REPORTING

Report Date:	JAN-22-2023
Receipt Date:	JAN-17-2023
Collection Date:	JAN-16-2023
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
PIK3CA E545K	~ Alpelisib	Yes	0.1%
KRAS G12V	None	Yes	0.5%
ARID1A M2001fs	None	Yes	0.2%

Variants of Uncertain Clinical Significance
BRCA2 Y2222C (0.2%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Additional Biomarkers

Biomarker	Additional Details
MSI-High	NOT DETECTED

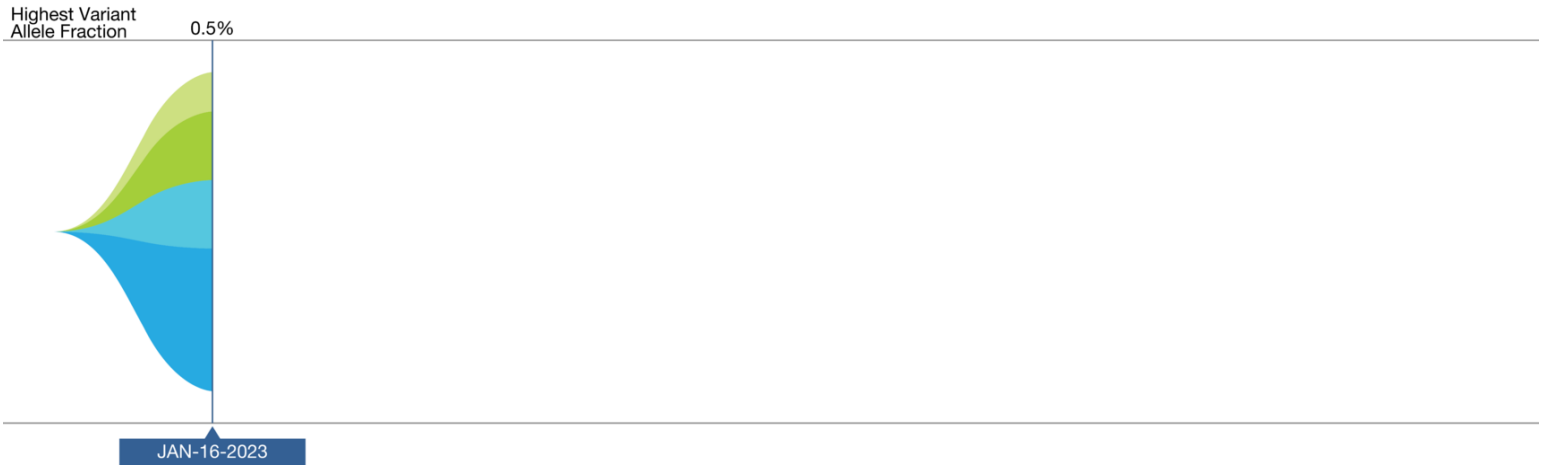
Alterations or biomarkers that were "NOT DETECTED" have been excluded from the summary table above.

We evaluated this sample for 74 genes, including the following guideline-recommended genes for NSCLC

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

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.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	
KRAS G12V	0.5%	
ARID1A M2001fs	0.2%	
BRCA2 Y2222C	0.2%	Variants of Uncertain Clinical Significance §
PIK3CA E545K	0.1%	

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 A0647943 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
PIK3CA E545K	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Taipei City, Taiwan
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
KRAS G12V	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Taipei City, Taiwan
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
ARID1A M2001fs	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.

Deletion (Del): The following alteration was detected in this patient: *ARID1A* M2001fs. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

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 amplifications of this gene.

Guardant360 reports fusion events involving 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 A0647943 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 E545K	NCT03006172 Reference Study ID Number: GO39374 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	To Evaluate the Safety, Tolerability, and Pharmacokinetics of Inavolisib Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer	Phase 1	Nashville, TN; Boston, MA (2); New York, NY (2); Canada; France; United Kingdom (3); Spain (2)
	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Las Vegas, NV; Cleveland, OH; Newark, DE; Nashville, TN; Taiwan; Australia; Korea, Republic of (2); United Kingdom (3); Israel (3); France (5); Spain (7)
	NCT03842228 See https://clinicaltrials.gov/show/NCT03842228	Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations	Phase 1	Houston, TX; Austin, TX; Galveston, TX; Boston, MA (3)
	NCT04551521 Richard Schlenk, Prof. Dr.,richard.schlenk@nct-heidelberg.de,+49622156 x6228	CRAFT: The NCT-PMO-1602 Phase II Trial	Phase 2	Germany (6)
	NCT04586335 Jason Sudia, PhD, MPH,jason.sudia@haihepharma.com,9083801329	Study of CYH33 in Combination With Olaparib an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.	Phase 1	China
	NCT04591431 Silvia Violetti,silvia.violetti@clinicaltrialsfmp.it, +390683977939	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	Phase 2	Italy (41)
KRAS G12V	NCT03190941 NCI SB Immunotherapy Recruitment Center,IRC@nih.gov,(866) 820-4505	Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12V Variant of Mutated RAS in HLA-A*11:01 Patients	Phase 1 /Phase 2	Bethesda, MD
	NCT03284502 See https://clinicaltrials.gov/show/NCT03284502	HM95573 in Combination With Either Cobimetinib or Cetuximab in Patients With Locally Advanced or Metastatic Solid Tumors	Phase 1	Korea, Republic of (9)
	NCT03337698 Reference Study ID Number: BO39610 https://forpatients.roche.com/,global-roche-genentech-trials@gene.com,888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)	Phase 1 /Phase 2	Las Vegas, NV; Cleveland, OH; Newark, DE; Nashville, TN; Taiwan; Australia; Korea, Republic of (2); United Kingdom (3); Israel (3); France (5); Spain (7)
	NCT03600701 See https://clinicaltrials.gov/show/NCT03600701	Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer	Phase 2	Detroit, MI; Oklahoma City, OK; Winston-Salem, NC; Pittsburgh, PA; New York, NY; Columbus, OH; Washington, DC; Birmingham, AL; Clemmons, NC; Tampa, FL; Lebanon, NH; Charlottesville, VA
	NCT04620330 Verastem Call Center, clinicaltrials@verastem.com,781-292-4204	A Study of Avutometinib (VS-6766) + Defactinib in Recurrent KRAS G12V, Other KRAS and BRAF Non-Small Cell Lung Cancer	Phase 2	Grapevine, TX; Saint Louis, MO; Columbia, MD; Saint Petersburg, FL; Portland, OR; Houston, TX; Duarte, CA; Detroit, MI; Baton Rouge, LA; Boston, MA; Pittsburgh, PA; Washington, DC; Aurora, CO; Nashville, TN; Fairfax, VA; Philadelphia, PA; Columbus, OH; Hackensack, NJ; Niles, IL; Atlanta, GA; Fort Myers, FL; Dallas, TX; Lake Success, NY; Lone Tree, CO; Fort Worth, TX; Chattanooga, TN;

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Chicago, IL (2); Italy (4); France (5); Germany (3); Spain (5)
	NCT04870034 See https://clinicaltrials.gov/show/NCT04870034	Binimetinib and Palbociclib Before Surgery for the Treatment of Operable KRAS-Positive Lung, Colorectal, or Pancreatic Cancer	Early Phase 1	Buffalo, NY
ARID1A M2001fs	NCT03209401 See https://clinicaltrials.gov/show/NCT03209401	Niraparib Plus Carboplatin in Patients With Homologous Recombination Deficient Advanced Solid Tumor Malignancies	Phase 1	Charlotte, NC; Hackensack, NJ; Washington, DC (2)
	NCT03842228 See https://clinicaltrials.gov/show/NCT03842228	Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations	Phase 1	Houston, TX; Austin, TX; Galveston, TX; Boston, MA (3)
	NCT04104776 Medical Information,medinfo@morphosys.com,(844) 667-1992	A Study of CPI-0209 in Patients With Advanced Solid Tumors and Lymphomas	Phase 1 /Phase 2	Seattle, WA; Grand Rapids, MI; Atlanta, GA; New York, NY; Cincinnati, OH; Chicago, IL; Baltimore, MD; Bronx, NY; San Antonio, TX; Hackensack, NJ; Ann Arbor, MI; Charlottesville, VA; Boston, MA (2); United Kingdom; Spain
	NCT04266912 Timothy A. Yap,tyap@mdanderson.org,713-563-1930	Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors	Phase 1 /Phase 2	Houston, TX
	NCT04586335 Jason Sudia, PhD, MPH,jason.sudia@haihepharma.com,9083801329	Study of CYH33 in Combination With Olaparib an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.	Phase 1	China

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
ARID1A M2001fs	ABBV-075		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor)
	ABBV-744		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Prostate carcinoma, Acute myeloid leukemia (AML))
	AZD5153		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	AZD5305		PARP inhibitor.	Phase 2 (Solid Tumor)
	AZD9574		PARP1 inhibitor (brain penetrant).	Phase 2 (Glioma, Pancreatic carcinoma, Prostate carcinoma, Ovarian carcinoma, Breast carcinoma)
	Berzosertib		Atr inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Neuroendocrine carcinoma, Small cell carcinoma, Osteosarcoma, Prostate carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Gastroesophageal junction carcinoma, Urothelial carcinoma, Bladder carcinoma, Leiomyosarcoma, Renal pelvis carcinoma, Lung cancer)
	BI 894999		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor)
	Birabresib		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Prostate carcinoma, Breast carcinoma (triple negative), Hematologic malignancies, Acute myeloid leukemia (AML))
	BMS-986158		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 2 (Solid Tumor)
	Ceralasertib		Atr inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Lung cancer)
	CPI-0209		2nd generation Ezh2 inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Lymphoma)
	CPI-0610		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Lymphoma, Multiple myeloma (MM), Myelodysplastic Syndrome (MDS))
	CPI-1205		Ezh2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Prostate carcinoma)
	DS-3201b		Ezh1/2 inhibitor.	Phase 2 (Small cell lung carcinoma (SCLC), Adult T-cell leukemia/lymphoma (ATLL))
	Elimusertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Head and neck squamous cell carcinoma (HNSCC))
	Fluzoparib		PARP inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Pancreatic carcinoma, Ovarian carcinoma, Breast carcinoma)
	FT-1101		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Acute myeloid leukemia (AML), Non-Hodgkin lymphoma (NHL), Myelodysplastic Syndrome (MDS))
	GS-5829		Bromodomain and extra-terminal domain (BET) protein inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Prostate carcinoma, Breast carcinoma)
	GSK2820151		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor)
	IDX-1197		PARP inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	INCB054329		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 2 (Solid Tumor)
	INCB057643		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma, Hematologic malignancies)
	Niraparib	Zejula	PARP inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Ovarian carcinoma)
	ODM-207		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 2 (Solid Tumor)
	Olaparib	Lynparza	PARP inhibitor.	Phase 2 (Lung adenocarcinoma) FDA Approved in other indications (Pancreatic adenocarcinoma with germline BRCA1/2 mutation, Prostate cancer with HRR gene mutation, Ovarian carcinoma, Ovarian carcinoma with BRCA1/2 mutation, Breast carcinoma with germline BRCA1/2 mutation)
	Pamiparib		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Gastric carcinoma, Gastroesophageal junction carcinoma)
	PF-06821497		Ezh2 inhibitor.	Phase 1 (Prostate carcinoma, Small cell lung carcinoma (SCLC), Follicular lymphoma (FL), Diffuse large B-cell lymphoma (DLBCL))
	PLX2853		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Uveal melanoma, Small cell lung carcinoma (SCLC), Brain and Central Nervous System Tumors, Non-Hodgkin lymphoma (NHL))
	RG6146		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML), Myelodysplastic Syndrome (MDS), Diffuse large B-cell lymphoma (DLBCL))
	RP-3500		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	RP12146		PARP inhibitor.	Phase 1 (Gastric carcinoma, Pancreatic carcinoma, Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Breast carcinoma, Cholangiocarcinoma, Colorectal carcinoma (CRC))
	Rucaparib	Rubraca	PARP inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma)
	SHR2554		Ezh2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Breast carcinoma, Gastrointestinal carcinoma, Cholangiocarcinoma, B-cell lymphoma)
	Stenoparib		PARP inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Pancreatic carcinoma, Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma, Colorectal carcinoma (CRC))
	Talazoparib	Talzenna	PARP inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma with germline BRCA1/2 mutation)
	Tazemetostat	Tazverik	Ezh2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Follicular

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				lymphoma with EZH2 mutation, Epithelioid sarcoma, Follicular lymphoma (FL))
	Trotabresib		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Non-Hodgkin lymphoma (NHL))
	Veliparib		PARP inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Glioblastoma, Ovarian carcinoma, Ovarian carcinosarcoma, Breast carcinoma, Lung cancer)
	VX-803		Atr inhibitor.	Phase 1 (Solid Tumor)
	ZEN003694		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 2 (Prostate carcinoma, Breast carcinoma (triple negative))
PIK3CA E545K	ABTL0812		Inhibitor of mTORC1/mTORC2 /Dhfr.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Endometrial carcinoma)
	Alpelisib	Piqray	p-110-alpha inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HR+, HER2-) with a PIK3CA mutation, as determined by a validated test)
	Apitolisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Breast carcinoma)
	Archexin	Archexin	Akt1 antisense oligonucleotide.	Phase 1 (Solid Tumor) Phase 2 (Pancreatic carcinoma, Renal cell carcinoma)
	ARQ 751		Akt inhibitor.	Phase 1 (Solid Tumor)
	ASN003		Dual Braf and PI3K inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	AT13148		Multi-AGC (Akt, p70S6K) small molecule kinase inhibitor.	Phase 1 (Solid Tumor)
	Bimiralisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma (triple negative), Primary central nervous system lymphoma (PCNSL))
	Buparlisib		PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Head and neck squamous cell carcinoma (HNSCC), Breast carcinoma)
	Capivasertib		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Prostate carcinoma, Breast carcinoma)
	CC-115		DNA-PK/dual mTORC1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma)
	Copanlisib	Aliqopa	PI3K inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Follicular lymphoma (FL))
	CYH33		p110-alpha-specific small molecule inhibitor.	Phase 1 (Solid Tumor)
	Fimepinostat		PI3K/HDAC inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Thyroid carcinoma, Diffuse large B-cell lymphoma (DLBCL))
	Gedatolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	HS-10352		p110-alpha-specific small molecule inhibitor.	Phase 1 (Breast carcinoma)
	Inavolisib		PI3K inhibitor.	Phase 1 (Solid Tumor)
	Ipatasertib		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Prostate carcinoma, Breast carcinoma)
	ME-344		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Small cell lung carcinoma (SCLC))
	Miransertib		Akt inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	MK-2206		Akt inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Gallbladder carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Hodgkin lymphoma (HL), Lymphoma, Melanoma, Carcinoid tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Small cell lung carcinoma (SCLC), Adenoid cystic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Gastrointestinal neuroendocrine carcinoma, Mucinous colon adenocarcinoma, Breast carcinoma, Chronic lymphocytic leukemia (CLL), Acute myeloid leukemia (AML), Cholangiocarcinoma, Thymic neoplasm, Peritoneal papillary serous carcinoma, Lung cancer, Colorectal carcinoma (CRC), Diffuse large B-cell lymphoma (DLBCL))
	MSC2363318A		Akt1, Akt3, and p70S6K inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma)
	Onatasertib		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor, Bladder neuroendocrine carcinoma, Multiple myeloma (MM), Diffuse large B-cell lymphoma (DLBCL))
	Paxalisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Glioblastoma, Breast carcinoma)
	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))
	Pilaralisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Endometrial carcinoma, Breast carcinoma)
	RMC-5552		mTORC1-specific inhibitor.	Phase 1 (Solid Tumor)
	Samotolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Prostate carcinoma)
	Sapanisertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Uterine carcinosarcoma, Hepatocellular carcinoma (HCC), Lymphoma, Merkel cell carcinoma, Anaplastic thyroid carcinoma, Pancreatic neuroendocrine tumor, Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Ovarian carcinoma, Urothelial carcinoma, Bladder carcinoma, Breast carcinoma, Multiple myeloma (MM), Non-Hodgkin lymphoma (NHL), Lung cancer, Sarcoma, Acute lymphoblastic leukemia (ALL))
	Serabelisib		PI3K inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Endometrial

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				carcinoma, Renal cell carcinoma, Breast carcinoma (triple negative))
	SF1126		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC))
	TAS-117		Akt inhibitor.	Phase 2 (Solid Tumor)
	TAS0612		Akt/p70S6K/p90RSK1 multikinase inhibitor.	Phase 1 (Solid Tumor)
	Triciribine		DNA synthesis and Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Breast carcinoma)
	Uprosertib		Akt inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Uveal melanoma, Breast carcinoma, Cervical carcinoma, Acute myeloid leukemia (AML), Multiple myeloma (MM))
	Vistusertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Glioblastoma, Meningioma, Small cell lung carcinoma (SCLC), Solid Tumor, Diffuse large B-cell lymphoma (DLBCL))
KRAS G12V	Anti-KRAS G12V mTCR cells		Peripheral blood lymphocytes transduced with a murine T-Cell receptor recognizing K-Ras G12V.	Phase 2 (Cancer)
	ASN007		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	ASTX029		ERK1/2 kinase inhibitor.	Phase 2 (Solid Tumor)
	BBP-398		Shp-2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	BI 1701963		Pan-K-Ras inhibitor targeting the interaction of K-Ras and SOS-1.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	BI 3011441		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Binimetinib	Mektovi	MEK1,2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation)
	Cobimetinib	Cotellic	MEK1,2 inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Melanoma with BRAF V600E/K mutation, Histiocytic and dendritic cell neoplasms)
	CS3006		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Defactinib		Focal adhesion kinase (FAK) inhibitor, upstream of MAPK pathway.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Lymphoma, Solid Tumor, Multiple myeloma (MM))
	E6201		MEK1,2, Mekk1, and Flt3 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	ERAS-601		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	GI-4000		Mutant K-Ras vaccine.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Colorectal carcinoma (CRC))
	HH2710		ERK1/2 kinase inhibitor.	Phase 2 (Solid Tumor)
	HMPL-295		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	JAB-3068		Shp-2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Esophageal carcinoma)
	JAB-3312		Shp-2 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	KO-947		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	KRAS G12V-specific T-cells		Mutant KRAS G12V-specific TCR transduced autologous T-cells.	Phase 2 (Pancreatic carcinoma)
	LTT462		ERK1/2 kinase inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Mirdametinib		MEK1,2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Neurofibroma, Breast carcinoma, Neurofibromatosis type 1, Low grade glioma, Lung cancer, Colorectal carcinoma (CRC))
	MK-8353		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor)
	PF-07284892		Small molecule inhibitor of Shp-2, a central node in RAS/MAPK signaling.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	Pimasertib		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Pancreatic ductal adenocarcinoma, Ovarian carcinoma, Hematologic malignancies, Colorectal carcinoma (CRC))
	Refametinib		MEK1,2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Gallbladder carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Breast carcinoma, Cholangiocarcinoma, Colorectal carcinoma (CRC), Combined hepatocellular carcinoma and cholangiocarcinoma)
	RMC-4630		Small molecule inhibitor of Shp-2, a central node in RAS/MAPK signaling.	Phase 2 (Solid Tumor)
	Selumetinib	Koselugo	MEK1,2 inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (NF1-related plexiform neurofibroma)
	SHR7390		MEK1,2 inhibitor.	Phase 1 (Solid Tumor)
	Temuterkib		ERK1/2 kinase inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Pancreatic ductal adenocarcinoma, Solid Tumor)
	Trametinib	Mekinist	MEK1,2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Melanoma with BRAF V600 mutation)
	Ulixertinib		ERK1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, Melanoma, Histiocytic and dendritic cell neoplasms, Langerhans cell histiocytosis (LCH), Uveal melanoma, Acute myeloid leukemia (AML), Gastrointestinal carcinoma, Non-Hodgkin lymphoma (NHL), Myelodysplastic Syndrome (MDS))
	V941		Mutant K-Ras vaccine.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Pancreatic carcinoma, Colorectal

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				carcinoma (CRC))

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
PIK3CA E545K	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].	Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which have been approved in specific cancer indications, including the PI3K inhibitors alpelisib and copanlisib, and the mTOR inhibitors everolimus and temsirolimus. [4-6]. 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. [5,7-10]. Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development. [11-13]. The p110-alpha inhibitor alpelisib has been approved for the treatment of men and postmenopausal women with PIK3CA-mutated, hormone receptor positive, Her2 negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy. [14].	PIK3CA mutations have been reported in EGFR-mutant NSCLC patients following emergence of resistance to osimertinib and have been associated with osimertinib resistance in preclinical NSCLC models. Combined treatment with osimertinib and a PI3K inhibitor reversed the resistance. [15-18] .
KRAS G12V	The KRAS gene is one of the most commonly mutated genes in human malignancies, with high incidences in pancreatic, colorectal, and lung cancers. [19-21]. KRAS mutation, particularly G12C, has been associated with smoking in NSCLC patients; additionally, KRAS mutations have also been associated with adenocarcinoma histology and are generally mutually exclusive with EGFR mutations and ALK rearrangements. [22-34]. Studies analyzing KRAS mutation association with PD-L1 expression in NSCLC patients have reported mixed results; while two older large meta-analyses have reported no association or negative association, smaller studies and one newer large meta-analysis have reported a positive association. [27,34-49].	Many of the current attempts to target K-Ras are directed against its downstream signaling pathways, Raf /MEK/ERK and PI3K/Akt/mTOR. [50,51]. Clinical studies have suggested limited efficacy of MEK inhibitors in KRAS mutant tumors; however, combinations of MEK inhibitors with other targeted therapies may still be relevant. [52-61]. Other clinical approaches are being investigated preclinically and clinically in the context of KRAS-mutant tumors, including FAK and Shp-2 inhibitors. [62-67]. In addition, inhibitors specifically targeting KRAS G12C and cell-based therapies targeting KRAS G12V and G12D are being investigated clinically and preclinically. [68-71]. Sotorasib and adagrasib have been FDA-approved in patients with locally advanced or metastatic non-small cell lung carcinoma harboring a KRAS G12C mutation, as determined by an FDA-approved test, following treatment with at least one prior systemic therapy. [72-76]. Studies analyzing KRAS mutation association with clinical benefit of PD-1 /PD-L1 inhibitors to NSCLC patients have reported mixed results, with some	In some cancer types, such as colorectal cancer (CRC) and non-small cell lung cancer (NSCLC), activating KRAS mutations and KRAS amplification have been associated with resistance to Egfr-targeted therapies. [81-89]. While some studies have suggested that KRAS mutation status may predict lack of response to the Egfr inhibitors erlotinib and gefitinib in NSCLC patients, a retrospective study suggests that there is no significant difference in response to Egfr tyrosine kinase inhibitors among NSCLC patients with KRAS wild-type and KRAS mutation, when EGFR mutation status is included in the analysis. [90-94]. Case studies of NSCLC patients harboring ALK mutations or EML4-ALK fusions have reported the emergence of KRAS alterations upon acquired resistance to crizotinib, demonstrating a role for KRAS in crizotinib resistance in NSCLC. [95-99].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		studies reporting no significant association while other studies have reported that KRAS mutation correlated with improved clinical outcome of NSCLC patients treated with PD-1/PD-L1 inhibitors. [37,77-80].	
ARID1A M2001fs	Loss of Arid1a has been associated with mismatch repair deficiency in cancer, including endometrial and colorectal carcinoma. [100-102]. 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. [103]. 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. [104].	There are no approved targeted therapies to address ARID1A alterations at this time; however, ARID1A alterations may predict sensitivity to Ezh2 inhibitors. [105]. Ezh2 inhibitors, such as tazemetostat, are currently being evaluated in clinical trials in patients with solid tumors or B-cell lymphomas. [106-108]. In addition, ARID1A-deficient preclinical cancer models exhibit sensitivity to Atr, PARP, and BET domain inhibitors and clinical trials are evaluating these agents in patients with loss of Arid1a expression or ARID1A mutations. [109-120].	

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