PATIENT Chang, Chuan	**TUMOR TYPE** Head and neck adenoid cystic carcinoma	**REPORT DATE** 02 Sep 2021
	COUNTRY CODE TW	**ORDERED TEST #** ORD-1166616-01

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 Head and neck adenoid cystic carcinoma
NAME Chang, Chuan
DATE OF BIRTH 12 February 1949
SEX Male
MEDICAL RECORD # 30068678

PHYSICIAN

ORDERING PHYSICIAN Mu-Hsin Chang, Peter
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Head and Neck
SPECIMEN ID S110-21891 A (PF21002)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 31 July 2021
SPECIMEN RECEIVED 16 August 2021

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.

NF2 Y217*
PIK3R1 S36fs*2
KDM6A E47fs*15
NOTCH1 S2467fs*11

0 Therapies with Clinical Benefit   **13** Clinical Trials

0 Therapies with Lack of Response

BIOMARKER FINDINGS	ACTIONABILITY	
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 BENEFIT (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**
NF2 - Y217*	none	none
10 Trials *see p. 5*		
PIK3R1 - S36fs*2	none	none
3 Trials *see p. 7*		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

KDM6A - E47fs*15 .... p. 4   *NOTCH1 -* S2467fs*11 .... p. 4

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

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

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BIOMARKER FINDINGS

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BIOMARKER
Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES
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
A large genomic study of 1,045 adenoid cystic carcinoma (ACC) samples (177 primary and 868 relapsed or refractory) found no evidence of microsatellite instability[6]. Smaller studies have also generally reported low incidence of MSI in ACC[7-8]. Published data investigating the prognostic implications of MSI in adenoid cystic carcinomas are limited (PubMed, Aug 2021).

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[9]. 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[9-11]. 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[12-14]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[9,11,13-14].

BIOMARKER
Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES
On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[15-17], anti-PD-1 therapies[15-18], and combination nivolumab and ipilimumab[19-24]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[15-18,25]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[15]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[26] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[16]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[18,25]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS
Adenoid cystic carcinomas harbor a median tissue TMB of <2 mutations per megabase (muts/Mb), and less than 2% of cases have high TMB (>20 muts/Mb)[6,27]. The prognostic significance of TMB in adenoid cystic carcinoma has not been extensively studied (PubMed, Sep 2020).

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[28-29] and cigarette smoke in lung cancer[30-31], treatment with temozolomide-based chemotherapy in glioma[32-33], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[34-38], and microsatellite instability (MSI)[34,37-38]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[16-17,25].

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GENOMIC FINDINGS

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GENE
NF2

ALTERATION
Y217*

TRANSCRIPT ID
NM_000268

CODING SEQUENCE EFFECT
651C>G

VARIANT ALLELE FREQUENCY (% VAF)
21.4%

POTENTIAL TREATMENT STRATEGIES

NF2 inactivating alterations may indicate sensitivity to mTOR inhibitors[39-42]. Two case studies reported clinical benefit for patients with NF2-mutated cancers, including urothelial carcinoma[43] and metaplastic breast cancer[44-45] treated with everolimus and temsirolimus, respectively. Loss or inactivation of NF2 may also predict sensitivity to FAK inhibitors based on clinical data in mesothelioma[46] and meningioma[47] and strong preclinical data[48-50]. Limited preclinical and clinical evidence in vestibular schwannoma suggests possible sensitivity of NF2-deficient tumors to the pan-ERBB inhibitor lapatinib[51-52]. Similarly, on the basis of limited clinical[53] and preclinical[54-56] evidence, NF2 inactivation may predict sensitivity to MEK inhibitors, such as approved agents trametinib and cobimetinib. These and other relevant compounds are being investigated in clinical trials. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[57], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[58].

FREQUENCY & PROGNOSIS

NF2 alterations were not found in any of 261 adenoid cystic carcinoma samples analyzed in the literature[59-63]. Published data investigating the prognostic implications of NF2 alteration in adenoid cystic carcinoma are limited (PubMed, Mar 2020).

FINDING SUMMARY

Merlin, encoded by NF2, coordinates cell contact with growth signals; the inactivation of Merlin disrupts this mechanism and can lead to unrestrained growth despite cell contact[64]. Alterations such as seen here may disrupt NF2 function or expression[65-71].

POTENTIAL GERMLINE IMPLICATIONS

Heterozygous germline NF2 loss or inactivation is associated with neurofibromatosis type 2, which results in the development of vestibular schwannomas, meningiomas, ependymomas, and ocular disturbances[72-74]. Prevalence for this disorder in the general population is estimated to be 1:25,000[74]. In the appropriate clinical context, germline testing of NF2 is recommended.

GENE
PIK3R1

ALTERATION
S36fs*2

TRANSCRIPT ID
NM_181523

CODING SEQUENCE EFFECT
105delG

VARIANT ALLELE FREQUENCY (% VAF)
66.6%

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical[75-76] and preclinical[77-78] data, PIK3R1 alteration may predict sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. In patients with PIK3R1 mutation and no other alterations in the PI3K-AKT-mTOR pathway, 2 CRs have been achieved by patients with endometrial cancer treated with the pan-PI3K inhibitor pilaralisib[75], and 1 PR has been achieved by a patient with breast cancer treated with the PI3K-alpha inhibitor alpelisib in combination with ribociclib and letrozole[79]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[78,80-83] or AKT[84-85]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[86].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[34], glioblastoma (GBM; 11%)[87], uterine carcinosarcoma (11%)(cBioPortal, 2021)[88-89], and lower grade glioma (5%)[90]. PIK3R1 is often inactivated by in-frame insertions or deletions (indels), and the majority of this class of mutation (80%) was observed in endometrial carcinoma[91-93], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[91]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[94] and metastasis-free survival in breast cancer[95]. PIK3R1 expression is not associated with overall survival in neuroendocrine tumors[96].

FINDING SUMMARY

PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[97]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[98-101], promote tumorigenesis[77,84,98], and promote hyperplasia in the context of PTEN-deficiency[102]. Alterations such as seen here may disrupt PIK3R1 function or expression[78,85-86,92-93,103-111].

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<div style="text-align: right">**GENOMIC FINDINGS**</div>

GENE

KDM6A

ALTERATION
E47fs*15

TRANSCRIPT ID
NM_021140

CODING SEQUENCE EFFECT
137_138insAG

VARIANT ALLELE FREQUENCY (% VAF)
88.0%

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to address
KDM6A alterations in cancer.

FREQUENCY & PROGNOSIS
KDM6A mutations have been reported in 3.9% of
samples analyzed, with the highest incidence in
tumors of the urinary tract (31%), endometrium
(7%), and salivary gland (6%) (COSMIC, 2021)[112].
KDM6A mutations or copy number alterations
have also been identified in medulloblastoma
(8.9%)[113], adenoid cystic carcinoma (6.7%)[59], and
metastatic prostate cancer (10%)[114]. KDM6A
inactivation has been found as a recurrent
tumorigenic event in male T-cell acute
lymphoblastic leukemia (T-ALL), and loss of

KDM6A increased the sensitivity of T-ALL cells to
therapies targeting histone H3 lysine 27
methylation in preclinical assays[115]. However,
KDM6A overexpression has been noted in breast
cancer and renal cell carcinoma, and correlated
with inferior prognosis in patients with breast
cancer[116-118].

FINDING SUMMARY
KDM6A encodes a histone H3 lysine 27
demethylase UTX, which functions as a
transcriptional regulator[119]. A significant number
of inactivating KDM6A mutations have been
found across multiple tumor types, suggesting a
role as a tumor suppressor[119].

GENE

NOTCH1

ALTERATION
S2467fs*11

TRANSCRIPT ID
NM_017617

CODING SEQUENCE EFFECT
7397_7398insTT

VARIANT ALLELE FREQUENCY (% VAF)
13.9%

POTENTIAL TREATMENT STRATEGIES
NOTCH1 inhibitors and gamma-secretase
inhibitors (GSIs) may be potential therapeutic
approaches in the case of NOTCH1 activating
mutations[120-127]. In a Phase 2 study, the GSI AL101
(BMS-906024) elicited PR in 15% (6/39) and SD in
54% (21/39) of patients with metastatic adenoid
cystic carcinoma (ACC) harboring NOTCH
activating alterations[128]. Additional responses to
AL101 have been reported in a patient with
gastroesophageal junction adenocarcinoma
harboring multiple NOTCH1 mutations, a patient
with T-cell acute lymphoblastic leukemia (T-ALL)

harboring a NOTCH1 HD domain mutation, and a
patient with ACC harboring a single NOTCH1
mutation[129]. On the basis of clinical data in non-
Hodgkin lymphoma, NOTCH1 activating
alterations may be associated with sensitivity to
the approved PI3K inhibitor copanlisib[130]; this is
further supported by limited preclinical data that
suggest that NOTCH1 may be a negative regulator
of PTEN[131-132]. A patient with tracheal ACC
harboring two somatic NOTCH1 mutations
achieved a partial response to the
NOTCH1-targeting antibody brontictuzumab;
upon progression, an additional NOTCH1
mutation and an FBXW7 inactivating mutation
were identified[133]. NOTCH1 signaling promotes
cell growth and invasion and impairs apoptosis in
models of salivary gland ACC[134], and ACC tumor
xenografts with activating NOTCH1 mutations
and high levels of NICD were sensitive to gamma-
secretase inhibitors in preclinical studies[135].

FREQUENCY & PROGNOSIS
NOTCH1 mutations have been reported in 5-23%
of ACC cases[59,62,133,136-137], with the majority of
mutations occurring in gain-of-function hotspots
and leading to NICD overexpression[133,137]. In one
study of ACC, patients with NOTCH1 mutations

were more likely to present with solid histology
and/or advanced stage disease, and were more
prone to metastasis in the liver and bone
compared with NOTCH1 wild-type patients[133].
Although NOTCH1 mutation was significantly
associated with shorter median relapse-free (13 vs.
34 months) and overall survival (30 vs. 122
months), NOTCH1 mutation did not
independently predict prognosis when histology
and stage were taken into account[133].

FINDING SUMMARY
NOTCH1 encodes a member of the NOTCH family
of receptors, which are involved in cell fate
determination and various developmental
processes. Depending on cellular context,
NOTCH1 can act as either a tumor suppressor or
an oncogene[138-139]. Upon binding of membrane-
bound ligands, the NOTCH1 intracellular domain
(NICD) is cleaved and forms part of a transcription
factor complex that regulates downstream target
genes involved in cell fate determination,
proliferation, and apoptosis[140-141]. NOTCH1
alterations that disrupt the PEST domain (amino
acids 2424-2555), such as observed here, have been
shown to stabilize intracellular NOTCH1 and
cause a modest increase in activity[142-143].

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CLINICAL TRIALS

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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
NF2

ALTERATION
Y217*

RATIONALE
Inactivation or loss of NF2 results in the dysregulation of mTOR and FAK pathway signaling. Therefore, mTOR and/or FAK inhibitors may be relevant for patients with NF2 inactivating mutations.

NCT03239015 — PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

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

LOCATIONS: Shanghai (China)

NCT04803318 — PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03297606 — PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT02758587 — PHASE 1/2

Study of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition in Advanced Solid Malignancies (FAK-PD1)

TARGETS
FAK, PD-1

LOCATIONS: Edinburgh (United Kingdom), Glasgow (United Kingdom), Leicester (United Kingdom), Belfast (United Kingdom), Southampton (United Kingdom)

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CLINICAL TRIALS

NCT03065062 — PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT02159989 — PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT03217669 — PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT01552434 — PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT01582191 — PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02321501 — PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

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CLINICAL TRIALS

GENE
PIK3R1

ALTERATION
S36fs*2

RATIONALE
On the basis of clinical and strong preclinical data, PIK3R1 loss or inactivation may indicate sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors.

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)	

NCT03711058	**PHASE 1/2**
Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer	**TARGETS** PD-1, PI3K
LOCATIONS: Maryland	

NCT03502733	**PHASE 1**
Copanlisib and Nivolumab in Treating Patients With Metastatic Solid Tumors or Lymphoma	**TARGETS** PI3K, PD-1
LOCATIONS: Maryland, Texas	

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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.

ACVR1B
V509G

MTOR
T1834_T1837del

STK11
F354L

ORDERED TEST # ORD-1166616-01   **APPENDIX**   Genes Assayed in FoundationOne®CDx

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

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

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	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	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)

FOUNDATIONONE®CDx

PATIENT
Chang, Chuan

TUMOR TYPE
Head and neck adenoid cystic
carcinoma

REPORT DATE
02 Sep 2021

ORDERED TEST # ORD-1166616-01

APPENDIX   About FoundationOne®CDx

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 Alterations and Therapies
Biomarker and Genomic Findings
Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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. 2021. 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. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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.

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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%.

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

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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 4.2.0

The median exon coverage for this sample is 855x

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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. Ho AS, et al. J. Clin. Invest. (2019) pmid: 31483290
7. Ishwad CS, et al. Int. J. Cancer (1995) pmid: 7591306
8. Wang F, et al. Ann Transl Med (2020) pmid: 32647675
9. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
10. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
11. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
12. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
13. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
14. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
15. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
16. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
17. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
18. Cristescu R, et al. Science (2018) pmid: 30309915
19. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
20. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
21. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
22. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
23. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
24. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
25. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
26. Legrand et al., 2018; ASCO Abstract 12000
27. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
28. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
29. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
30. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
31. Rizvi NA, et al. Science (2015) pmid: 25765070
32. Johnson BE, et al. Science (2014) pmid: 24336570
33. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
34. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
35. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
36. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
37. Nature (2012) pmid: 22810696
38. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
39. López-Lago MA, et al. Mol. Cell. Biol. (2009) pmid: 19451229
40. James MF, et al. Mol. Cell. Biol. (2009) pmid: 19451225
41. Pachow D, et al. Clin. Cancer Res. (2013) pmid: 23406776
42. Iyer G, et al. Science (2012) pmid: 22923433
43. Ali SM, et al. Eur. Urol. (2015) pmid: 25630452
44. Ganesan P, et al. Mol. Cancer Ther. (2014) pmid: 25253784
45. Moulder S, et al. Ann. Oncol. (2015) pmid: 25878190
46. Soria JC, et al. Ann. Oncol. (2016) pmid: 27733373

47. Brastianos et al., 2020; ASCO Abstract 2502
48. Poulikakos PI, et al. Oncogene (2006) pmid: 16652148
49. Shapiro IM, et al. Sci Transl Med (2014) pmid: 24848258
50. Shah NR, et al. Gynecol. Oncol. (2014) pmid: 24786638
51. Ammoun S, et al. Neuro-oncology (2010) pmid: 20511180
52. Karajannis MA, et al. Neuro-oncology (2012) pmid: 22844108
53. Subbiah et al., 2011; ASCO Abstract 2100
54. Garcia-Rendueles ME, et al. Cancer Discov (2015) pmid: 26359368
55. Ammoun S, et al. Cancer Res. (2008) pmid: 18593924
56. Yi C, et al. Cancer Cell (2011) pmid: 21481793
57. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
58. Patterson et al., 2018; AACR Abstract 3891
59. Ho AS, et al. Nat. Genet. (2013) pmid: 23685749
60. Ross JS, et al. Am. J. Surg. Pathol. (2014) pmid: 24418857
61. Mitani Y, et al. Clin. Cancer Res. (2016) pmid: 26631609
62. Stephens PJ, et al. J. Clin. Invest. (2013) pmid: 23778141
63. Martelotto LG, et al. J. Pathol. (2015) pmid: 26095796
64. Curto M, et al. Br. J. Cancer (2008) pmid: 17971776
65. Laulajainen M, et al. J. Cell. Mol. Med. (2012) pmid: 22325036
66. Lallemand D, et al. J. Cell. Sci. (2009) pmid: 19910496
67. Sherman L, et al. Oncogene (1997) pmid: 9395247
68. Li W, et al. EMBO Rep. (2012) pmid: 22482125
69. Manetti ME, et al. Biol Open (2012) pmid: 23213372
70. Stokowski RP, et al. Am. J. Hum. Genet. (2000) pmid: 10712203
71. Mani T, et al. Mol. Cell. Biol. (2011) pmid: 21402777
72. Evans GR, et al. Adv. Otorhinolaryngol. (2011) pmid: 21358190
73. Lu-Emerson C, et al. Rev Neurol Dis (2009) pmid: 19898272
74. Asthagiri AR, et al. Lancet (2009) pmid: 19476995
75. Matulonis U, et al. Gynecol. Oncol. (2015) pmid: 25528496
76. Pitz MW, et al. Neuro-oncology (2015) pmid: 25605819
77. Thorpe LM, et al. Proc. Natl. Acad. Sci. U.S.A. (2017) pmid: 28630349
78. Sun M, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20713702
79. Juric et al., 2016; SABCS Abstract P3-14-01
80. Basho RK, et al. JAMA Oncol (2017) pmid: 27893038
81. Myers AP, et al. Gynecol. Oncol. (2016) pmid: 27016228
82. Day TA, et al. Clin. Cancer Res. (2019) pmid: 30420444
83. Ou O, et al. Cancer Lett. (2014) pmid: 25193464
84. Li X, et al. Nat Commun (2019) pmid: 30755611
85. Quayle SN, et al. PLoS ONE (2012) pmid: 23166678
86. Cheung LW, et al. Cancer Cell (2014) pmid: 25284480
87. Brennan CW, et al. Cell (2013) pmid: 24120142
88. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
89. Gao J, et al. Sci Signal (2013) pmid: 23550210
90. Cancer Genome Atlas Research Network, et al. N. Engl. J. Med. (2015) pmid: 26061751
91. Ye K, et al. Nat. Med. (2016) pmid: 26657142
92. Cheung LW, et al. Cancer Discov (2011) pmid: 21984976
93. Urick ME, et al. Cancer Res. (2011) pmid: 21478295
94. Munkley J, et al. Oncoscience (2015) pmid: 26501081
95. Cizkova M, et al. BMC Cancer (2013) pmid: 24229379

96. Qian ZR, et al. J. Clin. Oncol. (2013) pmid: 23980085
97. Huang CH, et al. Cell Cycle (2008) pmid: 18418043
98. Taniguchi CM, et al. Cancer Res. (2010) pmid: 20530665
99. Luo J, et al. Cell Metab. (2006) pmid: 16679293
100. Ueki K, et al. J. Biol. Chem. (2003) pmid: 14504291
101. Mauvais-Jarvis F, et al. J. Clin. Invest. (2002) pmid: 11781359
102. Luo J, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 16006513
103. Jaiswal BS, et al. Cancer Cell (2009) pmid: 19962665
104. Ko HR, et al. Cell Death Dis (2014) pmid: 24651434
105. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
106. Huang CH, et al. Science (2007) pmid: 18079394
107. Bousquet C, et al. EMBO J. (2006) pmid: 16917505
108. Oliver MD, et al. Biosci. Rep. (2017) pmid: 28143957
109. Philp AJ, et al. Cancer Res. (2001) pmid: 11606375
110. Lucas CL, et al. J. Exp. Med. (2014) pmid: 25488983
111. Chen L, et al. Nat Commun (2018) pmid: 29636477
112. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
113. Robinson G, et al. Nature (2012) pmid: 22722829
114. Grasso CS, et al. Nature (2012) pmid: 22722839
115. Van der Meulen J, et al. Blood (2015) pmid: 25320243
116. Wang L, et al. Nat Commun (2013) pmid: 23792809
117. Kim JH, et al. Cancer Res. (2014) pmid: 24491801
118. Shen Y, et al. BMC Cancer (2012) pmid: 23057811
119. van Haaften G, et al. Nat. Genet. (2009) pmid: 19330029
120. Debeb BG, et al. Breast Cancer Res. Treat. (2012) pmid: 22547109
121. Fouladi M, et al. J. Clin. Oncol. (2011) pmid: 21825264
122. Groth C, et al. Semin. Cell Dev. Biol. (2012) pmid: 22309842
123. Kamstrup MR, et al. Blood (2010) pmid: 20538790
124. Kridel R, et al. Blood (2012) pmid: 22210878
125. Krop I, et al. J. Clin. Oncol. (2012) pmid: 22547604
126. Rosati E, et al. Int. J. Cancer (2013) pmid: 23001755
127. Samon JB, et al. Mol. Cancer Ther. (2012) pmid: 22504949
128. Ferrarotto et al., 2020; ESMO Abstract 919MO
129. Knoechel B, et al. Cold Spring Harb Mol Case Stud (2015) pmid: 27148573
130. Dreyling M, et al. Ann. Oncol. (2017) pmid: 28633365
131. Palomero T, et al. Nat. Med. (2007) pmid: 17873882
132. Liu S, et al. Urol. Oncol. (2013) pmid: 21993533
133. Ferrarotto R, et al. J. Clin. Oncol. (2017) pmid: 27870570
134. Su BH, et al. Oncotarget (2014) pmid: 25149541
135. Stoeck A, et al. Cancer Discov (2014) pmid: 25104330
136. Morris LG, et al. JAMA Oncol (2016) pmid: 27442865
137. Hartmaier RJ, et al. Cancer Res. (2017) pmid: 28235761
138. Wang NJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22006338
139. Klinakis A, et al. Nature (2011) pmid: 21562564
140. Penton AL, et al. Semin. Cell Dev. Biol. (2012) pmid: 22306179
141. Kopan R, et al. Cell (2009) pmid: 19379690
142. Aster JC, et al. Mol. Cell. Biol. (2000) pmid: 11003647
143. Weng AP, et al. Science (2004) pmid: 15472075