GENE
EGFR

ALTERATION
amplification, EGFRvIII

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]. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy[61,63-64,68-69]; however, a small subset of patients has experienced clinical benefit[63-64,68]. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma[58,70-72]. 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[73]. 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[74-75]. 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)[76]. 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)[77].

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)[78-81]. 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[78-81]. 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[82-83]. 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[84]. The EGFRvIII mutation has been variously reported in 6-46% of GBM samples[58,85-92]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[93-94]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[95]. 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[96].

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[97]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[98-100]. 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[85]. This deletion has shown to result in ligand-independent (constitutive) phosphorylation and activation of EGFR, as well as consequent tumorigenesis[85,101].

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)[102].

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
BARD1

ALTERATION
A25fs*41

TRANSCRIPT ID
NM_000465

CODING SEQUENCE EFFECT
69_70GC>TCCGGGAACGAGCCTCGTTCCGCGT

VARIANT ALLELE FREQUENCY (% VAF)
61.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical benefit from rucaparib has been observed in a patient with BARD1-mutated ovarian cancer[103]. On the basis of preclinical evidence, tumors with BARD1 inactivation may be sensitive to PARP inhibitors[104-107].

FREQUENCY & PROGNOSIS

BARD1 mutations have been reported in fewer than 1% of low-grade glioma and glioblastoma samples across several genomic studies[79-80,108]. Published data investigating the prognostic implications of BARD1 alterations in gliomas and astrocytomas are limited (PubMed, Oct 2021).

FINDING SUMMARY

BARD1 encodes the BRCA1-associated RING domain 1 protein, which is required for stabilization and nuclear localization of BRCA1 as well as formation of the E3 ubiquitin ligase[109]. The BARD1 ANK repeats and BRCT motifs play important roles in chromosome stability, and both these regions and the RING domain are necessary for homology-directed repair[104,110-111]. Alterations such as seen here may disrupt BARD1 function or expression.

GENE
HGF

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of several preclinical studies in different cancer types, high HGF gene expression may associate with sensitivity to MET-targeted therapies, such as the approved multikinase inhibitors crizotinib and cabozantinib[112-116]. However, this hypothesis has not been extensively tested in clinical studies. Whereas patients with glioblastoma and high tumor HGF gene expression experienced longer survival and a higher objective response rate (5/14 vs. 0/16) on the MET-targeting antibody onartuzumab combined with the anti-VEGF antibody bevacizumab than with placebo plus bevacizumab[117], tumor HGF gene expression did not predict significant benefit from onartuzumab added to the EGFR-inhibitor erlotinib for patients with non-small cell lung cancer[118]. Anti-HGF antibodies, such as ficlatuzumab, are also under clinical investigation[119-120].

— Potential Resistance —

Preclinical studies have shown that increased HGF protein levels can induce resistance of EGFR-mutant lung tumors to EGFR inhibitors and of BRAF-mutant melanoma cells to RAF inhibitors; this resistance could be overcome by combination therapy with MET inhibitors[121-126].

FREQUENCY & PROGNOSIS

HGF amplification has been reported most frequently in esophagogastric carcinoma (2-4%), prostate carcinoma (0-5%), and mucosal melanoma (3%), but rarely in other solid tumors[127-128]. HGF expression within tumor glioma cells is associated with high-grade glioma and increased microvessels, and tumor-derived HGF expression has been shown to correlate with reduced survival time[129]. Elevated expression of HGF and MET mRNA have been reported in GBM[130-131], and HGF expression in GBM models has been shown to be associated with responsiveness to MET inhibition[112].

FINDING SUMMARY

HGF encodes hepatocyte growth factor, also known as scatter factor, an activating ligand of the receptor tyrosine kinase MET. Certain splice isoforms of HGF may also act as MET antagonists[132-133]. HGF plays an important role in normal development, acting as a growth factor in a number of different tissues[132-133]. HGF and its receptor, MET, have been implicated in growth, invasion, and metastasis of many solid tumors[133]. HGF has been reported to be amplified in cancer[134], and may be biologically relevant in this context[135-136].

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
MDM4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Numerous small molecules targeting MDM4 or the MDM2-MDM4 complex, including nutlins, are in preclinical and clinical development[137-143] and have been shown to be effective against cancer cells in the presence of a wild-type p53 allele[144-147]. However, higher MDM4 protein expression has been reported in Nutlin-3 non-responder chronic lymphocytic leukemia patients than in responder patients[148]. Additional therapeutic mechanisms that target MDM4 are also in preclinical development[142-143].

FREQUENCY & PROGNOSIS

In the TCGA dataset, amplification of MDM4 was observed in 8.5% of glioblastoma cases[79]. MDM4 amplification or amplification of the 1q32.1 chromosomal locus, which encompasses MDM4 and PIK3C2B, has been frequently reported, particularly in Grade 3 and 4 astrocytoma or glioblastoma multiforme (GBM) cases; one study reported MDM4 amplification in 27% (23/86) of astrocytoma samples[149-154]. A study also reported MDM4 amplification in 4% (4/106) of GBMs and in 4% (1/27) of anaplastic oligodendrogliomas; MDM4 amplification was not detected in any of the 56 low-grade (Grade 1 or 2) gliomas investigated[154]. The association of MDM4 amplification with tumor grade in astrocytomas is unclear[149-150].

FINDING SUMMARY

MDM4 acts as a negative regulator of p53, but a fraction of MDM4 localized to the mitochondria acts in concert with p53 to promote apoptosis[155]. MDM4 has been reported to be amplified in cancer and therapies targeting MDM4 or MDM2 have been shown to increase levels of the tumor suppressor p53 in cancer cells[134,147,156-157].

GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[158-161]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[162-163], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[164-170]; 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[171-172], the clinical relevance of p14ARF as a predictive biomarker is not clear. 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[165,167-168,173-175].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[80] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[79] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[134,176]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[91,177-178]. 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[179]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[84]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[180]. 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[177,181]. 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[182-183].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[184-185]. 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[186-187]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[188-189]. One or more alterations observed here are predicted to result in p16INK4a loss of function[190-211]. One or more alterations seen here are predicted to result in p14ARF loss of function[194,211-214]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[215].

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[216]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[217-218]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[219-221]. 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[222-224]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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[225]. 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[226]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[225,227-228], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[229]; dual PRMT1 and PRMT5 inhibition may be more effective[230-232]. 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[233-243]. 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[244].

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[245-246]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[247], gastrointestinal stromal tumors[248], mantle cell lymphoma (MCL)[249], melanoma[250-251], gastric cancer[252], myxofibrosarcoma[253], nasopharyngeal carcinoma[254], ovarian carcinoma[245] and non-small cell lung cancer[255]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[256] or in astrocytoma[257]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[258], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[259]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[260-261], esophageal cancer[262-263], osteosarcoma[264], and CRC[265].

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[266-267]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[247,268-269], thereby reducing intracellular arginine methylation[225,227,270] and altering cell signaling[269,271]. 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

PIK3C2B

ALTERATION

amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies known to effectively target mutations in PIK3C2B.

FREQUENCY & PROGNOSIS

Although PIK3C2B mutation has not been reported for many tumor types, microarray analysis of glioblastoma cell lines revealed that increased gene expression of PIK3C2B significantly correlated with insensitivity to erlotinib[272]. In addition, 8% of 465 glioblastoma multiforme (GBM) tumor samples analyzed in one study demonstrated copy number amplification of PIK3C2B[152]. Although elevated expression of PIK3C2B has been observed in GBM, it is unclear if this plays any role in oncogenesis.

FINDING SUMMARY

PI3K signaling is implicated in the regulation of metabolic control, immunity, angiogenesis and cardiovascular homeostasis, and is one of the most frequently dysregulated pathways in cancer. In contrast to class I PI3Ks, including p110-alpha and p110-beta, the functional roles of class II PI3Ks, encoded by PIK3C2A, PIK3C2B, and PIK3C2G, are not well understood[273].

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
30.7%

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[274]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[275]. 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[276].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[277-278], 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[277-281]. 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%)[277,279]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[84]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[282]. 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[277,279,282-283]. 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[284]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[285-287]. 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)[288-290], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[288].

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)[291]. 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)[102].

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Cetuximab

Assay findings association

EGFR
amplification, 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[73].

SUPPORTING DATA

A clinical trial of cetuximab with bevacizumab (an anti-VEGF monoclonal antibody) in patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone[292]. In preclinical trials, cetuximab, matuzumab, and panitumumab were reported to be ineffective at blocking EGFR dimerization and activation in GBM cells expressing EGFR extracellular domain mutations[293]. However, another study demonstrated that in patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly better progression-free survival (PFS) and numerical (although not statistically significant) improvement in overall survival (OS)[92]. A Phase 3 trial of combined cetuximab and platinum/5-FU in patients with HNSCC demonstrated improved response compared to platinum/5-FU alone, but EGFR amplification was not shown to predict response to this treatment[74]. A Phase 3 study of patients with pancreatic adenocarcinoma did not report any improved outcome in patients treated with a combination of cetuximab plus gemcitabine vs gemcitabine alone[294]. In a Phase 1/2 trial of 36 patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cetuximab in combination with doxorubicin, stable disease was reported in approximately 63% of patients[295]. A Phase 1 study of the combination therapy of cetuximab, erlotinib, and bevacizumab reported stable disease in 21% (7/34) of patients with non-small cell lung cancer (NSCLC)[296].

Panitumumab

Assay findings association

EGFR
amplification, 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[73].

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[297]. Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer[298-300] 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[301-303] and others have reported no benefit[304-306] . A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility[307]. Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)[308-309] ; biliary tract cancers, including cholangiocarcinoma[310-311] ; and renal cell carcinoma (RCC)[312].

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

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

GENE
BARD1

RATIONALE
Tumors with BARD1 inactivating mutation or loss may be sensitive to PARP inhibitors.

ALTERATION
A25fs*41

NCT04123366

PHASE 2

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

TARGETS
PARP, PD-1

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

NCT03742895

PHASE 2

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

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Nedlands (Australia), Port Macquarie (Australia), Darlinghurst (Australia), Adana (Turkey), Ankara (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT04715620

PHASE 2

Niraparib Combined With Radiotherapy in rGBM

TARGETS
PARP

LOCATIONS: Tianjin (China)

NCT05035745

PHASE 1/2

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

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04614909

PHASE NULL

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

TARGETS
PARP

LOCATIONS: Arizona

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)

NCT02484404

PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, VEGFRs, PDGFRA, PDGFRB, KIT, PD-L1

LOCATIONS: Maryland

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

GENE
EGFR

ALTERATION
amplification, 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.

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

NCT02303678

PHASE 1

D2C7 for Adult Patients With Recurrent Malignant Glioma

TARGETS
EGFRvIII

LOCATIONS: North Carolina

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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: Heidelberg (Australia), Melbourne (Australia), Edmonton (Canada), Oregon, California, Arizona, Toronto (Canada), Oklahoma, Missouri, Pennsylvania

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
HGF

ALTERATION
amplification - equivocal

RATIONALE
HGF amplification or activating mutations may predict sensitivity to therapeutic agents targeting its receptor, MET, or to agents directly targeting HGF.

NCT03175224

PHASE 1/2

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

TARGETS
MET

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

NCT04887194

PHASE 1

PK Study to Assess Drug-drug Interaction and QTc Between Sitravatinib and a Cocktail of Substrates

TARGETS
AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB, PD-1

LOCATIONS: Texas, Virginia

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
MDM4

ALTERATION
amplification

RATIONALE
Tumors with MDM4 amplification or overexpression and wild-type p53 may be sensitive to inhibitors of MDM-p53 interactions.

NCT03725436

PHASE 1

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

TARGETS
MDM2, MDM4

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.

CD70
G29D

CREBBP
V1924M

CSF1R
T621M

EGFR
rearrangement

GNAS
A280T

GRM3
amplification

MSH2
E809K

NOTCH3
G1347R

PDCD1 (PD-1)
A202_R203insGA

PDGFRA
R293H

STK11
R106W

TSC2
I797N

XRCC2
T129I

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*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

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

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

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

MR Suite Version 6.1.0

The median exon coverage for this sample is 674x

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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. Tanaka S, et al. Sci Rep (2019) pmid: 30644426
69. Blumenthal DT, et al. J. Neurooncol. (2016) pmid: 27531351
70. Franceschi E, et al. Br. J. Cancer (2007) pmid: 17353924
71. Chakravarti A, et al. Int. J. Radiat. Oncol. Biol. Phys. (2013) pmid: 23182702
72. Hegi ME, et al. Mol. Cancer Ther. (2011) pmid: 21471286
73. Jiang Z, et al. PLoS ONE (2013) pmid: 23441167
74. Licitra L, et al. Ann. Oncol. (2011) pmid: 21048039
75. Smyth EC, et al. Gut (2021) pmid: 33199443
76. Lassman et al., 2019; Neuro-Oncology Abstract ACTR-21
77. Van Den Bent M, et al. Neuro Oncol (2020) pmid: 31747009
78. Jonsson P, et al. Clin. Cancer Res. (2019) pmid: 31263031
79. Brennan CW, et al. Cell (2013) pmid: 24120142
80. Ceccarelli M, et al. Cell (2016) pmid: 26824661
81. Thomas AA, et al. Neuro-oncology (2017) pmid: 28472509
82. Lee JC, et al. PLoS Med. (2006) pmid: 17177598
83. Vivanco I, et al. Cancer Discov (2012) pmid: 22588883
84. Yan et al. 2020; DOI:10.1200/PO.19.00385
85. Nishikawa R, et al. Proc. Natl. Acad. Sci. U.S.A. (1994) pmid: 8052651
86. Shinojima N, et al. Cancer Res. (2003) pmid: 14583498
87. Nishikawa R, et al. Brain Tumor Pathol (2004) pmid: 15700833
88. Viana-Pereira M, et al. Anticancer Res. () pmid: 18507036
89. Yoshimoto K, et al. Clin. Cancer Res. (2008) pmid: 18223223
90. Larysz D, et al. Folia Neuropathol (2011) pmid: 21455841
91. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
92. Lv S, et al. Int. J. Oncol. (2012) pmid: 22752145
93. Srividya MR, et al. J. Clin. Pathol. (2010) pmid: 20702468
94. Das P, et al. J Clin Neurosci (2011) pmid: 20888234
95. Smith JS, et al. J. Natl. Cancer Inst. (2001) pmid: 11504770
96. Montano N, et al. Neoplasia (2011) pmid: 22241957
97. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
98. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
99. Bhargava R, et al. Mod. Pathol. (2005) pmid: 15920544
100. Yang YL, et al. Chin. Med. J. (2012) pmid: 22490401
101. Nedergaard MK, et al. BioDrugs (2012) pmid: 22385404
102. Louis DN, et al. Neuro Oncol (2021) pmid: 34185076
103. O'Malley et al., 2017; AACR-NCI-EORTC Abstract LB-A12
104. Wu W, et al. Cancer Res. (2015) pmid: 25634209
105. Wang Y, et al. J. Clin. Invest. (2016) pmid: 27454289
106. Ozden O, et al. Sci Rep (2016) pmid: 27197561
107. Zhao W, et al. Nature (2017) pmid: 28976962
108. Nature (2008) pmid: 18772890
109. Gynecol. Oncol. (2010) pmid: 19959210
110. Laufer M, et al. J. Biol. Chem. (2007) pmid: 17848578
111. Westermark UK, et al. Mol. Cell. Biol. (2003) pmid: 14560035
112. Zhang Y, et al. Clin. Cancer Res. (2013) pmid: 23386689
113. Xie Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22203985
114. Kentsis A, et al. Nat. Med. (2012) pmid: 22683780
115. Xie Q, et al. Genes Cancer (2013) pmid: 24167653
116. Wanjala J, et al. Mol. Cancer Ther. (2015) pmid: 25381262
117. Cloughesy et al., 2015; ASCO Abstract 2015
118. Koeppen H, et al. Clin. Cancer Res. (2014) pmid: 24687921
119. Patnaik A, et al. Br. J. Cancer (2014) pmid: 24901237
120. Iveson T, et al. Lancet Oncol. (2014) pmid: 24965569
121. Yano S, et al. Cancer Res. (2008) pmid: 19010923
122. Turke AB, et al. Cancer Cell (2010) pmid: 20129249
123. Nakade J, et al. J Thorac Oncol (2014) pmid: 24828661
124. Nanjo S, et al. PLoS ONE (2013) pmid: 24386407
125. Chen X, et al. Anticancer Drugs (2013) pmid: 23962905
126. Straussman R, et al. Nature (2012) pmid: 22763439
127. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
128. Nguyen B, et al. Cell (2022) pmid: 35120664
129. Guo YF, et al. World J Surg Oncol (2012) pmid: 22741575
130. Garnett J, et al. Neoplasia (2013) pmid: 23359207
131. Kunkel P, et al. Neuro-oncology (2001) pmid: 11296484
132. Stamos J, et al. EMBO J. (2004) pmid: 15167892
133. Tolbert WD, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20624990
134. Gao J, et al. Sci Signal (2013) pmid: 23550210
135. Zack TI, et al. Nat. Genet. (2013) pmid: 24071852
136. Beroukhim R, et al. Nature (2010) pmid: 20164920
137. Vaseva AV, et al. Cell Death Dis (2011) pmid: 21562588
138. Wang H, et al. Neoplasia (2011) pmid: 21750655
139. Wang H, et al. Mol. Cancer Ther. (2011) pmid: 21075910
140. Reed D, et al. J. Biol. Chem. (2010) pmid: 20080970
141. Smalley KS, et al. Cancer Res. (2007) pmid: 17210701
142. Vogel SM, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 23035244
143. Mandke P, et al. PLoS ONE (2012) pmid: 22870278
144. Hirose M, et al. Oncoscience (2014) pmid: 25621298
145. Chang YS, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23946421
146. Bernal F, et al. Cancer Cell (2010) pmid: 21075307
147. Wade M, et al. Nat. Rev. Cancer (2013) pmid: 23303139
148. Bo MD, et al. Br. J. Haematol. (2010) pmid: 20507307
149. Arjona D, et al. Diagn. Mol. Pathol. (2005) pmid: 16319692

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

150. Schiffman JD, et al. Cancer Res. (2010) pmid: 20068183
151. Nobusawa S, et al. Brain Pathol. (2010) pmid: 20406234
152. Rao SK, et al. J. Neurooncol. (2010) pmid: 19609742
153. Jin G, et al. Neuro-oncology (2010) pmid: 20472715
154. Riemenschneider MJ, et al. Cancer Res. (1999) pmid: 10626796
155. Mancini F, et al. EMBO J. (2009) pmid: 19521340
156. Danovi D, et al. Mol. Cell. Biol. (2004) pmid: 15199139
157. Bieging KT, et al. Nat. Rev. Cancer (2014) pmid: 24739573
158. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
159. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
160. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
161. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
162. Elvin JA, et al. Oncologist (2017) pmid: 28283584
163. Gao J, et al. Curr Oncol (2015) pmid: 26715889
164. Gopalan et al., 2014; ASCO Abstract 8077
165. Peguero et al., 2016; ASCO Abstract 2528
166. Konecny et al., 2016; ASCO Abstract 5557
167. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
168. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
169. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
170. Johnson DB, et al. Oncologist (2014) pmid: 24797823
171. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
172. Gamble LD, et al. Oncogene (2012) pmid: 21725357
173. Shapiro et al., 2013; ASCO Abstract 2500
174. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
175. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
176. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
177. Sottoriva A, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23412337
178. Weber RG, et al. Oncogene (2007) pmid: 16909113
179. Nakamura M, et al. Brain Pathol. (2001) pmid: 11303791
180. Chakravarti A, et al. Clin. Cancer Res. (2001) pmid: 11489817
181. Feng J, et al. Cancer (2012) pmid: 21713760
182. Raabe EH, et al. Clin. Cancer Res. (2011) pmid: 21636552
183. Liu W, et al. J. Exp. Clin. Cancer Res. (2011) pmid: 21843312
184. Quelle DE, et al. Cell (1995) pmid: 8521522
185. Mutat. Res. (2005) pmid: 15878778
186. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
187. Oncogene (1999) pmid: 10498883
188. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
189. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
190. Ruas M, et al. Oncogene (1999) pmid: 10498896
191. Jones R, et al. Cancer Res. (2007) pmid: 17909018
192. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
193. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
194. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
195. Gombart AF, et al. Leukemia (1997) pmid: 9324288
196. Yang R, et al. Cancer Res. (1995) pmid: 7780957
197. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
198. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
199. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
200. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
201. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
202. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
203. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
204. Koh J, et al. Nature (1995) pmid: 7777061
205. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
206. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
207. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
208. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
209. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
210. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
211. Rutter JL, et al. Oncogene (2003) pmid: 12853981
212. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
213. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
214. Zhang Y, et al. Cell (1998) pmid: 9529249
215. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
216. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
217. Adv Exp Med Biol (2010) pmid: 20687502
218. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
219. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
220. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
221. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
222. Kaufman DK, et al. Neurology (1993) pmid: 8414022
223. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
224. Chan AK, et al. Clin Neuropathol () pmid: 28699883
225. Marjon K, et al. Cell Rep (2016) pmid: 27068473
226. Heist et al., 2019; AACR-NCI-EORTC Abstract B116
227. Mavrakis KJ, et al. Science (2016) pmid: 26912361
228. Endoscopy (1989) pmid: 2691236
229. Guccione E, et al. Nat. Rev. Mol. Cell Biol. (2019) pmid: 31350521
230. Fedoriw A, et al. Cancer Cell (2019) pmid: 31257072
231. Srour N, et al. Cancer Cell (2019) pmid: 31287990
232. Gao G, et al. Nucleic Acids Res. (2019) pmid: 30916320
233. Hansen LJ, et al. Cancer Res. (2019) pmid: 31040154
234. Tang B, et al. Cancer Res. (2018) pmid: 29844120
235. Munshi PN, et al. Oncologist (2014) pmid: 24928612
236. de Oliveira SF, et al. PLoS ONE (2016) pmid: 26751376
237. Lubin M, et al. PLoS ONE (2009) pmid: 19478948
238. Tang B, et al. Cancer Biol. Ther. (2012) pmid: 22825330
239. Collins CC, et al. Mol. Cancer Ther. (2012) pmid: 22252602
240. Bertino JR, et al. Cancer Biol. Ther. (2011) pmid: 21301207
241. Coulthard SA, et al. Mol. Cancer Ther. (2011) pmid: 21282358
242. Miyazaki S, et al. Int. J. Oncol. (2007) pmid: 17912432
243. Efferth T, et al. Blood Cells Mol. Dis. () pmid: 11987241
244. Kindler HL, et al. Invest New Drugs (2009) pmid: 18618081
245. Wei R, et al. Sci Rep (2016) pmid: 27929028
246. Zhao M, et al. BMC Genomics (2016) pmid: 27556634
247. Kirovski G, et al. Am. J. Pathol. (2011) pmid: 21356366
248. Huang HY, et al. Clin. Cancer Res. (2009) pmid: 19887491
249. Marcé S, et al. Clin. Cancer Res. (2006) pmid: 16778103
250. Meyer S, et al. Exp. Dermatol. (2010) pmid: 20500769
251. Wild PJ, et al. Arch Dermatol (2006) pmid: 16618867
252. Kim J, et al. Genes Chromosomes Cancer (2011) pmid: 21412930
253. Li CF, et al. Oncotarget (2014) pmid: 25426549
254. He HL, et al. Medicine (Baltimore) (2015) pmid: 26656376
255. Su CY, et al. Eur J Surg Oncol (2014) pmid: 24969958
256. Mirebeau D, et al. Haematologica (2006) pmid: 16818274
257. Becker AP, et al. Pathobiology (2015) pmid: 26088413
258. Snezhkina AV, et al. Oxid Med Cell Longev (2016) pmid: 27433286
259. Bistulfi G, et al. Oncotarget (2016) pmid: 26910893
260. Antonopoulou K, et al. J. Invest. Dermatol. (2015) pmid: 25407435
261. Maccioni L, et al. BMC Cancer (2013) pmid: 23816148
262. Hyland PL, et al. Int J Epidemiol (2016) pmid: 26635288
263. Lin X, et al. Cancer Sci. (2017) pmid: 27960044
264. Zhi L, et al. J Cancer (2016) pmid: 27994653
265. Gu F, et al. Br. J. Cancer (2013) pmid: 23361049
266. Limm K, et al. PLoS ONE (2016) pmid: 27479139
267. Tang B, et al. G3 (Bethesda) (2014) pmid: 25387827
268. Limm K, et al. Eur. J. Cancer (2013) pmid: 23265702
269. Stevens AP, et al. J. Cell. Biochem. (2009) pmid: 19097084
270. Kryukov GV, et al. Science (2016) pmid: 26912360
271. Limm K, et al. Eur. J. Cancer (2014) pmid: 25087184
272. Löw S, et al. Anticancer Res. () pmid: 19189657
273. Biswas K, et al. J. Biol. Chem. (2013) pmid: 23192342
274. Nat Rev Clin Oncol (2017) pmid: 27245281
275. Duperret EK, et al. Mol Ther (2018) pmid: 29249395
276. Chiappori AA, et al. Ann Oncol (2015) pmid: 25467017
277. Killela PJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23530248
278. Killela PJ, et al. Oncotarget (2014) pmid: 24722048
279. Nonoguchi N, et al. Acta Neuropathol. (2013) pmid: 23955565
280. Liu X, et al. Cell Cycle (2013) pmid: 23603989
281. Koelsche C, et al. Acta Neuropathol. (2013) pmid: 24154961
282. Arita H, et al. Acta Neuropathol. (2013) pmid: 23764841
283. Reitman ZJ, et al. Acta Neuropathol. (2013) pmid: 24217890
284. Shay JW, et al. Semin. Cancer Biol. (2011) pmid: 22015685
285. Shay JW, et al. Eur. J. Cancer (1997) pmid: 9282118
286. Kim NW, et al. Science (1994) pmid: 7605428
287. Hanahan D, et al. Cell (2000) pmid: 10647931
288. Horn S, et al. Science (2013) pmid: 23348503
289. Huang FW, et al. Science (2013) pmid: 23348506
290. Vinagre J, et al. Nat Commun (2013) pmid: 23887589
291. Weller M, et al. Nat Rev Clin Oncol (2021) pmid: 33293629
292. Hasselbalch B, et al. Neuro-oncology (2010) pmid: 20406901
293. Gajadhar AS, et al. Mol. Cancer Res. (2012) pmid: 22232519
294. Philip PA, et al. J. Clin. Oncol. (2010) pmid: 20606093
295. Slovin SF, et al. Clin Genitourin Cancer (2009) pmid: 19815486
296. Falchook GS, et al. Oncotarget (2013) pmid: 23435217
297. Whittle JR, et al. J Clin Neurosci (2015) pmid: 26279503
298. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
299. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896
300. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
301. Vermorken JB, et al. Lancet Oncol (2013) pmid: 23746666
302. Wirth LJ, et al. Ann. Oncol. (2010) pmid: 19892746
303. Siano M, et al. Oncologist (2017) pmid: 28592616

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

304. Mesía R, et al. Lancet Oncol (2015) pmid: 25596660
305. Giralt J, et al. Lancet Oncol (2015) pmid: 25596659
306. Siu LL, et al. JAMA Oncol (2016) pmid: 27930762
307. Waddell T, et al. Lancet Oncol. (2013) pmid: 23594787
308. Crawford J, et al. J Thorac Oncol (2013) pmid: 24389433
309. Schuette W, et al. Clin Lung Cancer (2015) pmid: 26094080
310. Leone F, et al. Cancer (2016) pmid: 26540314
311. Vogel A, et al. Eur J Cancer (2018) pmid: 29413685
312. Rowinsky EK, et al. J. Clin. Oncol. (2004) pmid: 15210739

Electronically signed by Donna Ferguson, M.D. | 19 April 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531