REPORTING

Report Date:	OCT-23-2023
Receipt Date:	OCT-19-2023
Collection Date:	OCT-18-2023
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
MET Y1230H	⊗ Bozitinib, Crizotinib, Tepotinib	Yes	1.1%
MET D1228N	⊗ Capmatinib, Crizotinib, Savolitinib	Yes	0.2%
TP53 S241Y	None	Yes	0.7%

Variants of Uncertain Clinical Significance
BRCA1 E1004Q (0.1%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Comments

Reported by: SB32

Additional Biomarkers

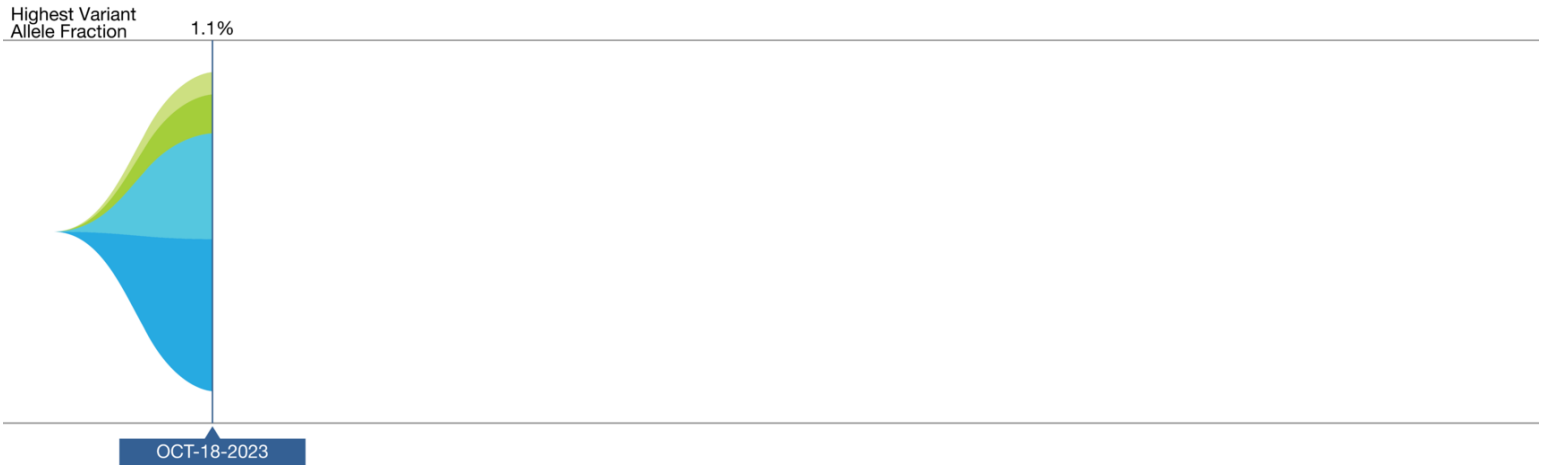
Biomarker	Additional Details
MSI-High	NOT DETECTED

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	
MET Y1230H	1.1%	
TP53 S241Y	0.7%	
MET D1228N	0.2%	
BRCA1 E1004Q	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 A0876987 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
MET Y1230H	NCT04928846 ABBVIE CALL CENTER, abbvieclinicaltrials@abbvie.com,844-663-3742	A Study to Assess Disease Activity and Adverse Events of Intravenous (IV) Telisotuzumab Vedotin Compared to IV Docetaxel in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3	Kaohsiung City, Taiwan Hualien City, Taiwan Hsinchu City, Taiwan Taipei City, Taiwan (3) Additional trial sites available
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
MET D1228N	NCT04928846 ABBVIE CALL CENTER, abbvieclinicaltrials@abbvie.com,844-663-3742	A Study to Assess Disease Activity and Adverse Events of Intravenous (IV) Telisotuzumab Vedotin Compared to IV Docetaxel in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3	Kaohsiung City, Taiwan Hualien City, Taiwan Hsinchu City, Taiwan Taipei City, Taiwan (3) Additional trial sites available
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 S241Y	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			

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.

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 A0876987 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)
MET Y1230H	NCT01639508 Alexander Drilon, MD,646-888-4206	Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	Phase 2	Basking Ridge, NJ; Uniondale, NY; Harrison, NY; Montvale, NJ; Commack, NY; New York, NY; Middletown, NJ
	NCT02609776 Study Contact,Participate-In-This-Study@its.jnj.com	Study of Amivantamab, a Human Bispecific EGFR and cMet Antibody, in Participants With Advanced Non-Small Cell Lung Cancer	Phase 1	Saint Louis, MO; Philadelphia, PA; Orange, CA; Portland, OR; Santa Monica, CA; Houston, TX; Detroit, MI; Rochester, MN; West Hollywood, CA; Boston, MA; La Jolla, CA; Tampa, FL; Fairfax, VA; New York, NY (3); Canada; Japan (7); United Kingdom (3); France (7)
	NCT04116541 Jean-Yves BLAY, MD,jean-yves.blay@lyon.unicancer.fr,+33478785126	A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/Characteristics in Advanced / Metastatic Tumors.	Phase 2	France (8)
	NCT04928846 ABBVIE CALL CENTER, abbvieclinicaltrials@abbvie.com,844-663-3742	A Study to Assess Disease Activity and Adverse Events of Intravenous (IV) Telisotuzumab Vedotin Compared to IV Docetaxel in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3	Pinehurst, NC; Brooklyn, NY; Sioux Falls, SD; Elmhurst, IL; Zanesville, OH; Reno, NV; Springfield, MO; Honolulu, HI; Los Angeles, CA; Renton, WA; Rancho Mirage, CA; Hattiesburg, MS; Ocala, FL; Ypsilanti, MI; Farmington, NM; Kansas City, MO; Slovakia; Denmark; South Africa; Mexico; Czechia (2); Portugal (2); Greece (2); Sweden (2); Netherlands (4); Austria (6); China (35); Poland (3); Korea, Republic of (5); Brazil (7); France (4); Chile (5); Bulgaria (3); Argentina (4); Romania (5); Japan (38); United Kingdom (2); Spain (4); Turkey (9); Belgium (5); Taiwan (8); Italy (5); Israel (2); Australia (2); Germany (5)
	NCT05176483 Exelixis Clinical Trials,druginfo@exelixis.com,1-888-EXELIXIS (888-393-5494)	Study of XL092 in Combination With Immuno-Oncology Agents in Subjects With Solid Tumors	Phase 1	Milwaukee, WI; Phoenix, AZ; Newark, DE; New Haven, CT; Austin, TX; Chicago, IL; Longview, TX; Baltimore, MD; Myrtle Beach, SC; Portland, OR; Durham, NC; Henderson, NV; Tucson, AZ; Rochester, MN; Cleveland, OH; Boston, MA; Indianapolis, IN; Nashville, TN; Plano, TX; Solvang, CA; Charlottesville, VA; New York, NY (2); Detroit, MI (2); Pittsburgh, PA (2); Omaha, NE (2); FL (5); Italy; New Zealand (2); Austria (2); Belgium (2); Poland (4); Israel (5); France (2); Australia (4); Switzerland (3); Spain (13)
MET D1228N	NCT01639508 Alexander Drilon, MD,646-888-4206	Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	Phase 2	Basking Ridge, NJ; Uniondale, NY; Harrison, NY; Montvale, NJ; Commack, NY; New York, NY; Middletown, NJ
	NCT02609776 Study Contact,Participate-In-This-Study@its.jnj.com	Study of Amivantamab, a Human Bispecific EGFR and cMet Antibody, in Participants With Advanced Non-Small Cell Lung Cancer	Phase 1	Saint Louis, MO; Philadelphia, PA; Orange, CA; Portland, OR; Santa Monica, CA; Houston, TX; Detroit, MI; Rochester, MN; West Hollywood, CA;

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Boston, MA; La Jolla, CA; Tampa, FL; Fairfax, VA; New York, NY (3); Canada; Japan (7); United Kingdom (3); France (7)
	NCT04116541 Jean-Yves BLAY, MD,jean-yves.blay@lyon.unicancer.fr,+33478785126	A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/Characteristics in Advanced / Metastatic Tumors.	Phase 2	France (8)
	NCT04928846 ABBVIE CALL CENTER, abbvieclinicaltrials@abbvie.com,844-663-3742	A Study to Assess Disease Activity and Adverse Events of Intravenous (IV) Telisotuzumab Vedotin Compared to IV Docetaxel in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3	Pinehurst, NC; Brooklyn, NY; Sioux Falls, SD; Elmhurst, IL; Zanesville, OH; Reno, NV; Springfield, MO; Honolulu, HI; Los Angeles, CA; Renton, WA; Rancho Mirage, CA; Hattiesburg, MS; Ocala, FL; Ypsilanti, MI; Farmington, NM; Kansas City, MO; Slovakia; Denmark; South Africa; Mexico; Czechia (2); Portugal (2); Greece (2); Sweden (2); Netherlands (4); Austria (6); China (35); Poland (3); Korea, Republic of (5); Brazil (7); France (4); Chile (5); Bulgaria (3); Argentina (4); Romania (5); Japan (38); United Kingdom (2); Spain (4); Turkey (9); Belgium (5); Taiwan (8); Italy (5); Israel (2); Australia (2); Germany (5)
	NCT05176483 Exelixis Clinical Trials,druginfo@exelixis.com,1-888-EXELIXIS (888-393-5494)	Study of XL092 in Combination With Immuno-Oncology Agents in Subjects With Solid Tumors	Phase 1	Milwaukee, WI; Phoenix, AZ; Newark, DE; New Haven, CT; Austin, TX; Chicago, IL; Longview, TX; Baltimore, MD; Myrtle Beach, SC; Portland, OR; Durham, NC; Henderson, NV; Tucson, AZ; Rochester, MN; Cleveland, OH; Boston, MA; Indianapolis, IN; Nashville, TN; Plano, TX; Solvang, CA; Charlottesville, VA; New York, NY (2); Detroit, MI (2); Pittsburgh, PA (2); Omaha, NE (2); FL (5); Italy; New Zealand (2); Austria (2); Belgium (2); Poland (4); Israel (5); France (2); Australia (4); Switzerland (3); Spain (13)
TP53 S241Y	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 (2)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
MET D1228N Y1230H	ABBV-400		anti-Met antibody-drug conjugate.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	AL2846		Met small molecule inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Altiratinib		Met/VEGFR/TIE2/Trk inhibitor.	Phase 1 (Solid Tumor)
	AMG 337		Met and Ron inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor)
	Amivantamab	Rybrevant	Bispecific anti-Met/Egfr antibody.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (NSCLC with EGFR exon 20 insertion)
	AZD9592		Bispecific anti-Met/Egfr antibody drug conjugate.	Phase 1 (Solid Tumor)
	BPI-9016M		Met/Axl inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Cabozantinib	Cometriq	Multi-kinase inhibitor with targets including Met, Ret, VEGFR-2, Tie2, and Kit.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Thyroid carcinoma, well differentiated, Hepatocellular carcinoma (HCC), Renal cell carcinoma, Thyroid medullary carcinoma)
	Elzovantinib		Met/Src/CSF-1R inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Emibetuzumab		Anti-Met monoclonal antibody.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Ficlatuzumab		Anti-HGF monoclonal antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Pancreatic carcinoma, Head and neck squamous cell carcinoma (HNSCC))
	Glesatinib		Multitargeted small molecule kinase inhibitor (Met/Tie-2/VEGFR1, 2,3/Ron).	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Lung cancer)
	Glumetinib		Met inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	GST-HG161		Met inhibitor.	Phase 1 (Solid Tumor)
	HS-10241		Met inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	Merestinib		Multi-kinase inhibitor targeting Met, Ros1, Axl, Flt3, and other proteins.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gallbladder carcinoma, Cholangiocarcinoma, Lung cancer)
	Ningetinib		Multi-kinase inhibitor targeting Axl, Met, VEGFR-2, and Flt3.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Renal cell carcinoma)
	OMO-1		Met inhibitor.	Phase 2 (Solid Tumor)
	REGN5093		anti-Met bispecific antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	REGN5093-M114		Anti-Met bispecific antibody drug conjugate.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	RXDX-106		Met and TAM (Tyro3, Axl, Mer) inhibitor.	Phase 1 (Solid Tumor)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	SAR125844		Met inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	SHR-A1403		anti-Met antibody-drug conjugate.	Phase 1 (Solid Tumor)
	Sitravatinib		Multi-kinase inhibitor.	Phase 3 (Lung adenocarcinoma) Phase 2 (Non-small cell lung carcinoma (NSCLC), Renal cell carcinoma, Urothelial carcinoma, Liposarcoma)
	Sym015		Anti-Met antibody mixture.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor)
	Telisotuzumab vedotin		Anti-Met antibody drug conjugate.	Phase 1 (Solid Tumor)
	XL092		Multi-kinase inhibitor.	Phase 1 (Solid Tumor)
TP53 S241Y	Adavosertib		Wee1 tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (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))
	Alisertib		Aurora kinase A inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	AMG 900		Aurora kinase A/B/C inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	AT9283		Aurora kinase A/B, Jak2, Jak3, Bcr-Abl inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Acute myeloid leukemia (AML), Multiple myeloma (MM), Acute lymphoblastic leukemia (ALL))
	ATO	Trisenox	PML-RARA inhibitor. Inhibits multiple signaling pathways, including the Hedgehog pathway.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) 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))
	COTI-2		Reactivates mutant p53.	Phase 1 (Endometrial carcinoma, Head and neck squamous cell carcinoma (HNSCC), Ovarian carcinoma, Cervical carcinoma)
	Debio 0123		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	ENMD-2076		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Fibrolamellar hepatocellular carcinoma, Ovarian carcinoma, Breast carcinoma, Fallopian tube adenocarcinoma, Sarcoma)
	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)
	Kevetrin		Blocks Mdm2-p53 interaction, restoring transcriptional activity of	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
			p53.	
	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)
	SNS-314		Aurora kinase A/B inhibitor.	Phase 1 (Solid Tumor)
	SY-4835		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	TAS-119		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor)
	TT-00420		Aurora kinase A/B inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Breast carcinoma (triple negative))

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
MET Y1230H	Met protein activation or overexpression promotes angiogenesis, resistance to apoptosis, proliferation, and invasion of cancer cells. [1-4]. Activation of Met, resulting from either MET mutation or amplification, has been reported to promote cell growth and tumorigenesis in preclinical NSCLC models. [5-7]. Met protein expression in NSCLC has been associated with a predisposition to the development of brain metastases. [8,9].	Increased Met expression, possibly as a result of MET mutation or amplification, may lead to enhanced Met activation and may therefore confer sensitivity to Met inhibitors. [10,11]. Crizotinib and cabozantinib target multiple kinases, including Met, and have been FDA-approved for certain indications. [12-17]. However, MET Y1248H has been associated with acquired resistance to crizotinib and tepotinib in non-small cell lung carcinoma (NSCLC) cases and shown to confer resistance to crizotinib, capmatinib, savolitinib, and topotinib in several preclinical studies. [18-24]. This mutation has also been shown to confer sensitivity to cabozantinib and glesatinib in preclinical studies and in NSCLC case reports. [21,21-26].	MET amplification or elevated Met expression has been implicated in acquired resistance to Egfr inhibitors in some cancer types; studies are currently investigating combination therapy with Met inhibitors and Egfr inhibitors in this setting. [27-30]. Met activation has been implicated as one key mechanism of resistance to Egfr-targeted therapy in NSCLC. [8,28,31-34].
MET D1228N	Met protein activation or overexpression promotes angiogenesis, resistance to apoptosis, proliferation, and invasion of cancer cells. [1-4]. Activation of Met, resulting from either MET mutation or amplification, has been reported to promote cell growth and tumorigenesis in preclinical NSCLC models. [5-7]. Met protein expression in NSCLC has been associated with a predisposition to the development of brain metastases. [8,9].	Increased Met expression, possibly as a result of MET mutation or amplification, may lead to enhanced Met activation and may therefore confer sensitivity to Met inhibitors. [10,11]. Crizotinib and cabozantinib target multiple kinases, including Met, and have been FDA-approved for certain indications. [12-17]. However, MET D1246N has been reported as an acquired mutation in crizotinib- and capmatinib-resistant non-small cell lung carcinoma cases, and has been shown to confer resistance to crizotinib, capmatinib and savolitinib. [21,21-36]. Although preclinical data have reported sensitivity of MET D1246N to cabozantinib and glesatinib, case studies have reported increases in D1246N allelic fraction during cabozantinib or glesatinib treatment in NSCLC patients. [18,20,37].	MET amplification or elevated Met expression has been implicated in acquired resistance to Egfr inhibitors in some cancer types; studies are currently investigating combination therapy with Met inhibitors and Egfr inhibitors in this setting. [27-30]. Met activation has been implicated as one key mechanism of resistance to Egfr-targeted therapy in NSCLC. [8,28,31-34].
TP53 S241Y	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [38]. 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. [39-41]. 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	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. [58-60]. 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. [61-63]. Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients	Mutations in TP53 may increase resistance to ionizing radiation therapy. [70,71].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	nucleus, and several studies have shown that it may have oncogenic gain-of-function effects. [42-46]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. [47]. TP53 mutation and expression of p53 have been correlated with the lung squamous cell carcinoma subtype, and p53 expression in lung squamous cell carcinoma has also been associated with disease stage and higher grade tumors. [48-51]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. [52-56]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients. [57].	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. [64-69].	

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