REPORTING

Report Date:	APR-02-2024
Receipt Date:	MAR-28-2024
Collection Date:	MAR-26-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

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Additional Recipient: N/A

Complete Tumor Response Map on page 2

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

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

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 3)	% cfDNA or Amplification
TP53 V172F	None	Yes	2.7%
CDKN2A Y44*	None	Yes	1.0%
GNAS R201H	None	Yes	0.1%
SMAD4 Y353N	None	No	1.2%

Variants of Uncertain Clinical Significance
STK11 R147P (3.7%), *FGFR2* R399L (0.7%), *FGFR2* Splice Site SNV (0.1%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Comments

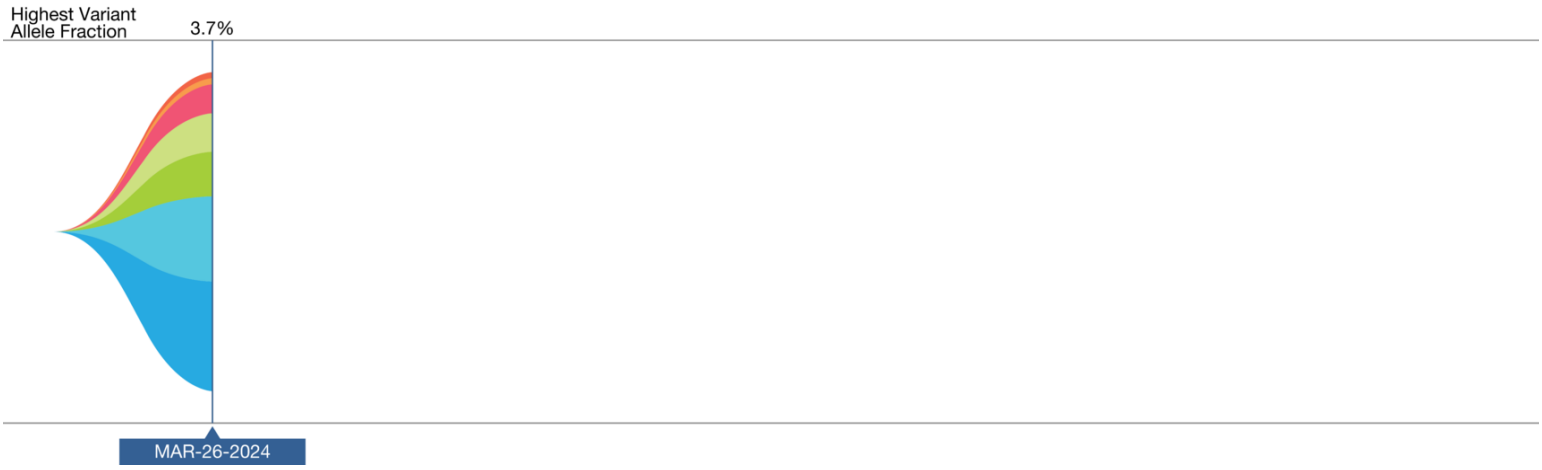
Reported by: AA23

Additional Biomarkers

Biomarker	Additional Details
MSI-High	NOT DETECTED

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. 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.



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GNAS R201H	0.1%	
FGFR2 Splice Site SNV	0.1%	Variants of Uncertain Clinical 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 A1004485 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
TP53 V172F	NCT04768868 Jian Wang,Jian. wang@impacttherapeutics.com,+86 18613056501	The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients With Advanced Solid Tumors	Phase 1	Taipei, Taiwan Taoyuan, Taiwan Taichung, Taiwan Tainan, Taiwan (2)
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
CDKN2A Y44*	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
GNAS R201H	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

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

Splice Site: Splice site variants disrupt the donor and/or acceptor splice site(s), leading to abnormal mRNA splicing and altered protein levels and/or function.

***Nonsense mutation:** A point mutation that results in a premature stop codon.

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 74 cancer-associated genes to identify somatic alterations. Cell-free DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using the Illumina platform 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 variants, gene amplifications, fusions, short insertions/deletions (longest detected, 70 base pairs), and splice site disrupting events (see Table 1). Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Guardant360 panel. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue. MSI status is currently not reported for earlier panel versions. 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, such as low cfDNA concentration, may result in reduced analytic sensitivity. Guardant360 cannot discern the source of 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, splice site mutations, and insertion and deletion variants (indels) in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

AKT1	*ALK* #	*APC*	*AR* †	*ARAF*	*ARID1A*	*ATM*	*BRAF* †	*BRCA1*
BRCA2	*CCND1* †	*CCND2* †	*CCNE1* †	*CDH1*	*CDK12*	*CDK4* †	*CDK6* †	*CDKN2A*
CTNNB1	*DDR2*	*EGFR* †	*ERBB2* †	*ESR1*	*EZH2*	*FBXW7*	*FGFR1* †	*FGFR2* # †
FGFR3 #	*GATA3*	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*IDH2*
JAK2	*JAK3*	*KIT* †	*KRAS* †	*MAP2K1*	*MAP2K2*	*MAPK1*	*MAPK3*	*MET* †
MLH1	*MPL*	*MTOR*	*MYC* †	*NF1*	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*
NTRK1 #	*NTRK3*	*PDGFRA* †	*PIK3CA* †	*PTEN*	*PTPN11*	*RAF1* †	*RB1*	*RET* #
RHEB	*RHOA*	*RIT1*	*ROS1* #	*SMAD4*	*SMO*	*STK11*	*TERT* ‡	*TP53*
TSC1	*VHL*							

‡ Guardant360 reports alterations in the promoter region of this gene.

Guardant360 reports fusion events involving this gene.

† Guardant360 reports amplifications of this gene.

About the Test

The 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 interpreted in the context of other clinical information and 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. Drug and trial information are based on the diagnosis 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 the indicated 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: Martina Lefterova, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, USA

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 A1004485 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)
TP53 V172F	NCT02769962 Danielle F Pinkiert, R.N.,danielle.pinkiert@nih.gov,(240) 858-7566	Trial of EP0057, a Nanoparticle Camptothecin With Olaparib in People With Relapsed /Refractory Small Cell Lung Cancer	Phase 1 /Phase 2	Bethesda, MD
	NCT03968653 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors	Phase 1	Spain; Netherlands (3)
	NCT04768868 Jian Wang,Jian.wang@impacttherapeutics.com,+86 18613056501	The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients With Advanced Solid Tumors	Phase 1	Louisville, KY; Boston, MA; Atlanta, GA; Dallas, TX; Fairway, KS; San Antonio, TX; China (4); Taiwan (5)
	NCT04869475 Min Shi, MD & Ph. D,sm11998@rjh.com.cn,+86-21-64370045	Arsenic Trioxide in Refractory Solid Tumors With Rescuable p53 Mutation	Phase 2	China
	NCT05109975 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	A Study to Evaluate Safety and Preliminary Anti-tumor Activity of Debio 0123 as Monotherapy in Adult Participants With Advanced Solid Tumors	Phase 1	Grand Rapids, MI; San Antonio, TX; Switzerland; Spain (7)
CDKN2A Y44*	NCT02693535 Pam Mangat, MS,tapur@asco.org,www.tapur.org	TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer	Phase 2	Phoenix, AZ; Manchester, NH; Charlotte, NC; Portland, OR; Fargo, ND; Concord, NH; Houston, TX; Chapel Hill, NC; Cedar City, UT; Omaha, NE; Birmingham, AL; Portsmouth, NH; Hilton Head Island, SC; Nashville, TN; Fairfax, VA; Kettering, OH; Sioux Falls, SD; Saint George, UT; Chicago, IL; Seattle, WA; Indianapolis, IN; Cincinnati, OH; Salt Lake City, UT; West Chester, OH; Bismarck, ND; Bluffton, SC (3); FL (37); NY (5); WI (16); ME (19); GA (6); MI (11); CA (21); PA (5); CT (7); NM (5)
	NCT02925234 E.E. Voest, prof.,DRUP@nki.nl, 0031205129111	The Drug Rediscovery Protocol (DRUP Trial)	Phase 2	Netherlands (35)
	NCT03297606 Janet Dancey,jdancey@ctg.queensu.ca, 613-533-6430	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)	Phase 2	Canada (9)
	NCT05705505 Victor Moyo, MD,vmoyo@onconova.us, 484 535 1402	Study of Narazaciclib (ON 123300) Plus Letrozole in Endometrial Cancer and Other Gynecologic Malignancies	Phase 1 /Phase 2	Tucson, AZ; Mineola, NY; Greenville, SC; Minneapolis, MN; Eugene, OR; New York, NY; Dallas, TX; Fort Worth, TX
	NCT06243185 Xiao Shang, PhD,shang.mm@163.com, 13810073050	Dalpiciclib Combined With Letrozole in HR+ /HER2 - Gynecologic Solid Tumors	Phase 2	China
GNAS R201H	NCT02925234 E.E. Voest, prof.,DRUP@nki.nl, 0031205129111	The Drug Rediscovery Protocol (DRUP Trial)	Phase 2	Netherlands (35)
	NCT03905148 BeiGene,clinicaltrials@beigene.com,1 (877) 828-5568	Study of the Safety and Pharmacokinetics of BGB-283 (Lifirafenib) and PD-0325901 (Mirdametinib) in Participants With Advanced or Refractory Solid Tumors	Phase 1	Houston, TX; Santa Monica, CA; Australia (4)
	NCT04341181	ProTarget - A Danish Nationwide Clinical Trial	Phase 2	Denmark (7)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	Ulrik Lassen, Prof.,ulrik.lassen@regionh.dk,+45 3545 8923	on Targeted Cancer Treatment Based on Genomic Profiling		
	NCT04720976 Jacobio Pharmaceuticals, clinicaltrials@jacobiopharma.com,86 10 56315466	JAB-3312 Based Combination Therapy in Adult Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Oklahoma City, OK; Saint Louis, MO; Phoenix, AZ; New York, NY; Chicago, IL; New Haven, CT; Jacksonville, FL; Los Angeles, CA; Houston, TX; Detroit, MI; Rochester, MN; Indianapolis, IN; Scottsdale, AZ; Orange City, FL; Salt Lake City, UT
	NCT05097599 Stephanie Bush,stephanie.bush@strataoncology.com,(734) 527-1000	Strata PATH™ (Precision Indications for Approved Therapies)	Phase 2	Kettering, OH; Madison, WI; West Palm Beach, FL; Fort Myers, FL; Newark, DE; Saint Petersburg, FL; Tallahassee, FL; Nashville, TN

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
CDKN2A Y44*	Abemaciclib	Verzenio	Cdk4/6/9 inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (Breast carcinoma (hormone receptor +, HER2-))
	Alvocidib		Cdk inhibitor targeting several Cdks, including Cdk1, Cdk2, Cdk4, Cdk5, Cdk6, Cdk7, and Cdk9.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Melanoma, Non-small cell lung carcinoma (NSCLC), Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Germ cell tumor, Esophageal carcinoma, Breast carcinoma, Chronic lymphocytic leukemia (CLL), Acute myeloid leukemia (AML), Multiple myeloma (MM), B-cell lymphoma, Testicular cancer, Lung cancer, Sarcoma, Colorectal carcinoma (CRC), Acute lymphoblastic leukemia (ALL), Myelodysplastic Syndrome (MDS))
	Dalpiciclib		Cdk4/6 inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Breast carcinoma)
	FCN-437c		Cdk4/6 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma)
	FN-1501		Multikinase inhibitor of Cdk2/4/6 and Flt3.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	Lerociclib		Cdk4/6 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC), Breast carcinoma)
	Narazaciclib		Ark5 and Cdk4 multi-kinase inhibitor.	Phase 1 (Solid Tumor)
	Palbociclib	Ibrance	Cdk4/6 inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (Breast carcinoma (hormone receptor +, HER2-))
	PF-06873600		Cdk2/4/6 inhibitor.	Phase 2 (Ovarian carcinoma, Breast carcinoma)
	PF-07220060		Cdk4 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Liposarcoma)
	PF-07224826		CDK2/4/6 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC), Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma, Liposarcoma)
	RGT-419B		CDK2/4/6 inhibitor.	Phase 1 (Solid Tumor)
	Ribociclib	Kisqali	Cdk4/6 inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (Breast carcinoma (hormone receptor +, HER2-))
	SPH4336		Cdk4/6 inhibitor.	Phase 2 (Solid Tumor) Phase 3 (Breast carcinoma)
	TQB3616		Cdk4/6 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC), Breast carcinoma)
	Trilaciclib	Cosela	Cdk4/6 inhibitor.	FDA Approved in other indications (Small cell lung carcinoma (SCLC))
	Voruciclib		Multikinase inhibitor of Cdk1/4/6/9.	Phase 1 (Solid Tumor) Phase 1 (Marginal zone lymphoma (MZL), Brain and Central Nervous System Tumors, Hematologic malignancies, Chronic lymphocytic leukemia (CLL), Acute myeloid leukemia (AML), Mantle cell lymphoma (MCL), Follicular lymphoma (FL), Diffuse large B-cell lymphoma (DLBCL), Small lymphocytic lymphoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
TP53 V172F	Adavosertib		Wee1 tyrosine kinase inhibitor.	Phase 2 (Cervical adenocarcinoma) Phase 2 (Lymphoma, Embryonal tumor with multi-layered rosettes (ETMR), Medulloblastoma, Small cell lung carcinoma (SCLC), Solid Tumor, Primary myelofibrosis (PMF), Ovarian carcinosarcoma, Acute myeloid leukemia (AML), MDS/MPN, unclassifiable, Chronic myelomonocytic leukemia (CMML), Peritoneal papillary serous carcinoma, Myelodysplastic Syndrome (MDS))
	AL8326		Aurora kinase B/VEGFRs/Fgfr multi-kinase inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Small cell lung carcinoma (SCLC))
	Alisertib		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	ATO	Trisenox	PML-RARA inhibitor. Inhibits multiple signaling pathways, including the Hedgehog pathway.	Phase 2 (Cervical carcinoma) FDA Approved in other indications (Acute myeloid leukemia (AML), Acute promyelocytic leukemia (APL))
	AZD2811		Nanoparticle formulation of Aurora kinase B inhibitor barasertib (AZD1152).	Phase 1 (Solid Tumor) Phase 2 (Acute myeloid leukemia (AML), Myelodysplastic Syndrome (MDS))
	Azenosertib		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (High-grade serous ovarian carcinoma, Uterine serous/clear cell carcinoma, Osteosarcoma, Ovarian epithelial carcinoma, Colorectal adenocarcinoma, Acute myeloid leukemia (AML), Fallopian tube carcinoma, Peritoneal carcinoma, Pancreatic adenocarcinoma)
	Debio 0123		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	EP0042		Aurora kinase A/B and Flt3 inhibitor.	Phase 2 (Acute myeloid leukemia (AML), Chronic myelomonocytic leukemia (CMML), Myelodysplastic Syndrome (MDS))
	IMP7068		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	JAB-2485		Aurora kinase A inhibitor.	Phase 2 (Solid Tumor)
	LY3295668		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Small cell lung carcinoma (SCLC), Breast carcinoma (triple negative), Breast carcinoma (hormone receptor +, HER2-))
	SGT-53		TP53 gene therapy delivered via transferrin-targeted nanoparticles.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma, Pancreatic carcinoma)
	SY-4835		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	TAS-119		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor)
	Tinengotinib		Aurora kinase A/B inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Breast carcinoma (triple negative))
GNAS R201H	BI 3011441		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Binimetinib	Mektovi	MEK1,2 inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	Cobimetinib	Cotellic	MEK1,2 inhibitor.	Phase 2 (Solid Tumor) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation, Histiocytic and dendritic cell

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				neoplasms)
	CS3006		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	E6201		MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	IMM-1-104		MEK1, 2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Non-small cell lung carcinoma (NSCLC), Pancreatic ductal adenocarcinoma)
	Mirdametinib		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioma, Non-small cell lung carcinoma (NSCLC), Neurofibroma, Breast carcinoma, Glioneuronal tumor, Neurofibromatosis type 1, Lung cancer, Colorectal carcinoma (CRC))
	PF-07799544		MEK Brain Penetrant Inhibitor.	Phase 1 (Glioma, Melanoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma, Colorectal carcinoma (CRC))
	Pimasertib		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Pancreatic ductal adenocarcinoma, Ovarian carcinoma, Hematologic malignancies, Colorectal carcinoma (CRC))
	Selumetinib	Koselugo	MEK1,2 inhibitor.	Phase 1 (Solid Tumor) FDA Approved in other indications (NF1-related plexiform neurofibroma)
	SHR7390		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Trametinib	Mekinist	MEK1,2 inhibitor.	Phase 2 (Cervical carcinoma) FDA Approved in other indications (Melanoma with BRAF V600 mutation)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
TP53 V172F	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. (1). 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. (2-4). 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. (5-9). TP53 overexpression has been reported to inhibit cell proliferation, migration, invasion, and colony formation in cervical cancer cell lines in a preclinical study. (10).	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. (11-13). Inhibition of components of the DNA damage checkpoint, including Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function. (14-16). Clinical trials of the Wee1 inhibitor adavosertib (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. (17-22).	Mutations in TP53 may increase resistance to ionizing radiation therapy. (23,24).
CDKN2A Y44*	Because the CDKN2A and CDKN2B gene products encode proteins that act as tumor suppressors, deletion or loss of activity may result in deregulation of the p16INK4a/Cdk4 /Cyclin/Rb and/or the Mdm2/p53 pathways, and altered regulation of the cell cycle. (25,26). Expression of p16INK4a has also been reported to correspond with genomic integration infections of high-risk human papillomavirus (hrHPV). (27,28). A meta-analysis of 15 studies including 1633 cervical cancer cases reported that p16INK4a overexpression was associated with the absence of lymph node metastasis. (29).	There are currently no drugs that directly target inactivating mutations or loss of CDKN2A. Because p16INK4a is known to inhibit Cdk4, tumors with CDKN2A alterations may be sensitive to Cdk4/6 inhibitors. (26,30). p14ARF has been reported to function as a tumor suppressor through stabilization and activation of p53, via a mechanism of Mdm2 inhibition. (26,32). However, as the alteration in p16INK4a reported here corresponds to a non-coding region of the p14ARF transcript (IGV), Mdm2 inhibition is not expected to be a relevant therapeutic approach.	
GNAS R201H	Activating mutations in GNAS occur predominantly at R201. GNAS R201H and R201C are mutations commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with activating GNAS mutations. (33-35). One study reported that all GNAS-mutant cervical adenocarcinoma specimens analyzed were positive for HPV infection and/or p16INKa expression, but not any of the lobular endocervical glandular hyperplasia specimens. (36).	At present there are no clinical studies or therapies directly targeted to GNAS mutation in cancer. However, based on preclinical evidence, tumors with GNAS mutations may be sensitive to inhibitors of the MAPK pathway, which are currently under clinical investigation. (37).	
SMAD4	A dual role for the TGF-beta/Smad4	At present there are no therapies	

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
Y353N	signaling network in cancer has been described based on preclinical data, with a tumor suppressor function in tumor initiation, and a tumor-promoting function in later stages of invasion and metastasis. [38]. Germline mutations in SMAD4 have been implicated in juvenile polyposis syndrome (JPS), a disorder linked to increased risk of gastrointestinal malignancies, including colorectal polyps and cancer, and gastric polyps. [39,40]. Low nuclear Smad4 expression has been significantly associated with adenocarcinoma histology in a cohort of 21 cervical carcinoma cases. [41]. SMAD4 depletion has been reported to increase cell and tumor growth in preclinical models of cervical cancer. [42,43].	available to address the loss of SMAD4 in cancer.Several compounds that are selectively cytotoxic to Smad4 (DPC4) deficient tumor cells as compared to Smad4 wild-type cells have been identified in preclinical studies. [44,45].	

References

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