REPORTING

Report Date:	MAR-03-2024
Receipt Date:	FEB-27-2024
Collection Date:	FEB-26-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Chih-Hsueh Chen
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Ph: +886 963 820 633 | Fax: N/A
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
FBXW7 Y545C	None	Yes	0.7%
ARID1A R727fs	None	Yes	0.3%
ARID1A E2120fs	None	Yes	0.2%
SMAD4 S474*	None	No	0.4%

Variants of Uncertain Clinical Significance
ATM K2440E (4.6%), *ROS1* L1947V (0.3%), *ATM* I576V (0.1%), *CCNE1* R95G (0.1%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
ARID1A I1816I (0.5%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Comments

Reported by: VL

Additional Biomarkers

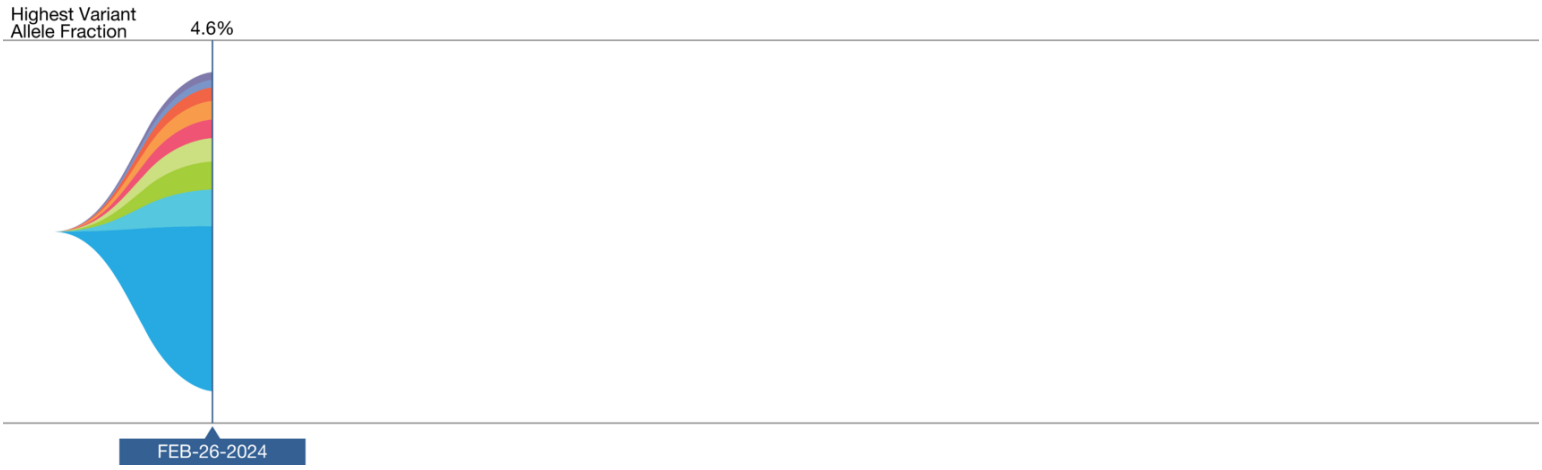
Biomarker	Additional Details
MSI-High	NOT DETECTED

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	
ATM K2440E	4.6%	Variants of Uncertain Clinical Significance §
FBXW7 Y545C	0.7%	
ARID1A I1816I	0.5%	Synonymous Alteration §
SMAD4 S474*	0.4%	
ROS1 L1947V	0.3%	Variants of Uncertain Clinical Significance §
ARID1A R727fs	0.3%	
ARID1A E2120fs	0.2%	
ATM I576V	0.1%	Variants of Uncertain Clinical Significance §
CCNE1 R95G	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 A0975870 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
ARID1A R727fs	NCT05450692 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Phase III Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Non Small Cell Lung Cancer (NSCLC) Whose Disease Progressed On or After Prior Anti PD (L) 1 Therapy And Platinum Based Chemotherapy	Phase 3	Yunlin, Taiwan Taipei City, Taiwan Taipei, Taiwan Tainan, Taiwan Additional trial sites available
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
ARID1A E2120fs	NCT05450692 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Phase III Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Non Small Cell Lung Cancer (NSCLC) Whose Disease Progressed On or After Prior Anti PD (L) 1 Therapy And Platinum Based Chemotherapy	Phase 3	Yunlin, Taiwan Taipei City, Taiwan Taipei, Taiwan Tainan, Taiwan Additional trial sites available
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
FBXW7 Y545C	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.

Synonymous Alteration: This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Deletion (Del): The following alteration was detected in this patient: *ARID1A* E2120fs, R727fs. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

***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 A0975870 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)
ARID1A R727fs	NCT02264678 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Ascending Doses of Ceralasertib in Combination With Chemotherapy and/or Novel Anti Cancer Agents	Phase 1 /Phase 2	Duarte, CA; Philadelphia, PA; Boston, MA; New York, NY; Irvine, CA; Charlotte, NC; Los Angeles, CA (2); Canada (3); Hungary (2); Belgium (2); Korea, Republic of (2); United Kingdom (9); France (4); Spain (3)
	NCT03682289 Early Phase Clinical Trials Recruitment, EarlyPhaseClinicalTrials@ucsf.edu,877-827-3222	Ceralasertib (AZD6738) Alone and in Combination With Olaparib or Durvalumab in Patients With Solid Tumors	Phase 2	San Francisco, CA
	NCT03739710 US GSK Clinical Trials Call Center, GSKClinicalSupportHD@gsk.com,877-379-3718	Platform Trial of Novel Regimens Versus Standard of Care (SoC) in Participants With Non-small Cell Lung Cancer (NSCLC)	Phase 2	Los Angeles, CA; Nashville, TN; Chattanooga, TN; Bronx, NY (2); Germany; Canada (3); Italy (4); France (4); Spain (3)
	NCT03742895 Toll Free Number,Trialsites@merck.com, 1-888-577-8839	Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)	Phase 2	Harrison, NY; Seattle, WA; New York, NY; Baltimore, MD; Middletown, NJ; Colombia; Argentina; United Kingdom; Switzerland; Ireland; Denmark; Australia; Spain (2); Canada (2); Turkey (7); Korea, Republic of (2); Guatemala (4); Mexico (3); Israel (2); France (3); Peru (5)
	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	Grand Rapids, MI; Atlanta, GA; New York, NY; Chicago, IL; San Antonio, TX; Hackensack, NJ; Charlottesville, VA; Seattle, WA (2); Boston, MA (2); Korea, Republic of; Poland (3); United Kingdom (5); Italy (3); France (8); Spain (11)
	NCT04390737 Jia Wang,jia.wang@haihepharma.com, +86 21 20568888	Evaluate the Safety and Clinical Activity of HH2853	Phase 1 /Phase 2	Rochester, MN; Phoenix, AZ; San Antonio, TX; Jacksonville, FL; China (9)
	NCT05252390 Nuvation Bio Inc., clinicaltrials@nuvationbio.com,332-208-6102	NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Denver, CO; Baltimore, MD; Morristown, NJ; Los Angeles, CA; Tucson, AZ; Houston, TX; Newport Beach, CA; Detroit, MI; Huntersville, NC; Boston, MA; Norfolk, VA; Aurora, CO; Billings, MT; Lone Tree, CO; Fort Worth, TX; Summit, NJ; Nashville, TN; Fairfax, VA; Philadelphia, PA (3); New York, NY (2); Dallas, TX (2); Tampa, FL (2); Australia (5)
	NCT05450692 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Phase III Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Non Small Cell Lung Cancer (NSCLC) Whose Disease Progressed On or After Prior Anti PD (L)1 Therapy And Platinum Based Chemotherapy	Phase 3	Rockville, MD; Orlando, FL; Greenville, SC; Allentown, PA; Whittier, CA; Winston-Salem, NC; Baltimore, MD; Los Angeles, CA; Tucson, AZ; Houston, TX; Kingwood, TX; Cleveland, OH; Atlanta, GA; Hattiesburg, MS; Canton, OH; Chandler, AZ; Argentina (6); Romania (11); Hungary (3); Hong Kong (3); Japan (19); United Kingdom (5); Spain (19); India (3); Canada (7); Netherlands (4); Belgium (3); Ireland (5); China (30); Taiwan (8); Poland (7);

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Korea, Republic of (7); Brazil (5); Italy (11); Serbia (5); France (14); Australia (4); Germany (9)
	NCT05687136 See https://clinicaltrials.gov/ct2/show/NCT05687136	Testing the Combination of Two Anti-cancer Drugs, Peposertib (M3814) and M1774 for Advanced Solid Tumors	Phase 1	Boston, MA
ARID1A E2120fs	NCT02264678 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Ascending Doses of Ceralasertib in Combination With Chemotherapy and/or Novel Anti Cancer Agents	Phase 1 /Phase 2	Duarte, CA; Philadelphia, PA; Boston, MA; New York, NY; Irvine, CA; Charlotte, NC; Los Angeles, CA (2); Canada (3); Hungary (2); Belgium (2); Korea, Republic of (2); United Kingdom (9); France (4); Spain (3)
	NCT03682289 Early Phase Clinical Trials Recruitment, EarlyPhaseClinicalTrials@ucsf.edu,877-827-3222	Ceralasertib (AZD6738) Alone and in Combination With Olaparib or Durvalumab in Patients With Solid Tumors	Phase 2	San Francisco, CA
	NCT03739710 US GSK Clinical Trials Call Center, GSKClinicalSupportHD@gsk.com,877-379-3718	Platform Trial of Novel Regimens Versus Standard of Care (SoC) in Participants With Non-small Cell Lung Cancer (NSCLC)	Phase 2	Los Angeles, CA; Nashville, TN; Chattanooga, TN; Bronx, NY (2); Germany; Canada (3); Italy (4); France (4); Spain (3)
	NCT03742895 Toll Free Number,Trialsites@merck.com, 1-888-577-8839	Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)	Phase 2	Harrison, NY; Seattle, WA; New York, NY; Baltimore, MD; Middletown, NJ; Colombia; Argentina; United Kingdom; Switzerland; Ireland; Denmark; Australia; Spain (2); Canada (2); Turkey (7); Korea, Republic of (2); Guatemala (4); Mexico (3); Israel (2); France (3); Peru (5)
	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	Grand Rapids, MI; Atlanta, GA; New York, NY; Chicago, IL; San Antonio, TX; Hackensack, NJ; Charlottesville, VA; Seattle, WA (2); Boston, MA (2); Korea, Republic of; Poland (3); United Kingdom (5); Italy (3); France (8); Spain (11)
	NCT04390737 Jia Wang,jia.wang@haihepharma.com, +86 21 20568888	Evaluate the Safety and Clinical Activity of HH2853	Phase 1 /Phase 2	Rochester, MN; Phoenix, AZ; San Antonio, TX; Jacksonville, FL; China (9)
	NCT05252390 Nuvation Bio Inc., clinicaltrials@nuvationbio.com,332-208-6102	NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Denver, CO; Baltimore, MD; Morristown, NJ; Los Angeles, CA; Tucson, AZ; Houston, TX; Newport Beach, CA; Detroit, MI; Huntersville, NC; Boston, MA; Norfolk, VA; Aurora, CO; Billings, MT; Lone Tree, CO; Fort Worth, TX; Summit, NJ; Nashville, TN; Fairfax, VA; Philadelphia, PA (3); New York, NY (2); Dallas, TX (2); Tampa, FL (2); Australia (5)
	NCT05450692 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Phase III Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Non Small Cell Lung Cancer (NSCLC) Whose Disease Progressed On or After Prior Anti PD (L)1 Therapy And Platinum Based Chemotherapy	Phase 3	Rockville, MD; Orlando, FL; Greenville, SC; Allentown, PA; Whittier, CA; Winston-Salem, NC; Baltimore, MD; Los Angeles, CA; Tucson, AZ; Houston, TX; Kingwood, TX; Cleveland, OH; Atlanta, GA; Hattiesburg, MS; Canton, OH; Chandler, AZ; Argentina (6); Romania (11); Hungary (3); Hong Kong (3); Japan (19); United Kingdom (5);

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Spain (19); India (3); Canada (7); Netherlands (4); Belgium (3); Ireland (5); China (30); Taiwan (8); Poland (7); Korea, Republic of (7); Brazil (5); Italy (11); Serbia (5); France (14); Australia (4); Germany (9)
	NCT05687136 See https://clinicaltrials.gov/ct2/show/NCT05687136	Testing the Combination of Two Anti-cancer Drugs, Peposertib (M3814) and M1774 for Advanced Solid Tumors	Phase 1	Boston, MA
FBXW7 Y545C	NCT03065062 Geoffrey Shapiro, MD, Geoffrey_Shapiro@dfci.harvard.edu,617-632-4942	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)
	NCT03994796 Priscilla Brastianos, MD, pbrastianos@partners.org,617-724-1074	Genetic Testing in Guiding Treatment for Patients With Brain Metastases	Phase 2	Deerfield Beach, FL; Minneapolis, MN; Midlothian, VA; Worcester, MA; Colorado Springs, CO; Berlin, VT; Neptune, NJ; Vancouver, WA; Boston, MA; Richmond, VA; Summit, NJ; Oklahoma City, OK; Edina, MN; Bremerton, WA; Jacksonville, FL; Kennewick, WA; Pennington, NJ; Kearney, NE; Jackson, MS; Rochester, MN; Atlanta, GA; Burlington, VT; Longmont, CO; Salt Lake City, UT; Lexington, KY; Coral Gables, FL; Shreveport, LA (2); NY (5); WI (19); IA (11); OH (17); ID (6); MI (46); CA (7); OR (5); IL (19); MT (7); PA (8); NC (8)
	NCT04851119 See https://clinicaltrials.gov/ct2/show/NCT04851119	Tegavivint for the Treatment of Recurrent or Refractory Solid Tumors, Including Lymphomas and Desmoid Tumors	Phase 1 /Phase 2	Philadelphia, PA; Saint Louis, MO; Minneapolis, MN; New York, NY; Chicago, IL; Orange, CA; San Francisco, CA; Memphis, TN; Los Angeles, CA; Seattle, WA; Houston, TX; Boston, MA; Indianapolis, IN; Atlanta, GA; Pittsburgh, PA; Cincinnati, OH; Washington, DC; Birmingham, AL; Aurora, CO; Ann Arbor, MI

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
ARID1A E2120fs R727fs	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))
	AMXI-5001		Dual PARP1/2 and microtubule polymerization inhibitor.	Phase 2 (Solid Tumor)
	ART0380		Atr inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	ATG-018		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Marginal zone lymphoma (MZL), Diffuse large B-cell lymphoma (DLBCL))
	ATRN-119		Atr inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	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)
	BMS-986158		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 2 (Solid Tumor)
	Camonsertib		Atr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	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-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))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	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)
	HH2853		Ezh1/2 inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Non-Hodgkin lymphoma (NHL))
	IDX-1197		PARP inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	IMP9064		Atr inhibitor.	Phase 1 (Solid Tumor)
	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)
	JAB-8263		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor)
	Niraparib	Zejula	PARP inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Prostate carcinoma with BRCA1/2 mutation, Ovarian carcinoma with BRCA1/2 mutation)
	NMS-03305293		PARP inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma)
	NUV-868		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Pancreatic carcinoma, Prostate carcinoma, Ovarian carcinoma, Breast carcinoma (triple negative))
	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)
	Pelabresib		Bromodomain and extra-terminal domain (BET) inhibitor.	Phase 1 (Lymphoma, Multiple myeloma (MM), Myelodysplastic Syndrome (MDS))
	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))
	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))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	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 (Prostate cancer with HRR gene mutation, 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 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))
	Tuvusertib		Atr inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Merkel cell carcinoma, Prostate carcinoma, Endometrial carcinoma, Ovarian carcinoma, Colorectal carcinoma (CRC))
	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))
FBXW7 Y545C	ABTL0812		Inhibitor of mTORC1/mTORC2 /Dhfr.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Pancreatic carcinoma, Endometrial carcinoma)
	Apitolisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Prostate carcinoma, Endometrial carcinoma, Renal cell carcinoma, Breast carcinoma)
	Bimiralisib		Dual PI3K/mTOR inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma (triple negative), Primary central nervous system lymphoma (PCNSL))
	CC-115		DNA-PK/dual mTORC1/2 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma)
	Gedatolisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	ME-344		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma, Small cell lung carcinoma (SCLC))
	Onatasertib		Dual mTORC1/mTORC2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor, Bladder neuroendocrine

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				carcinoma, Multiple myeloma (MM), Diffuse large B-cell lymphoma (DLBCL))
	Paxalisib		Dual PI3K/mTOR inhibitor.	Phase 2 (Glioblastoma, 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))
	Tegavivint		Wnt/beta-catenin pathway inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Hepatocellular carcinoma (HCC), Wilms tumor, Ewing sarcoma, Desmoid fibromatosis)
	Vistusertib		Dual mTORC1/mTORC2 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Meningioma, Small cell lung carcinoma (SCLC), Solid Tumor, Diffuse large B-cell lymphoma (DLBCL))

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
FBXW7 Y545C	FBXW7 inactivating mutations have been reported in a large variety of tumors and, combined with the oncogenic potential of several FBXW7 substrates, leads to the conclusion that FBXW7 is a general tumor suppressor. [1]. Fbxw7 has been reported to have a role in normal lung development, and low Fbxw7 expression in NSCLC has been linked to advanced tumor stage. [2,3]. Depletion of FBXW7 in NSCLC cell line models has been reported to result in increased invasion, migration, as well as tumor formation and metastasis. [4,5].	In preclinical studies, Fbxw7 inactivation stabilizes the mTOR signaling protein and confers sensitivity to rapamycin, an mTOR inhibitor. [6]. However, FBXW7 alterations have been shown to be not predictive of response to everolimus or temsirolimus in clinical studies. [7,8]. Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development. [9-11].	Fbxw7 inactivation may result in resistance to several types of chemotherapy, based on results from preclinical studies. [3,12-17]. Low Fbxw7 expression has been associated with resistance to cisplatin, docetaxel, doxorubicin, and Egfr-targeted therapies in NSCLC preclinical models. [3,5,14,14-19].
ARID1A R727fs	Loss of Arid1a has been associated with mismatch repair deficiency in cancer, including endometrial and colorectal carcinoma. [20-22]. 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. [23]. 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. [24]. A study analyzing a lung adenocarcinoma TCGA dataset has reported that ARID1A mutation correlated with a higher tumor mutational burden as compared with wild-type cases; in addition, low ARID1A expression was associated with an immunotherapy-sensitive phenotype in a cohort of 461 lung adenocarcinoma cases. [25].	There are no approved targeted therapies to address ARID1A alterations at this time; however, ARID1A alterations may predict sensitivity to Ezh2 inhibitors. [26]. Ezh2 inhibitors, such as tazemetostat, are currently being evaluated in clinical trials in patients with solid tumors or B-cell lymphomas. [27-29]. 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. [30-41].	
ARID1A E2120fs	Loss of Arid1a has been associated with mismatch repair deficiency in cancer, including endometrial and colorectal carcinoma. [20-22]. 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. [23]. 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. [24]. A study analyzing a lung adenocarcinoma TCGA dataset	There are no approved targeted therapies to address ARID1A alterations at this time; however, ARID1A alterations may predict sensitivity to Ezh2 inhibitors. [26]. Ezh2 inhibitors, such as tazemetostat, are currently being evaluated in clinical trials in patients with solid tumors or B-cell lymphomas. [27-29]. 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. [30-41].	

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	has reported that ARID1A mutation correlated with a higher tumor mutational burden as compared with wild-type cases; in addition, low ARID1A expression was associated with an immunotherapy-sensitive phenotype in a cohort of 461 lung adenocarcinoma cases. [25].		
SMAD4 S474*	A dual role for the TGF-beta/Smad4 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. [42]. 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. [43,44]. Loss of SMAD4 has been reported to play a role in NSCLC tumorigenesis; one study reported that loss of SMAD4 in airway epithelial cells in mice resulted in the formation and progression of lung tumors, while other studies showed that combined loss of SMAD4 and PTEN, but not of either gene alone, in airway epithelial cells led to the formation of metastatic lung adenosquamous tumors. [45-48]. In addition, several studies have correlated decreased or loss of Smad4 expression in NSCLC with lymph node metastasis, poor tumor differentiation, and advanced clinical stage. [49-54].	At present there are no therapies 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. [55,56].	

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