REPORTING

Report Date:	DEC-05-2017
Receipt Date:	NOV-28-2017
Collection Date:	NOV-27-2017
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Basel Yanes
Account: Dayton Blood and Cancer Center
Address: 400 Sugar Camp Cir Ste 200, Oakwood, OH, 45409, United States
Ph: (937) 262-7819 | Fax: (888) 974-3986
Additional Recipient: N/A

Complete Tumor Response Map on page 2

Summary of Somatic Alterations & Associated Treatment Options

KEY ✓ Approved in indication ~ Approved in other indication ✗ Lack of response

Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
PIK3CA H1047R	1.1%	~ Copanlisib	Yes
NFE2L2 E79Q	0.5%	~ Temsirolimus, Everolimus	Yes
TP53 L252P	1.1%	None	Yes
TP53 C176G	0.8%	None	Yes

Variants of Uncertain Significance

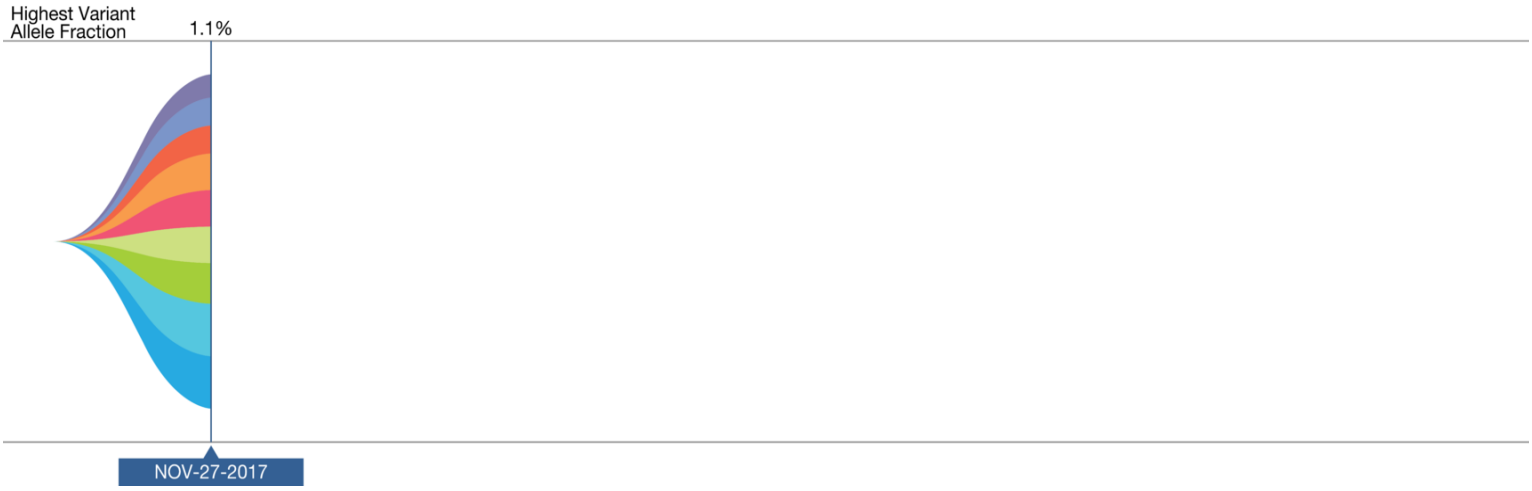
APC S7L (0.7%), *APC* P9S (0.7%), *ARID1A* I1097M (0.7%), *ARID1A* I1130M (0.5%), *FGFR1* R148H (0.4%)
The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

We evaluated 73 genes, including the following guideline-recommended genes for NSCLC:

EGFR (T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2* (HER2)	*RET*

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the mutant allele percentage (% cfDNA) of observed somatic variants at each sample submission time point. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (**portal.guardanthealth.com**) for the Tumor Response Map with all test dates.



Alteration	% cfDNA or Amp	
PIK3CA H1047R	1.1%	
TP53 L252P	1.1%	
TP53 C176G	0.8%	
ARID1A I1097M	0.7%	Variant of Uncertain Significance §
APC P9S	0.7%	Variant of Uncertain Significance §
APC S7L	0.7%	Variant of Uncertain Significance §
NFE2L2 E79Q	0.5%	
ARID1A I1130M	0.5%	Variant of Uncertain Significance §
FGFR1 R148H	0.4%	Variant of Uncertain Significance §

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Available Clinical Trials (within the same state as the ordering physician)

There may be additional trials not listed here. Visit: **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A80169 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
PIK3CA H1047R	NCT02483858 Tatsuo Satoh, Msc, tatsuo.satoh@piqur.com, +41 61 633 29 42	Study of Oral PQR309 in Patients With Advanced Solid Tumors	Phase 1	Cleveland, Ohio
	NCT02142803	TORC1/2 Inhibitor MLN0128 and Bevacizumab in Treating Patients With Recurrent Glioblastoma or Advanced Solid Tumors	Phase 1	Columbus, Ohio
	NCT02465060	NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma	Phase 2	Parma, Ohio Kettering, Ohio (3) Beachwood, Ohio Troy, Ohio (2) Additional trial sites available
	NCT02154490 Crystal Miwa, cmiwa@swog.org, 210-614-8808 x1019	Lung-MAP: Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IV Squamous Cell Lung Cancer	Phase 2/ Phase 3	Columbus, Ohio (7) Sandusky, Ohio Zanesville, Ohio Delaware, Ohio Additional trial sites available
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 C176G	NCT02448589 Takekazu Aoyama, MD PhD, aoyama@taihooncology.com, 1 (609) 750-5300	An Investigation of TAS-119 Monotherapy and in Combination With Docetaxel	Phase 1	Cleveland, Ohio
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
NFE2L2 E79Q	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 L252P	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			

More clinical trial options available at **portal.guardanthealth.com**

Definitions

Variant of Uncertain Significance: The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Comments

None

Interpretation

Somatic alterations were detected in the circulating cell-free DNA isolated from this patient's blood specimen. These genomic alterations are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatments. The percentage of altered cell-free DNA circulating (% cfDNA) in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn over, size, heterogeneity, vascularization, disease progression, and treatment.

Method and Limitations

Guardant360 sequences 73 cancer-associated genes to identify somatic alterations with high sensitivity. Cell-free DNA is extracted from plasma, and genomic alterations are analyzed by massively parallel sequencing of amplified target genes using the Illumina sequencing platforms and hg19 as the reference genome. All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Guardant360 include single nucleotide variations, amplifications, fusions, short insertions/deletions, and splice site-disrupting events (see Table 1). This version of the Guardant360 test is not validated for the detection of other types of genomic alterations, such as complex rearrangements or gene deletions. Certain sample or variant characteristics may result in reduced analytic sensitivity, such as low cell-free DNA concentration. Guardant360 cannot discern the source of the circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot easily distinguish germline variants from somatic alterations. Guardant360 is not validated for the detection of germline or de novo variants that are associated with hereditary cancer risk. Tissue genotyping should be considered when plasma genotyping is negative, if clinically appropriate.

Table 1: Genes on the Guardant360 Panel

Guardant360 reports single nucleotide variants and splice site mutations in all clinically relevant exons in 73 genes and reports other variant types in select genes as indicated below.

AKT1	*ALK* #	*APC* Ω	*AR* †	*ARAF*	*ARID1A* Ω	*ATM* Ω	*BRAF* †	*BRCA1* Ω
BRCA2 Ω	*CCND1* †	*CCND2* †	*CCNE1* †	*CDH1* Ω	*CDK4* †	*CDK6* †	*CDKN2A* Ω	*CTNNB1*
DDR2	*EGFR* †Ω	*ERBB2* †Ω	*ESR1*	*EZH2*	*FBXW7*	*FGFR1* †	*FGFR2* †#	*FGFR3* #
GATA3 Ω	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*IDH2*	*JAK2*
JAK3	*KIT* †Ω	*KRAS* †	*MAP2K1*	*MAP2K2*	*MAPK1*	*MAPK3*	*MET* †Ω	*MLH1* Ω
MPL	*MTOR* Ω	*MYC* †	*NF1* Ω	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*	*NTRK1* #
NTRK3	*PDGFRA* †Ω	*PIK3CA* †	*PTEN* Ω	*PTPN11*	*RAF1* †	*RB1* Ω	*RET* #	*RHEB*
RHOA	*RIT1*	*ROS1* #	*SMAD4* Ω	*SMO*	*STK11* Ω	*TERT* ‡	*TP53* Ω	*TSC1* Ω
VHL Ω								

Ω Guardant360 reports insertion and deletion variants (indels) in this gene.
‡ Guardant360 reports alterations in the promoter region of this gene.
# Guardant360 reports fusion events involving this gene for all known gene partners.
† Guardant360 reports amplifications of this gene.

About the Test

Guardant360 assay was developed and its performance characteristics were determined by Guardant Health, Inc. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This Test may be used for clinical purposes and should not be regarded as investigational or for research only. Guardant Health's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

The laboratory report should be considered in context with other clinical criteria (e.g. patient history, physical exam), as well as laboratory, pathology, and imaging studies by a qualified medical professional prior to initiating or changing a patient's treatment plan. The selection of any, all, or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) is entirely at the discretion of the treating medical professional. Drugs and trial information are based on the diagnosis as written on the submitted test request form; this information is not based on any supplemental information provided by the requesting medical professional, including pathology reports or other molecular studies Some drugs listed in this report may not be approved or cleared by the FDA for a particular use. Guardant Health makes no endorsement, express or implied, of any product, physician, or procedure contained in this report. This report makes no promises or guarantees that a particular medication will affect (or not affect) the clinical outcome of any patient.

Testing performed at: Guardant Health

Laboratory Director: Arthur Baca, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, United States

Additional information is available

Any therapeutic annotations are based on publicly available information. This information is described in the "Detailed Therapy Results" and "Relevance of Detected Alterations" sections.

Visit portal.guardanthealth.com or email clientservices@guardanthealth.com with A80169 in the subject line of the email for:

– Additional clinical trials
– Detailed Therapy Results
– Relevance of Detected Alterations
– References

If you would like to receive this additional information with every Guardant360 report, please call client services at 855.698.8887 to opt-in.

Additional information begins on the next page.

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
PIK3CA H1047R	NCT02576444 Manuel Avedissian, manuel.avedissian@yale.edu, 203-737-3669	OLAParib COmbinations	Phase 2	Boston, MA; New Haven, CT; Nashville, TN
	NCT01306045 Arlene W Berman, R.N., arleneb@mail.nih.gov, (301) 480-6096	Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	Phase 2	Bethesda, MD
	NCT03065062 Nicole Chau, MD, 617-632-3090	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	Phase 1	Boston, MA (3)
	NCT02483858 Tatsuo Satoh, Msc, tatsuo.satoh@piqur.com, +41 61 633 29 42	Study of Oral PQR309 in Patients With Advanced Solid Tumors	Phase 1	Houston, TX; Rochester, MN; Cleveland, OH; Buffalo, NY; Switzerland; Spain; United Kingdom (2)
	NCT02142803	TORC1/2 Inhibitor MLN0128 and Bevacizumab in Treating Patients With Recurrent Glioblastoma or Advanced Solid Tumors	Phase 1	Charlestown, MA; Boston, MA; Columbus, OH
	NCT01226316 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	Safety, Tolerability & Potential Anti-cancer Activity of Increasing Doses of AZD5363 in Different Treatment Schedules	Phase 1	Houston, TX; Oklahoma City, OK; Pittsburgh, PA; New York, NY; Aurora, CO; Charleston, SC; Los Angeles, CA (2); Nashville, TN (2); Singapore; Denmark; Canada (3); Japan (4); Italy (3); France (3); Spain (3)
	NCT02417701	TORC1/2 Inhibitor MLN0128 in Treating Patients With Stage IV or Recurrent Lung Cancer	Phase 2	New York, NY
	NCT02465060	NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma	Phase 2	Newport, RI; Jonesboro, AR; Sheridan, WY; Little Rock, AR; Berlin, VT; Hot Springs, AR; Mobile, AL; Cody, WY; Rapid City, SD; Scottsdale, AZ; Cheyenne, WY; Birmingham, AL; Sioux Falls, SD (2); Phoenix, AZ (2); Providence, RI (3); Burlington, VT (2); Washington, DC (3); DE (9); HI (16); TX (16); MA (10); MD (17); ME (6); IA (22); ID (13); MI (86); UT (13); MN (29); MO (34); IL (61); IN (12); MS (6); MT (8); AK (8); VA (11); NC (36); ND (5); NE (19); NH (5); NJ (15); NM (6); FL (19); NV (30); WA (58); NY (19); SC (29); WI (58); OH (73); GA (20); OK (6); CA (102); WV (7); OR (14); KS (18); CO (43); KY (15); CT (14); PA (49); LA (22); TN (14); Puerto Rico (4)

Continue to next page...

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	NCT02154490 Crystal Miwa, cmiwa@swog.org, 210-614-8808 x1019	Lung-MAP: Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IV Squamous Cell Lung Cancer	Phase 2/ Phase 3	Las Vegas, NV; Bangor, ME; Manchester, NH; Southhaven, MS; Reno, NV; Concord, NH; Huntington, WV; Berlin, VT; Cody, WY; Cedar City, UT; Rapid City, SD; Birmingham, AL; Pascagoula, MS; Parkersburg, WV; Oklahoma City, OK; Brewer, ME; Jonesboro, AR; Saint George, UT; Somerville, NJ; Morgantown, WV; Sheridan, WY; Las Cruces, NM; Little Rock, AR; Charleston, WV; Tulsa, OK; Jackson, MS; Augusta, ME; Oxford, MS; Hooksett, NH; Lebanon, NH; Murray, UT; Sioux Falls, SD (2); Tucson, AZ (2); Albuquerque, NM (2); Burlington, VT (2); DE (8); HI (11); TX (12); MA (5); MD (8); IA (22); ID (9); MI (41); MN (12); MO (22); IL (36); IN (13); MT (9); AK (7); VA (7); NC (8); ND (5); NE (9); FL (5); WA (27); NY (10); SC (11); WI (42); OH (35); GA (11); CA (36); OR (6); KS (32); CO (6); KY (9); CT (5); PA (22); LA (12); TN (8); Canada (4)
NFE2L2 E79Q	NCT01971515 Please Contact U.S. Medical Information Located in Rockland, MA, United States, 888-275-7376	First-in-Human Dose Escalation Trial in Subjects With Advanced Malignancies	Phase 1	Metairie, LA; Saint Louis, MO; New York, NY; Los Angeles, CA; Houston, TX; Miami, FL; Boston, MA; San Diego, CA; Burlington, VT; Dallas, TX; Birmingham, AL; San Antonio, TX; Charleston, SC; Detroit, MI (2)
	NCT02327169 Takeda Study Registration Call Center, globaloncologymedinfo@takeda.com, +1-844-662-8532	A Phase 1B Study of MLN2480 in Combination With MLN0128 or Alisertib, or Paclitaxel, or Cetuximab, or Irinotecan in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	Houston, TX; Philadelphia, PA; Boston, MA (2); United Kingdom (3); France (3); Spain (3)
	NCT02664935 Susie M Brown, lungmatrix@trials.bham.ac.uk, 01214147611	National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer	Phase 2	United Kingdom (9)
	NCT03239015 Xiao-dong Jiao, MD.PHD, pulava@163.com, +86-13817797639	Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event	Phase 2	China
	NCT01827384 Nancy Moore, R.N., nancy.moore@nih.gov, (301) 402-5640	Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors	Phase 2	Houston, TX; Saint Louis, MO; Bethesda, MD; Pittsburgh, PA; New Brunswick, NJ; Aurora, CO; Lexington, KY
	NCT01655225 There may be multiple sites in this clinical trial 1-877-CTLILLY (1-877-285-4559) or, 1-317-615-4559	A Study of LY3023414 in Participants With Advanced Cancer	Phase 1	Oklahoma City, OK; Philadelphia, PA; New York, NY; Santa Monica, CA; Nashville, TN (2); Puerto Rico; Italy
	NCT02784795 There may be multiple sites in this clinical trial. 1-877-CTLILLY (1-877-285-4559) or, 1-317-615-4559	A Study of LY3039478 in Participants With Advanced or Metastatic Solid Tumors	Phase 1	Houston, TX; Detroit, MI; Miami, FL; Boston, MA; La Jolla, CA; New York, NY; Denmark; France (3); Spain (3)
	NCT02029001 Jean-Yves BLAY, MD, jean-yves.blay@lyon.unicancer.fr, +33478785126	Adapting Treatment to the Tumor Molecular Alterations for Patients With Advanced Solid Tumors: My Own Specific Treatment	Phase 2	France (10)

Continue to next page...

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	NCT02583542 Ettore Ullo, bci-Torcmek@qmul.ac.uk, 02078828507 x8507	A Study of AZD2014 in Combination With Selumetinib in Patients With Advanced Cancers	Phase 1/ Phase 2	United Kingdom (4)
TP53 L252P	NCT02610075 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	Phase Ib Study to Determine MTD of AZD1775 Monotherapy in Patients With Locally Advanced or Metastatic Solid Tumours.	Phase 1	Denver, CO; Scottsdale, AZ; Nashville, TN
	NCT02617277 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	Safety, Tolerability and Pharmacokinetics of AZD1775 Plus MEDI4736 in Patients With Advanced Solid Tumours	Phase 1	Denver, CO; Sarasota, FL; Nashville, TN
	NCT03315091 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	Phase I Study to Assess the Effect of Food on AZD1775 Pharmacokinetics in Patients With Advanced Solid Tumours	Phase 1	Netherlands (3); United Kingdom (2); France (2)
	NCT01748825 Ashley B Bruns, ashley.bruns@nih.gov, (301) 594-4949	AZD1775 for Advanced Solid Tumors	Phase 1	Bethesda, MD
	NCT02780011 Houston Methodist Cancer Center, ccresearch@houstonmethodist.org, 713-441-0629	Alsertib (MLN8237) and Brentuximab Vedotin for Relapsed/Refractory CD30-Positive Lymphomas and Solid Malignancies	Phase 1	Houston, TX
TP53 C176G	NCT02134067 Takekazu Aoyama, MD, PhD, aoyama@taihopui.com, 609-750-5331	Dose-escalating, Safety, Tolerability and PK Study of TAS-119 in Combination With Paclitaxel in Patients With Advanced Solid Tumors	Phase 1	Saint Louis, MO; New York, NY; Aurora, CO; Nashville, TN
	NCT02579226 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	A Phase I Study of Safety, Tolerability, and PK of AZD2811 in Patients With Advanced Solid Tumors.	Phase 1	Denver, CO; Sarasota, FL; Nashville, TN
	NCT02448589 Takekazu Aoyama, MD PhD, aoyama@taihooncology.com, 1 (609) 750-5300	An Investigation of TAS-119 Monotherapy and in Combination With Docetaxel	Phase 1	Cleveland, OH; Netherlands; United Kingdom; Italy; Spain (2)
	NCT02719691 Matthew Lee, matthew.lee@ucdenver.edu, 303-848-0630	Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer	Phase 1	Aurora, CO
	NCT02513563	AZD1775 Plus Carboplatin-Paclitaxel in Squamous Cell Lung Cancer	Phase 2	Tampa, FL

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
PIK3CA H1047R	Sapanisertib		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Hepatocellular carcinoma (HCC), Lymphoma, Merkel cell carcinoma, Pancreatic neuroendocrine tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Thyroid carcinoma, Urothelial carcinoma, Bladder carcinoma, Breast carcinoma, Multiple myeloma (MM), Sarcoma, Acute lymphocytic leukemia (ALL))
	Alpelisib		PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	MK-2206		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Neuroendocrine carcinoma, Gallbladder carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Hodgkin lymphoma (HL), Lymphoma, Melanoma, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Adenoid cystic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Mucinous colon adenocarcinoma, Breast carcinoma, Chronic lymphocytic leukemia (CLL), Acute myelocytic leukemia (AML), Cholangiocarcinoma, Thymic neoplasm, Peritoneal papillary serous carcinoma, Lung cancer, Colorectal carcinoma (CRC), Diffuse large B-cell lymphoma (DLBCL))
	CUDC-907		PI3K/HDAC inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Thyroid carcinoma, Diffuse large B-cell lymphoma (DLBCL))
	CC-223		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor, Bladder neuroendocrine carcinoma, Multiple myeloma (MM), Diffuse large B-cell lymphoma (DLBCL))
	GSK2141795		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Endometrial carcinoma, Uveal melanoma, Breast carcinoma, Cervical carcinoma, Acute myelocytic leukemia (AML), Multiple myeloma (MM))
	Vistusertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Glioblastoma, Small cell lung carcinoma (SCLC), Solid Tumor, Diffuse large B-cell lymphoma (DLBCL))
	MSC2363318A		Akt1, Akt3, and p70S6K inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma)

Continue to next page...

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Taselisib		PI3K inhibitor.	Phase 3 (Lung squamous cell carcinoma) Phase 3 (Non-small cell lung carcinoma (NSCLC), Breast carcinoma, Lung cancer)
	ME-344		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Pancreatic carcinoma, Ovarian carcinoma, Endometrial adenocarcinoma, Breast carcinoma, Colorectal carcinoma (CRC))
	Perifosine		Akt inhibitor, induces apoptosis; mechanism of action is context-specific.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Multiple myeloma (MM), Colorectal carcinoma (CRC))
	ARQ 092		Akt inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	PQR309		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma (triple negative), Primary central nervous system lymphoma (PCNSL))
	LY3023414		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Prostate carcinoma)
	GDC-0068		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Prostate carcinoma)
	INK1117		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Renal cell carcinoma)
	CC-115		DNA-PK/mTOR protein complex (TORC1/2) dual kinase inhibitor.	Phase 1 (Solid Tumor)
	AZD5363		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Prostate carcinoma, Endometrial carcinoma, Breast carcinoma)
	Triciribine		DNA synthesis and Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Breast carcinoma)
	RX-0201	Archexin	Akt1 antisense oligonucleotide.	Phase 1 (Solid Tumor) Phase 2 (Pancreatic carcinoma, Renal cell carcinoma)
	XL147		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Endometrial carcinoma, Breast carcinoma)
	GDC-0077		PI3K inhibitor.	Phase 1 (Solid Tumor)
	Copanlisib	Aliqopa	PI3K inhibitor.	Phase 1 (Solid Tumor) FDA Approvedin other indications (Follicular lymphoma (FL))

Continue to next page...

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Apitolisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Breast carcinoma)
	Buparlisib		PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	Gedatolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Endometrial carcinoma, Acute myelocytic leukemia (AML), Lung cancer, Colorectal carcinoma (CRC))
	Afuresertib		Akt inhibitor.	Phase 2 (Leukemia, Ovarian epithelial carcinoma, Chronic lymphocytic leukemia (CLL), Multiple myeloma (MM))
	SF1126		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC))
NFE2L2 E79Q	GSK2141795		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Endometrial carcinoma, Uveal melanoma, Breast carcinoma, Cervical carcinoma, Acute myelocytic leukemia (AML), Multiple myeloma (MM))
	Gedatolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Endometrial carcinoma, Acute myelocytic leukemia (AML), Lung cancer, Colorectal carcinoma (CRC))
	Perifosine		Akt inhibitor, induces apoptosis; mechanism of action is context-specific.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Multiple myeloma (MM), Colorectal carcinoma (CRC))
	Sapanisertib		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Hepatocellular carcinoma (HCC), Lymphoma, Merkel cell carcinoma, Pancreatic neuroendocrine tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Thyroid carcinoma, Urothelial carcinoma, Bladder carcinoma, Breast carcinoma, Multiple myeloma (MM), Sarcoma, Acute lymphocytic leukemia (ALL))
	Temsirolimus	Torisel	mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approvedin other indications (Renal cell carcinoma)
	PQR309		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma (triple negative), Primary central nervous system lymphoma (PCNSL))

Continue to next page...

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	SF1126		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC))
	Triciribine		DNA synthesis and Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Breast carcinoma)
	CC-223		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor, Bladder neuroendocrine carcinoma, Multiple myeloma (MM), Diffuse large B-cell lymphoma (DLBCL))
	GDC-0068		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Prostate carcinoma)
	AZD8055		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Afuresertib		Akt inhibitor.	Phase 2 (Leukemia, Ovarian epithelial carcinoma, Chronic lymphocytic leukemia (CLL), Multiple myeloma (MM))
	Everolimus	Afinitor	mTOR inhibitor, immunosuppressant.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approvedin other indications (Renal cell carcinoma, Gastrointestinal neuroendocrine carcinoma, Lung carcinoid, Breast carcinoma, Subependymal giant cell astrocytoma)
	Apitolisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Breast carcinoma)
	RX-0201	Archexin	Akt1 antisense oligonucleotide.	Phase 1 (Solid Tumor) Phase 2 (Pancreatic carcinoma, Renal cell carcinoma)
	CC-115		DNA-PK/mTOR protein complex (TORC1/2) dual kinase inhibitor.	Phase 1 (Solid Tumor)
	ME-344		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Pancreatic carcinoma, Ovarian carcinoma, Endometrial adenocarcinoma, Breast carcinoma, Colorectal carcinoma (CRC))
	Ridaforolimus		mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Sarcoma)
	LY3023414		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Prostate carcinoma)

Continue to next page...

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	AZD5363		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Prostate carcinoma, Endometrial carcinoma, Breast carcinoma)
	MSC2363318A		Akt1, Akt3, and p70S6K inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma)
	MK-2206		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Neuroendocrine carcinoma, Gallbladder carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Hodgkin lymphoma (HL), Lymphoma, Melanoma, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Adenoid cystic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Mucinous colon adenocarcinoma, Breast carcinoma, Chronic lymphocytic leukemia (CLL), Acute myelocytic leukemia (AML), Cholangiocarcinoma, Thymic neoplasm, Peritoneal papillary serous carcinoma, Lung cancer, Colorectal carcinoma (CRC), Diffuse large B-cell lymphoma (DLBCL))
	ARQ 092		Akt inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Vistusertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Glioblastoma, Small cell lung carcinoma (SCLC), Solid Tumor, Diffuse large B-cell lymphoma (DLBCL))
TP53 L252P C176G	APR-246		Reactivates mutant p53.	Phase 2 (Ovarian serous carcinoma)
	Alisertib		AuroraA small molecule kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (T-cell Lymphoma)
	AT9283		AuroraA, B, Jak2, Jak3, Bcr-Abl kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Acute myelocytic leukemia (AML), Multiple myeloma (MM), Chronic myelocytic leukemia (CML), Acute lymphocytic leukemia (ALL))
	ALT-801		p53-targeted T-cell receptor-IL2 fusion.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Urothelial carcinoma, Bladder carcinoma, Urethral carcinoma, Multiple myeloma (MM))
	SGT-53		TP53 gene therapy delivered via transferrin-targeted nanoparticles.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma, Pancreatic carcinoma)
	AMG 900		AuroraA, B, C small molecule kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myelocytic leukemia (AML))

Continue to next page...

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	AZD2811		Nanoparticle formulation of Aurora kinase B inhibitor barasertib (AZD1152).	Phase 1 (Solid Tumor) Phase 2 (Acute myelocytic leukemia (AML), Myelodysplastic Syndrome (MDS))
	TAS-119		Selective AuroraA kinase inhibitor.	Phase 1 (Solid Tumor)
	ENMD-2076		AuroraA small molecule kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Fibrolamellar hepatocellular carcinoma, Ovarian carcinoma, Breast carcinoma (triple negative), Fallopian tube adenocarcinoma, Soft tissue sarcoma)
	Kevetrin		Blocks Mdm2-p53 interaction, restoring transcriptional activity of p53.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma)
	MK-1775		Wee1 tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Medulloblastoma, Head and neck squamous cell carcinoma (HNSCC), Small cell lung carcinoma (SCLC), Solid Tumor, Myeloproliferative neoplasm (MPN), Ovarian carcinosarcoma, Breast carcinoma (triple negative), Acute myelocytic leukemia (AML), MDS/MPN, unclassifiable, Peritoneal papillary serous carcinoma, Myelodysplastic Syndrome (MDS))
	SNS-314		AuroraA, B small molecule kinase inhibitor.	Phase 1 (Solid Tumor)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
PIK3CA H1047R	PIK3CA mutations are not mutually exclusive with EGFR or KRAS or BRAF mutations, and are associated with increased PI3K signaling and increased activation of Akt (1,2). PIK3CA mutations have been associated with activation of PI3K/Akt signaling and colony formation in NSCLC cell lines, and the PIK3CA H1047R activating mutation has been shown to drive tumorigenesis in combination with BRAF V600E in a mouse model of NSCLC (1,3). PIK3CA mutations and amplification have been reported to occur more frequently in lung squamous cell carcinoma as compared with lung adenocarcinoma in several studies, although two mutation studies did not find a statistically significant difference (4-10).	Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials (11,12). While PIK3CA activating alterations have been suggested to predict sensitivity to the mTOR inhibitors everolimus and temsirolimus, results from clinical studies have been mixed, with several reporting no associations between PIK3CA mutational status and response to therapy (11,13-16). Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development (17-19). A preclinical study in PIK3CA-mutated NSCLC cell lines reported sensitivity to the PI3K and mTOR inhibitor, PF-04691502 (20).	
NFE2L2 E79Q	Nrf2 normally functions to protect cells against oxidative and xenobiotic stress, thereby limiting DNA damage and preserving cellular health. Studies in mouse models suggest that loss of NFE2L2 can lead to increased susceptibility to tumors induced by exposure to chemicals (21-23). Other studies have reported Nrf2 expression levels are often increased in cancer upon NFE2L2 mutation and at least two studies have reported that knockdown of NFE2L2 in cancer cells decreases cell proliferation (24-28). Therefore, the role of NFE2L2 alteration in cancer may be context dependent (21,29). NFE2L2 mutations have been associated with advanced disease stage and squamous cell carcinoma histology in a study of 876 NSCLC patients (30).	Inhibitors of Nrf2 are in development (31,32). In addition, some studies suggest that PI3K/mTOR inhibitors may be relevant in tumors with Nrf2 activation (33-35).	Nrf2 has been reported to increase expression of multidrug resistance drug efflux pump proteins, and mediate chemoresistance in NSCLC cell lines (28,36-39).
TP53 L252P	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (40). Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias (41-43). Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects (44-48). TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis (49). TP53 mutation and expression of p53 have been correlated with the lung squamous cell carcinoma subtype, and p53 expression in lung squamous cell carcinoma has also been associated with disease stage and higher grade tumors (50-52).	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines (53-55). Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function (56-58). Clinical trials of the Wee1 inhibitor MK-1775 are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors (59-64).	Mutations in TP53 may increase resistance to ionizing radiation therapy (65,66).

Continue to next page...

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
TP53 C176G	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (40). Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias (41-43). Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects (44-48). TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis (49). TP53 mutation and expression of p53 have been correlated with the lung squamous cell carcinoma subtype, and p53 expression in lung squamous cell carcinoma has also been associated with disease stage and higher grade tumors (50-52).	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines (53-55). Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function (56-58). Clinical trials of the Wee1 inhibitor MK-1775 are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors (59-64).	Mutations in TP53 may increase resistance to ionizing radiation therapy (65,66).
APC S7L	APC is a tumor suppressor gene that was originally characterized based on the prominent role that inactivation of Apc plays in colorectal carcinogenesis; however, APC mutation and Wnt/beta-catenin pathway activation have subsequently been implicated in other tumor types as well (67-69). In the absence of functional Apc, beta-catenin accumulates and is translocated to the nucleus, where it promotes the transcription of genes promoting cellular proliferation (70). In addition, Apc has been reported to play a role in microtubule spindle formation and chromosomal segregation (71-73).	There are currently no approved therapies that target Apc deficiency in cancer. However, several potential therapies, including downstream Wnt pathway inhibitors such as PRI-724, are under investigation or in clinical trials (74,75). Cox-2 inhibitors, such as celecoxib, may reduce Wnt signaling (76,77). In addition, preclinical studies have reported that Apc inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated (78). TRAIL agonists are currently in clinical trials in some cancer types. In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.	
APC P9S	APC is a tumor suppressor gene that was originally characterized based on the prominent role that inactivation of Apc plays in colorectal carcinogenesis; however, APC mutation and Wnt/beta-catenin pathway activation have subsequently been implicated in other tumor types as well (67-69). In the absence of functional Apc, beta-catenin accumulates and is translocated to the nucleus, where it promotes the transcription of genes promoting cellular proliferation (70). In addition, Apc has been reported to play a role in microtubule spindle formation and chromosomal segregation (71-73).	There are currently no approved therapies that target Apc deficiency in cancer. However, several potential therapies, including downstream Wnt pathway inhibitors such as PRI-724, are under investigation or in clinical trials (74,75). Cox-2 inhibitors, such as celecoxib, may reduce Wnt signaling (76,77). In addition, preclinical studies have reported that Apc inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated (78). TRAIL agonists are currently in clinical trials in some cancer types. In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.	

Continue to next page...

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
ARID1A I1097M	Loss of Arid1a has been associated with mismatch repair deficiency in cancer, including endometrial and colorectal carcinoma (79,80). One study reported that loss of Arid1a expression was correlated with nodal metastasis, advanced disease stage, and poor differentiation in NSCLC; knockdown of Arid1a increased cell growth in NSCLC cell lines (81). Loss of ARID1A in a KRAS-activated and TP53-deficient lung adenocarcinoma mouse model has been reported to result in an increased number of high grade tumors as compared with control mice (82).	There are no approved targeted therapies to address ARID1A alterations at this time; however, ARID1A alterations may predict sensitivity to Ezh2 inhibitors (83). Ezh2 inhibitors, such as tazemetostat, are currently being evaluated in clinical trials in patients with solid tumors or B-cell lymphomas (84,85). In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.	
ARID1A I1130M	Loss of Arid1a has been associated with mismatch repair deficiency in cancer, including endometrial and colorectal carcinoma (79,80). One study reported that loss of Arid1a expression was correlated with nodal metastasis, advanced disease stage, and poor differentiation in NSCLC; knockdown of Arid1a increased cell growth in NSCLC cell lines (81). Loss of ARID1A in a KRAS-activated and TP53-deficient lung adenocarcinoma mouse model has been reported to result in an increased number of high grade tumors as compared with control mice (82).	There are no approved targeted therapies to address ARID1A alterations at this time; however, ARID1A alterations may predict sensitivity to Ezh2 inhibitors (83). Ezh2 inhibitors, such as tazemetostat, are currently being evaluated in clinical trials in patients with solid tumors or B-cell lymphomas (84,85). In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.	
FGFR1 R148H	FGFR1 alterations, including mutations, amplifications, and translocations have been observed in a wide range of cancer types. Furthermore, FGFR1 amplification has been identified as a driver mutation in some cancer types, including breast and lung carcinoma (86-92). FGFR1 amplification and Fgfr1 expression have been correlated with the squamous cell carcinoma subtype in non-small cell lung carcinoma (NSCLC) (93-96). FGFR1 amplification and increased Fgfr1 expression have been reported to play a role in tumor growth in NSCLC (89,97-100).	Tumors with FGFR1 amplification or activating mutations may be sensitive to Fgfr family inhibitors, and clinical trials of these agents are currently underway in solid tumors (101,102). Several multi-kinase inhibitors that target Fgfrs, including pazopanib, ponatinib, and lenvatinib, have been FDA-approved for certain indications and continue to be studied in clinical trials (103-109). In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.	FGFR1 amplification and Fgfr1 activation have been associated with acquired resistance to Egfr tyrosine kinase inhibitors in EGFR-mutant NSCLC (110-112).

References

1. Yamamoto H, Shigematsu H, Nomura M, Lockwood W, Sato M, Okumura N, Soh J, Suzuki M, Wistuba I, Fong K, Lee H, Toyooka S, Date H, Lam W, Minna J, Gazdar A "PIK3CA mutations and copy number gains in human lung cancers." Cancer research (2008) : 6913-21
2. Janku F, Lee J, Tsimberidou A, Hong D, Naing A, Falchook G, Fu S, Luthra R, Garrido-Laguna I, Kurzrock R "PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers." PloS one (2011) : e22769
3. Trejo C, Green S, Marsh V, Collisson E, Iezza G, Phillips W, McMahon M "Mutationally activated PIK3CA(H1047R) cooperates with BRAF(V600E) to promote lung cancer progression." Cancer research (2013) : 6448-61
4. Scheffler M, Bos M, Gardizi M, König K, Michels S, Fassunke J, Heydt C, Künstlinger H, Ihle M, Ueckeroth F, Albus K, Serke M, Gerigk U, Schulte W, Töpelt K, Nogova L, Zander T, Engel-Riedel W, Stoelben E, Ko Y, Randerath W, Kaminsky B, Panse J, Becker C, Hellmich M, Merkelbach-Bruse S, Heukamp L, Büttner R, Wolf J "PIK3CA mutations in non-small cell lung cancer (NSCLC): Genetic heterogeneity, prognostic impact and incidence of prior malignancies." Oncotarget (2014) :
5. Wang L, Hu H, Pan Y, Wang R, Li Y, Shen L, Yu Y, Li H, Cai D, Sun Y, Chen H "PIK3CA mutations frequently coexist with EGFR/KRAS mutations in non-small cell lung cancer and suggest poor prognosis in EGFR/KRAS wildtype subgroup." PloS one (2014) : e88291
6. An S, Chen Z, Su J, Zhang X, Zhong W, Yang J, Zhou Q, Yang X, Huang L, Guan J, Nie Q, Yan H, Mok T, Wu Y "Identification of enriched driver gene alterations in subgroups of non-small cell lung cancer patients based on histology and smoking status." PloS one (2012) : e40109
7. Spoerke J, O'Brien C, Huw L, Koeppen H, Fridlyand J, Brachmann R, Haverty P, Pandita A, Mohan S, Sampath D, Friedman L, Ross L, Hampton G, Amler L, Shames D, Lackner M "Phosphoinositide 3-kinase (PI3K) pathway alterations are associated with histologic subtypes and are predictive of sensitivity to PI3K inhibitors in lung cancer preclinical models." Clinical cancer research : an official journal of the American Association for Cancer Research (2012) : 6771-83
8. Stjernström A, Karlsson C, Fernandez O, Söderkvist P, Karlsson M, Thunell L "Alterations of INPP4B, PIK3CA and pAkt of the PI3K pathway are associated with squamous cell carcinoma of the lung." Cancer medicine (2014) : 337-48
9. Ji M, Guan H, Gao C, Shi B, Hou P "Highly frequent promoter methylation and PIK3CA amplification in non-small cell lung cancer (NSCLC)." BMC cancer (2011) : 147
10. Xu J, He J, Yang H, Luo X, Liang Z, Chen J, Cai Z, Xu J, Ren-Heidenreich L "Somatic mutation analysis of EGFR, KRAS, BRAF and PIK3CA in 861 patients with non-small cell lung cancer." Cancer biomarkers : section A of Disease markers (2012) : 63-9
11. Janku F, Tsimberidou A, Garrido-Laguna I, Wang X, Luthra R, Hong D, Naing A, Falchook G, Moroney J, Piha-Paul S, Wheler J, Moulder S, Fu S, Kurzrock R "PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors." Molecular cancer therapeutics (2011) : 558-65
12. Massacesi C, di Tomaso E, Fretault N, Hirawat S "Challenges in the clinical development of PI3K inhibitors." Annals of the New York Academy of Sciences (2013) : 19-23
13. Loi S, Michiels S, Baselga J, Bartlett J, Singhal S, Sabine V, Sims A, Sahmoud T, Dixon J, Piccart M, Sotiriou C "PIK3CA genotype and a PIK3CA mutation-related gene signature and response to everolimus and letrozole in estrogen receptor positive breast cancer." PloS one (2013) : e53292
14. Mackay H, Eisenhauer E, Kamel-Reid S, Tsao M, Clarke B, Karakasis K, Werner H, Trovik J, Akslen L, Salvesen H, Tu D, Oza A "Molecular determinants of outcome with mammalian target of rapamycin inhibition in endometrial cancer." Cancer (2014) : 603-10
15. Hortobagyi G, Chen D, Piccart M, Rugo H, Burris H, Pritchard K, Campone M, Noguchi S, Perez A, Deleu I, Shtivelband M, Masuda N, Dakhil S, Anderson I, Robinson D, He W, Garg A, McDonald E, Bitter H, Huang A, Taran T, Bachelot T, Lebrun F, Lebwohl D, Baselga J "Correlative Analysis of Genetic Alterations and Everolimus Benefit in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From BOLERO-2." Journal of clinical oncology : official journal of the American Society of Clinical Oncology (2016) : 419-26
16. Moynahan M, Chen D, He W, Sung P, Samoila A, You D, Bhatt T, Patel P, Ringeisen F, Hortobagyi G, Baselga J, Chandarlapaty S "Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR(+), HER2(-) advanced breast cancer: results from BOLERO-2." British journal of cancer (2017) : [Epub ahead of print]
17. Dienstmann R, Rodon J, Serra V, Tabernero J "Picking the point of inhibition: a comparative review of PI3K/AKT/mTOR pathway inhibitors." Molecular cancer therapeutics (2014) : 1021-31
18. Fumarola C, Bonelli M, Petronini P, Alfieri R "Targeting PI3K/AKT/mTOR pathway in non small cell lung cancer." Biochemical pharmacology (2014) : 197-207
19. Kolev V, Wright Q, Vidal C, Ring J, Shapiro I, Ricono J, Weaver D, Padval M, Pachter J, Xu Q "PI3K/mTOR dual inhibitor VS-5584 preferentially targets cancer stem cells." Cancer research (2015) : 446-55
20. Yuan J, Mehta P, Yin M, Sun S, Zou A, Chen J, Rafidi K, Feng Z, Nickel J, Engebretsen J, Hallin J, Blasina A, Zhang E, Nguyen L, Sun M, Vogt P, McHarg A, Cheng H, Christensen J, Kan J, Bagrodia S "PF-04691502, a potent and selective oral inhibitor of PI3K and mTOR kinases with antitumor activity." Molecular cancer therapeutics (2011) : 2189-99
21. Geismann C, Arlt A, Sebens S, Schäfer H "Cytoprotection "gone astray": Nrf2 and its role in cancer." OncoTargets and therapy (2014) : 1497-518
22. Khor T, Huang M, Prawan A, Liu Y, Hao X, Yu S, Cheung W, Chan J, Reddy B, Yang C, Kong A "Increased susceptibility of Nrf2 knockout mice to colitis-associated colorectal cancer." Cancer prevention research (Philadelphia, Pa.) (2008) : 187-91
23. Iida K, Itoh K, Kumagai Y, Oyasu R, Hattori K, Kawai K, Shimazui T, Akaza H, Yamamoto M "Nrf2 is essential for the chemopreventive efficacy of oltipraz against urinary bladder carcinogenesis." Cancer research (2004) : 6424-31
24. Shibata T, Ohta T, Tong K, Kokubu A, Odogawa R, Tsuta K, Asamura H, Yamamoto M, Hirohashi S "Cancer related mutations in NRF2 impair its recognition by Keap1-Cul3 E3 ligase and promote malignancy." Proceedings of the National Academy of Sciences of the United States of America (2008) : 13568-73
25. Lister A, Nedjadi T, Kitteringham N, Campbell F, Costello E, Lloyd B, Copple I, Williams S, Owen A, Neoptolemos J, Goldring C, Park B "Nrf2 is overexpressed in pancreatic cancer: implications for cell proliferation and therapy." Molecular cancer (2011) : 37
26. Gañán-Gómez I, Wei Y, Yang H, Boyano-Adánez M, García-Manero G "Oncogenic functions of the transcription factor Nrf2." Free radical biology & medicine (2013) : 750-64
27. Kim Y, Oh J, Kim M, Kang M, Park S, Han J, Eom H, Yoo N, Lee S "Oncogenic NRF2 mutations in squamous cell carcinomas of oesophagus and skin." The Journal of pathology (2010) : 446-51
28. Singh A, Boldin-Adamsky S, Thimmulappa R, Rath S, Ashush H, Coulter J, Blackford A, Goodman S, Bunz F, Watson W, Gabrielson E, Feinstein E, Biswal S "RNAi-mediated silencing of nuclear factor erythroid-2-related factor 2 gene expression in non-small cell lung cancer inhibits tumor growth and increases efficacy of chemotherapy." Cancer research (2008) : 7975-84
29. Osburn W, Kensler T "Nrf2 signaling: an adaptive response pathway for protection against environmental toxic insults." Mutation research (2008) : 31-9
30. Kawaguchi T, Koh Y, Ando M, Ito N, Takeo S, Adachi H, Tagawa T, Kakegawa S, Yamashita M, Kataoka K, Ichinose Y, Takeuchi Y, Serizawa M, Tamiya A, Shimizu S, Yoshimoto N, Kubo A, Isa S, Saka H, Matsumura A "Prospective Analysis of Oncogenic Driver Mutations and Environmental Factors: Japan Molecular Epidemiology for Lung Cancer Study." Journal of clinical oncology : official journal of the American Society of Clinical Oncology (2016) : 2247-57

Continue to next page...

References

31. Singh A, Venkannagari S, Oh K, Zhang Y, Rohde J, Liu L, Nimmagadda S, Sudini K, Brimacombe K, Gajghate S, Ma J, Wang A, Xu X, Shahane S, Xia M, Woo J, Mensah G, Wang Z, Ferrer M, Gabrielson E, Li Z, Rastinejad F, Shen M, Boxer M, Biswal S "Small Molecule Inhibitor of NRF2 Selectively Intervenes Therapeutic Resistance in KEAP1-Deficient NSCLC Tumors." ACS chemical biology (2016) : [Epub ahead of print]
32. Lu M, Ji J, Jiang Z, You Q "The Keap1-Nrf2-ARE Pathway As a Potential Preventive and Therapeutic Target: An Update." Medicinal research reviews (2016) : 924-63
33. Shibata T, Saito S, Kokubu A, Suzuki T, Yamamoto M, Hirohashi S "Global downstream pathway analysis reveals a dependence of oncogenic NF-E2-related factor 2 mutation on the mTOR growth signaling pathway." Cancer research (2010) : 9095-105
34. Liu D, Zhang Y, Wei Y, Liu G, Liu Y, Gao Q, Zou L, Zeng W, Zhang N "Activation of AKT pathway by Nrf2/PDGFA feedback loop contributes to HCC progression." Oncotarget (2016) : [Epub ahead of print]
35. Ali D, Mohammad D, Mujahed H, Jonson-Videsäter K, Nore B, Paul C, Lehmann S "Anti-leukaemic effects induced by APR-246 are dependent on induction of oxidative stress and the NFE2L2/HMOX1 axis that can be targeted by PI3K and mTOR inhibitors in acute myeloid leukaemia cells." British journal of haematology (2016) : 117-26
36. Mahaffey C, Mahaffey N, Holland W, Zhang H, Gandara D, Mack P, Forman H "Aberrant regulation of the MRP3 gene in non-small cell lung carcinoma." Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer (2012) : 34-9
37. Singh A, Misra V, Thimmulappa R, Lee H, Ames S, Hoque M, Herman J, Baylin S, Sidransky D, Gabrielson E, Brock M, Biswal S "Dysfunctional KEAP1-NRF2 interaction in non-small-cell lung cancer." PLoS medicine (2006) : e420
38. Tian Y, Wu K, Liu Q, Han N, Zhang L, Chu Q, Chen Y "Modification of platinum sensitivity by KEAP1/NRF2 signals in non-small cell lung cancer." Journal of hematology & oncology (2016) : 83
39. Tung M, Lin P, Wang Y, He T, Lee M, Yeh S, Chen C, Lee H "Mutant p53 confers chemoresistance in non-small cell lung cancer by upregulating Nrf2." Oncotarget (2015) : 41692-705
40. Brown C, Lain S, Verma C, Fersht A, Lane D "Awakening guardian angels: drugging the p53 pathway." Nature reviews. Cancer (2009) : 862-73
41. Malkin D, Li F, Strong L, Fraumeni J, Nelson C, Kim D, Kassel J, Gryka M, Bischoff F, Tainsky M "Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms." Science (New York, N.Y.) (1990) : 1233-8
42. Srivastava S, Zou Z, Pirollo K, Blattner W, Chang E "Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome." Nature (1991) : 747-9
43. Santibáñez-Koref M, Birch J, Hartley A, Jones P, Craft A, Eden T, Crowther D, Kelsey A, Harris M "p53 germline mutations in Li-Fraumeni syndrome." Lancet (1991) : 1490-1
44. Wang Y, Lin R, Tan Y, Chen J, Chen C, Wang Y "Wild-type p53 overexpression and its correlation with MDM2 and p14ARF alterations: an alternative pathway to non-small-cell lung cancer." Journal of clinical oncology : official journal of the American Society of Clinical Oncology (2005) : 154-64
45. Koga T, Hashimoto S, Sugio K, Yoshino I, Nakagawa K, Yonemitsu Y, Sugimachi K, Sueishi K "Heterogeneous distribution of P53 immunoreactivity in human lung adenocarcinoma correlates with MDM2 protein expression, rather than with P53 gene mutation." International journal of cancer. Journal international du cancer (2001) : 232-9
46. Kato S, Han S, Liu W, Otsuka K, Shibata H, Kanamaru R, Ishioka C "Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis." Proceedings of the National Academy of Sciences of the United States of America (2003) : 8424-9
47. Houben R, Hesbacher S, Schmid C, Kauczok C, Flohr U, Haferkamp S, Müller C, Schrama D, Wischhusen J, Becker J "High-level expression of wild-type p53 in melanoma cells is frequently associated with inactivity in p53 reporter gene assays." PloS one (2011) : e22096
48. Olivier M, Petitjean A, Marcel V, Pétré A, Mounawar M, Plymoth A, de Fromentel C, Hainaut P "Recent advances in p53 research: an interdisciplinary perspective." Cancer gene therapy (2009) : 1-12
49. Chang Y, Wu C, Shih J, Lee Y "Comparison of p53 and epidermal growth factor receptor gene status between primary tumors and lymph node metastases in non-small cell lung cancers." Annals of surgical oncology (2011) : 543-50
50. Mattioni M, Soddu S, Prodosmo A, Visca P, Conti S, Alessandrini G, Facciolo F, Strigari L "Prognostic role of serum p53 antibodies in lung cancer." BMC cancer (2015) : 148
51. Bircan A, Bircan S, Kapucuoglu N, Songur N, Ozturk O, Akkaya A "Maspin, VEGF and p53 expression in small biopsies of primary advanced lung cancer and relationship with clinicopathologic parameters." Pathology oncology research : POR (2010) : 553-61
52. Kim Y, Hammerman P, Kim J, Yoon J, Lee Y, Sun J, Wilkerson M, Pedamallu C, Cibulskis K, Yoo Y, Lawrence M, Stojanov P, Carter S, McKenna A, Stewart C, Sivachenko A, Oh I, Kim H, Choi Y, Kim K, Shim Y, Kim K, Song S, Na K, Choi Y, Hayes D, Kim J, Cho S, Kim Y, Ahn J, Ahn M, Getz G, Meyerson M, Park K "Integrative and comparative genomic analysis of lung squamous cell carcinomas in East Asian patients." Journal of clinical oncology : official journal of the American Society of Clinical Oncology (2014) : 121-8
53. Schuler P, Harasymczuk M, Visus C, Deleo A, Trivedi S, Lei Y, Argiris A, Gooding W, Butterfield L, Whiteside T, Ferris R "Phase I dendritic cell p53 peptide vaccine for head and neck cancer." Clinical cancer research : an official journal of the American Association for Cancer Research (2014) : 2433-44
54. Vermeij R, Leffers N, van der Burg S, Melief C, Daemen T, Nijman H "Immunological and clinical effects of vaccines targeting p53-overexpressing malignancies." Journal of biomedicine & biotechnology (2011) : 702146
55. Saito H, Ando S, Morishita N, Lee K, Dator D, Dy D, Shigemura K, Adhim Z, Nibu K, Fujisawa M, Shirakawa T "A combined lymphokine-activated killer (LAK) cell immunotherapy and adenovirus-p53 gene therapy for head and neck squamous cell carcinoma." Anticancer research (2014) : 3365-70
56. Ma C, Janetka J, Piwnica-Worms H "Death by releasing the breaks: CHK1 inhibitors as cancer therapeutics." Trends in molecular medicine (2011) : 88-96
57. Hirai H, Arai T, Okada M, Nishibata T, Kobayashi M, Sakai N, Imagaki K, Ohtani J, Sakai T, Yoshizumi T, Mizuarai S, Iwasawa Y, Kotani H "MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil." Cancer biology & therapy (2010) : 514-22
58. Bridges K, Hirai H, Buser C, Brooks C, Liu H, Buchholz T, Molkentine J, Mason K, Meyn R "MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells." Clinical cancer research : an official journal of the American Association for Cancer Research (2011) : 5638-48
59. Vilgelm A, Pawlikowski J, Liu Y, Hawkins O, Davis T, Smith J, Weller K, Horton L, McClain C, Ayers G, Turner D, Essaka D, Stewart C, Sosman J, Kelley M, Ecsedy J, Johnston J, Richmond A "Mdm2 and aurora kinase a inhibitors synergize to block melanoma growth by driving apoptosis and immune clearance of tumor cells." Cancer research (2015) : 181-93
60. Li Z, Sun Y, Chen X, Squires J, Nowroozizadeh B, Liang C, Huang J "p53 Mutation Directs AURKA Overexpression via miR-25 and FBXW7 in Prostatic Small Cell Neuroendocrine Carcinoma." Molecular cancer research : MCR (2014) :

Continue to next page...

References

61. Katayama H, Sen S "Functional significance of Aurora kinase A regulatory interactions with p53-ER complex in human breast cancer cells." Hormones & cancer (2011) : 117-24

62. Tentler J, Ionkina A, Tan A, Newton T, Pitts T, Glogowska M, Kabos P, Sartorius C, Sullivan K, Espinosa J, Eckhardt S, Diamond J "p53 Family Members Regulate Phenotypic Response to Aurora Kinase A Inhibition in Triple-Negative Breast Cancer." Molecular cancer therapeutics (2015) : 1117-29

63. Gully C, Velazquez-Torres G, Shin J, Fuentes-Mattei E, Wang E, Carlock C, Chen J, Rothenberg D, Adams H, Choi H, Guma S, Phan L, Chou P, Su C, Zhang F, Chen J, Yang T, Yeung S, Lee M "Aurora B kinase phosphorylates and instigates degradation of p53." Proceedings of the National Academy of Sciences of the United States of America (2012) : E1513-22

64. Marxer M, Ma H, Man W, Poon R "p53 deficiency enhances mitotic arrest and slippage induced by pharmacological inhibition of Aurora kinases." Oncogene (2014) : 3550-60

65. El-Deiry W "The role of p53 in chemosensitivity and radiosensitivity." Oncogene (2003) : 7486-95

66. Miyasaka A, Oda K, Ikeda Y, Sone K, Fukuda T, Inaba K, Makii C, Enomoto A, Hosoya N, Tanikawa M, Uehara Y, Arimoto T, Kuramoto H, Wada-Hiraike O, Miyagawa K, Yano T, Kawana K, Osuga Y, Fujii T "PI3K/mTOR pathway inhibition overcomes radioresistance via suppression of the HIF1-/VEGF pathway in endometrial cancer." Gynecologic oncology (2015) :

67. Fu Y, Zheng S, An N, Athanasopoulos T, Popplewell L, Liang A, Li K, Hu C, Zhu Y "?-catenin as a potential key target for tumor suppression." International journal of cancer. Journal international du cancer (2011) : 1541-51

68. Giles R, van Es J, Clevers H "Caught up in a Wnt storm: Wnt signaling in cancer." Biochimica et biophysica acta (2003) : 1-24

69. Prosperi J, Goss K "A Wnt-ow of opportunity: targeting the Wnt/beta-catenin pathway in breast cancer." Current drug targets (2010) : 1074-88

70. Hisamuddin I, Yang V "Molecular Genetics of Colorectal Cancer: An Overview." Current colorectal cancer reports (2006) : 53-59

71. Kaplan K, Burds A, Swedlow J, Bekir S, Sorger P, Näthke I "A role for the Adenomatous Polyposis Coli protein in chromosome segregation." Nature cell biology (2001) : 429-32

72. Green R, Kaplan K "Chromosome instability in colorectal tumor cells is associated with defects in microtubule plus-end attachments caused by a dominant mutation in APC." The Journal of cell biology (2003) : 949-61

73. Fodde R, Kuipers J, Rosenberg C, Smits R, Kielman M, Gaspar C, van Es J, Breukel C, Wiegant J, Giles R, Clevers H "Mutations in the APC tumour suppressor gene cause chromosomal instability." Nature cell biology (2001) : 433-8

74. Yamada T, Masuda M "Emergence of TNIK inhibitors in cancer therapeutics." Cancer science (2017) : 818-823

75. Katoh M, Katoh M "Molecular genetics and targeted therapy of WNT-related human diseases (Review)." International journal of molecular medicine (2017) : 587-606

76. Tuynman J, Vermeulen L, Boon E, Kemper K, Zwinderman A, Peppelenbosch M, Richel D "Cyclooxygenase-2 inhibition inhibits c-Met kinase activity and Wnt activity in colon cancer." Cancer research (2008) : 1213-20

77. Lu W, Tinsley H, Keeton A, Qu Z, Piazza G, Li Y "Suppression of Wnt/beta-catenin signaling inhibits prostate cancer cell proliferation." European journal of pharmacology (2009) : 8-14

78. Zhang L, Ren X, Alt E, Bai X, Huang S, Xu Z, Lynch P, Moyer M, Wen X, Wu X "Chemoprevention of colorectal cancer by targeting APC-deficient cells for apoptosis." Nature (2010) : 1058-61

79. Chou A, Toon C, Clarkson A, Sioson L, Houang M, Watson N, DeSilva K, Gill A "Loss of ARID1A expression in colorectal carcinoma is strongly associated with mismatch repair deficiency." Human pathology (2014) : 1697-703

80. Allo G, Bernardini M, Wu R, Shih I, Kalloger S, Pollett A, Gilks C, Clarke B "ARID1A loss correlates with mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas." Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc (2014) : 255-61

81. Zhang Y, Xu X, Zhang M, Bai X, Li H, Kan L, Niu H, He P "ARID1A is downregulated in non-small cell lung cancer and regulates cell proliferation and apoptosis." Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine (2014) :

82. Walter D, Venancio O, Buza E, Tobias J, Deshpande C, Gudiel A, Kim-Kiselak C, Cicchini M, Yates T, Feldser D "Systematic In Vivo Inactivation of Chromatin-Regulating Enzymes Identifies Setd2 as a Potent Tumor Suppressor in Lung Adenocarcinoma." Cancer research (2017) : 1719-1729

83. Bitler B, Aird K, Garipov A, Li H, Amatangelo M, Kossenkov A, Schultz D, Liu Q, Shih I, Conejo-Garcia J, Speicher D, Zhang R "Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers." Nature medicine (2015) : 231-238

84. Knutson S, Kawano S, Minoshima Y, Warholic N, Huang K, Xiao Y, Kadowaki T, Uesugi M, Kuznetsov G, Kumar N, Wigle T, Klaus C, Allain C, Raimondi A, Waters N, Smith J, Porter-Scott M, Chesworth R, Moyer M, Copeland R, Richon V, Uenaka T, Pollock R, Kuntz K, Yokoi A, Keilhack H "Selective Inhibition of EZH2 by EPZ-6438 Leads to Potent Antitumor Activity in EZH2-Mutant Non-Hodgkin Lymphoma." Molecular cancer therapeutics (2014) : 842-54

85. Copeland R "Molecular pathways: protein methyltransferases in cancer." Clinical cancer research : an official journal of the American Association for Cancer Research (2013) : 6344-50

86. Schwertfeger K "Fibroblast growth factors in development and cancer: insights from the mammary and prostate glands." Current drug targets (2009) : 632-44

87. Acevedo V, Ittmann M, Spencer D "Paths of FGFR-driven tumorigenesis." Cell cycle (Georgetown, Tex.) (2009) : 580-8

88. Ahmad I, Iwata T, Leung H "Mechanisms of FGFR-mediated carcinogenesis." Biochimica et biophysica acta (2012) : 850-60

89. Weiss J, Sos M, Seidel D, Peifer M, Zander T, Heuckmann J, Ullrich R, Menon R, Maier S, Soltermann A, Moch H, Wagener P, Fischer F, Heynck S, Koker M, Schöttle J, Leenders F, Gabler F, Dabow I, Querings S, Heukamp L, Balke-Want H, Ansén S, Rauh D, Baessmann I, Altmüller J, Wainer Z, Conron M, Wright G, Russell P, Solomon B, Brambilla E, Brambilla C, Lorimier P, Sollberg S, Brustugun O, Engel-Riedel W, Ludwig C, Petersen I, Sänger J, Clement J, Groen H, Timens W, Sietsma H, Thunnissen E, Smit E, Heideman D, Cappuzzo F, Ligorio C, Damiani S, Hallek M, Beroukhim R, Pao W, Klebl B, Baumann M, Buettner R, Ernestus K, Stoelben E, Wolf J, Nürnberg P, Perner S, Thomas R "Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer." Science translational medicine (2010) : 62ra93

90. Turner N, Pearson A, Sharpe R, Lambros M, Geyer F, Lopez-Garcia M, Natrajan R, Marchio C, Iorns E, Mackay A, Gillett C, Grigoriadis A, Tutt A, Reis-Filho J, Ashworth A "FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer." Cancer research (2010) : 2085-94

91. Loilome W, Joshi A, ap Rhys C, Piccirillo S, Vescovi A, Angelo V, Gallia G, Riggins G "Glioblastoma cell growth is suppressed by disruption of Fibroblast Growth Factor pathway signaling." Journal of neuro-oncology (2009) : 359-66

Continue to next page...

References

92. Yamada S, Yamaguchi F, Brown R, Berger M, Morrison R "Suppression of glioblastoma cell growth following antisense oligonucleotide-mediated inhibition of fibroblast growth factor receptor expression." Glia (1999) : 66-76

93. Zhao X, Weir B, LaFramboise T, Lin M, Beroukhim R, Garraway L, Beheshti J, Lee J, Naoki K, Richards W, Sugarbaker D, Chen F, Rubin M, Jänne P, Girard L, Minna J, Christiani D, Li C, Sellers W, Meyerson M "Homozygous deletions and chromosome amplifications in human lung carcinomas revealed by single nucleotide polymorphism array analysis." Cancer research (2005) : 5561-70

94. Inoue Y, Matsuura S, Kurabe N, Kahyo T, Mori H, Kawase A, Karayama M, Inui N, Funai K, Shinmura K, Suda T, Sugimura H "Clinicopathological and Survival Analysis of Japanese Patients with Resected Non-Small-Cell Lung Cancer Harboring NKX2-1, SETDB1, MET, HER2, SOX2, FGFR1, or PIK3CA Gene Amplification." Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer (2015) : 1590-600

95. Zhang J, Zhang L, Su X, Li M, Xie L, Malchers F, Fan S, Yin X, Xu Y, Liu K, Dong Z, Zhu G, Qian Z, Tang L, Schöttle J, Zhan P, Ji Q, Kilgour E, Smith P, Brooks A, Thomas R, Gavine P "Translating the therapeutic potential of AZD4547 in FGFR1-amplified non-small cell lung cancer through the use of patient-derived tumor xenograft models." Clinical cancer research : an official journal of the American Association for Cancer Research (2012) : 6658-67

96. Pu D, Liu J, Li Z, Zhu J, Hou M "Fibroblast Growth Factor Receptor 1 (FGFR1), Partly Related to Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) and Microvessel Density, is an Independent Prognostic Factor for Non-Small Cell Lung Cancer." Medical science monitor : international medical journal of experimental and clinical research (2017) : 247-257

97. Malchers F, Dietlein F, Schöttle J, Lu X, Nogova L, Albus K, Fernandez-Cuesta L, Heuckmann J, Gautschi O, Diebold J, Plenker D, Gardizi M, Scheffler M, Bos M, Seidel D, Leenders F, Richters A, Peifer M, Florin A, Mainkar P, Karre N, Chandrasekhar S, George J, Silling S, Rauh D, Zander T, Ullrich R, Reinhardt H, Ringeisen F, Büttner R, Heukamp L, Wolf J, Thomas R "Cell-autonomous and non-cell-autonomous mechanisms of transformation by amplified FGFR1 in lung cancer." Cancer discovery (2014) : 246-57

98. Wu J, Ji J, Weng B, Qiu P, Kanchana K, Wei T, Wang Y, Cai Y, Li X, Liang G "Discovery of novel non-ATP competitive FGFR1 inhibitors and evaluation of their anti-tumor activity in non-small cell lung cancer in vitro and in vivo." Oncotarget (2014) : 4543-53

99. Dutt A, Ramos A, Hammerman P, Mermel C, Cho J, Sharifnia T, Chande A, Tanaka K, Stransky N, Greulich H, Gray N, Meyerson M "Inhibitor-sensitive FGFR1 amplification in human non-small cell lung cancer." PloS one (2011) : e20351

100. Zhao D, Lu Y, Yang C, Zhou X, Xu Z "Activation of FGF receptor signaling promotes invasion of non-small-cell lung cancer." Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine (2015) : 3637-42

101. Turner N, Grose R "Fibroblast growth factor signalling: from development to cancer." Nature reviews. Cancer (2010) : 116-29

102. Socinski M "Multitargeted receptor tyrosine kinase inhibition: an antiangiogenic strategy in non-small cell lung cancer." Cancer treatment reviews (2011) : 611-7

103. Sternberg C, Davis I, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios C, Salman P, Gladkov O, Kavina A, Zarbá J, Chen M, McCann L, Pandite L, Roychowdhury D, Hawkins R "Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial." Journal of clinical oncology : official journal of the American Society of Clinical Oncology (2010) : 1061-8

104. Motzer R, Hutson T, Glen H, Michaelson M, Molina A, Eisen T, Jassem J, Zolnierek J, Maroto J, Mellado B, Melichar B, Tomasek J, Kremer A, Kim H, Wood K, Dutcus C, Larkin J "Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial." The Lancet. Oncology (2015) : 1473-82

105. Schlumberger M, Tahara M, Wirth L, Robinson B, Brose M, Elisei R, Habra M, Newbold K, Shah M, Hoff A, Gianoukakis A, Kiyota N, Taylor M, Kim S, Krzyzanowska M, Dutcus C, de las Heras B, Zhu J, Sherman S "Lenvatinib versus placebo in radioiodine-refractory thyroid cancer." The New England journal of medicine (2015) : 621-30

106. van der Graaf W, Blay J, Chawla S, Kim D, Bui-Nguyen B, Casali P, Schöffski P, Aglietta M, Staddon A, Beppu Y, Le Cesne A, Gelderblom H, Judson I, Araki N, Ouali M, Marreaud S, Hodge R, Dewji M, Coens C, Demetri G, Fletcher C, Dei Tos A, Hohenberger P "Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial." Lancet (2012) : 1879-86

107. Cortes J, Kim D, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, Nicolini F, Apperley J, Khoury H, Talpaz M, DiPersio J, DeAngelo D, Abruzzese E, Rea D, Baccarani M, Müller M, Gambacorti-Passerini C, Wong S, Lustgarten S, Rivera V, Clackson T, Turner C, Haluska F, Guilhot F, Deininger M, Hochhaus A, Hughes T, Goldman J, Shah N, Kantarjian H "A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias." The New England journal of medicine (2013) : 1783-96

108. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz H, Goldberg R, Sargent D, Cihon F, Cupit L, Wagner A, Laurent D "Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial." Lancet (2013) : 303-12

109. Demetri G, Reichardt P, Kang Y, Blay J, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki R, Bauer S, Nguyen B, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali P "Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial." Lancet (2013) : 295-302

110. Azuma K, Kawahara A, Sonoda K, Nakashima K, Tashiro K, Watari K, Izumi H, Kage M, Kuwano M, Ono M, Hoshino T "FGFR1 activation is an escape mechanism in human lung cancer cells resistant to afatinib, a pan-EGFR family kinase inhibitor." Oncotarget (2014) : 5908-19

111. Kim T, Song A, Kim D, Kim S, Ahn Y, Keam B, Jeon Y, Lee S, Chung D, Heo D "Mechanisms of Acquired Resistance to AZD9291, a Mutation-Selective, Irreversible EGFR Inhibitor." Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer (2015) :

112. Sharifnia T, Rusu V, Piccioni F, Bagul M, Imielinski M, Cherniack A, Pedamallu C, Wong B, Wilson F, Garraway L, Altshuler D, Golub T, Root D, Subramanian A, Meyerson M "Genetic modifiers of EGFR dependence in non-small cell lung cancer." Proceedings of the National Academy of Sciences of the United States of America (2014) : 18661-6