REPORTING

Report Date:	DEC-01-2021
Receipt Date:	NOV-26-2021
Collection Date:	NOV-25-2021
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Teh-Ying Chou
Account: Genconn Biotech Co., LTD
Address: F15., No 207-5 Sec 3 , Beixin Rd, New Taipei City, Xindian Dist, 23143, Taiwan
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
TP53 P278L	None	Yes	0.8%
TP53 H179R	None	Yes	0.1%
EGFR Amplification	None	Yes	Low (+)

Variants of Uncertain Clinical Significance
CDK12 S590A (0.4%)
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

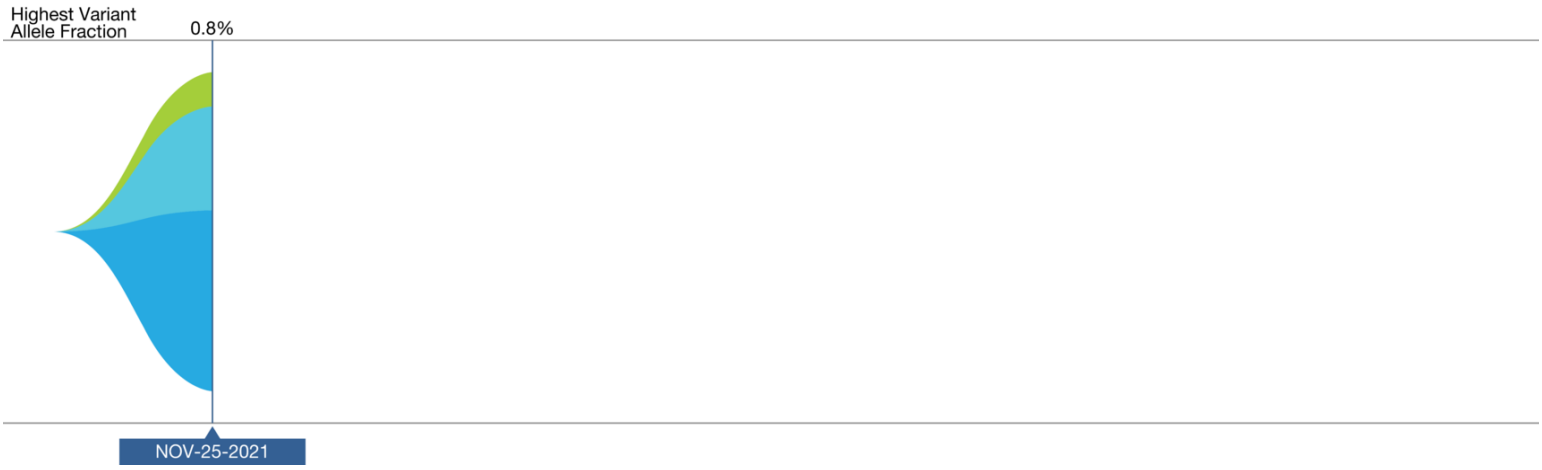
Alterations or biomarkers that were "NOT DETECTED" have been excluded from the summary table above.

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*

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	
TP53 P278L	0.8%	
CDK12 S590A	0.4%	Variants of Uncertain Clinical Significance §
TP53 H179R	0.1%	
EGFR Amplification Amplifications not graphed above	Low (+) Plasma Copy Number 2.3	

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 A0435653 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
EGFR Amplification	NCT02609776 Use link at the bottom of the page to see if you qualify for an enrolling site (see list). If you still have questions:,JNJ. CT@sylogent.com	Study of Amivantamab, a Human Bispecific EGFR and cMet Antibody, in Participants With Advanced Non-Small Cell Lung Cancer	Phase 1	Kaohsiung, Taiwan Taipei City, Taiwan Taipei, Taiwan Taichung, Taiwan (3)
	NCT04077463 Study Contact,JNJ.CT@sylogent.com,844-434-4210	A Study of Lazertinib as Monotherapy or in Combination With Amivantamab in Participants With Advanced Non-small Cell Lung Cancer	Phase 1	Kaohsiung, Taiwan Taipei City, Taiwan Tainan, Taiwan Taichung, Taiwan
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 P278L	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 H179R	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.

Amplification: Guardant360 detects amplifications in the genes listed in Table 1. Gene amplification results in increased copies of the gene present in the cfDNA. The reported absolute copy number value represents the average copy number for the detected gene that was detected in circulating cfDNA. With the exception of sex-linked genes such as *AR*, 2 copies are expected in the absence of amplification. As the absolute number of copies in circulation is dependent on both tumor fraction and the magnitude of the tumor amplification, amplifications are reported on a semi-quantitative scale.
For *CCNE1*, *EGFR* and *FGFR1*, three levels are reported:
Low (+): Amplification magnitude is below the 50th percentile of amplifications detected by Guardant360.
Medium (++): Amplification magnitude is between the 50th and 90th percentiles.
High (+++): Amplification magnitude is above the 90th percentile.

For *BRAF*, *CCND1*, *CCND2*, *CDK4*, *CDK6*, *ERBB2*, *FGFR2*, *KIT*, *KRAS*, *MET*, *PDGFRA*, *RAF1*, *MYC*, *PIK3CA* and *AR*, two levels are reported:
Medium (++): Amplification magnitude is below the 50th percentile of amplifications detected by Guardant360.
High (+++): Amplification magnitude is above the 50th percentile.

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.

Amplification was detected in the circulating cell-free DNA isolated from this patient’s blood specimen for the annotated gene(s). Unlike tissue-based gene amplification tests (e.g. IHC or FISH), Guardant360 assesses the total representation of a given gene in all circulating cell-free DNA present in the patient’s blood sample including material derived from the tumor and healthy tissue alike. As such, the absolute level of amplification present in the blood depends both on the tumor-derived cfDNA content and on the degree of amplification within that fraction and cannot be inferred from bulk cfDNA interrogation. For example, a positive Guardant360 test could represent a small population of cells with extremely high levels of the detected gene amplification. Alternatively, it could represent a large population of cells with low to medium levels of the detected gene amplifications. The exact correlation between amplification detected by Guardant360 compared to IHC or FISH and how each test differentially guides patient management is an area of active investigation.

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 A0435653 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)
EGFR Amplification	NCT01553942 Lecia V Sequist, MD MPH, lvsequist@partners.org,617-724-4000	Afatinib With CT and RT for EGFR-Mutant NSCLC	Phase 2	Boston, MA (2)
	NCT02609776 Use link at the bottom of the page to see if you qualify for an enrolling site (see list). If you still have questions:,JNJ. CT@sylogent.com	Study of Amivantamab, a Human Bispecific EGFR and cMet Antibody, in Participants With Advanced Non-Small Cell Lung Cancer	Phase 1	Detroit, MI; Saint Louis, MO; Rochester, MN; Philadelphia, PA; Bethesda, MD; Boston, MA; Chicago, IL; Portland, OR; Tampa, FL; Fairfax, VA; New York, NY (3); CA (5); Canada; Japan (10); China (16); Taiwan (6); Korea, Republic of (8); United Kingdom (3); Italy (3); France (7); Australia (4); Spain (11)
	NCT02795156 Sarah Cannon Development Innovations, LLC,CANN. InnovationsMedical@sarahcannon.com, 844-710-6157	Study Assessing Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations	Phase 2	Denver, CO; Milwaukee, WI; West Palm Beach, FL; Fort Myers, FL; Saint Petersburg, FL; Nashville, TN; Chattanooga, TN; Kansas City, MO
	NCT02947386 See https://clinicaltrials.gov/show /NCT02947386	Nimotuzumab and Nivolumab in Treating Patients With Advanced Non-small Cell Lung Cancer	Phase 1 /Phase 2	Buffalo, NY
	NCT04077463 Study Contact,JNJ.CT@sylogent.com, 844-434-4210	A Study of Lazertinib as Monotherapy or in Combination With Amivantamab in Participants With Advanced Non-small Cell Lung Cancer	Phase 1	Seattle, WA; Detroit, MI; Saint Louis, MO; Philadelphia, PA; Baltimore, MD; Portland, OR; Salt Lake City, UT; Tampa, FL; Fairfax, VA; Boston, MA (3); New York, NY (2); CA (5); Puerto Rico; Japan (7); China (14); Taiwan (4); Korea, Republic of (4); Italy (5); France (7); Germany (11); Spain (8)
	NCT04310007 See https://clinicaltrials.gov/show /NCT04310007	Testing the Addition of the Pill Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer	Phase 2	Mount Holly, NJ; Savannah, GA; Phoenix, AZ; Manchester, NH; Worcester, MA; Baltimore, MD; Fargo, ND; Richmond, IN; Bryan, TX; Fort Lauderdale, FL; Fort Smith, AR; Concord, NH; Huntington, WV; Cody, WY; Boston, MA; Birmingham, AL; Greenwood, SC; South Bend, IN; Kingman, AZ; West Haven, CT; Oklahoma City, OK; Glens Falls, NY; Sheridan, WY; Voorhees, NJ; Miami Beach, FL; Albuquerque, NM; Hot Springs, AR; Aventura, FL; Jamestown, ND; Cheyenne, WY; Moorestown, NJ; Bronx, NY (3); Atlanta, GA (2); NV (45); WA (28); WI (34); IA (22); OH (39); ID (13); MI (60); CA (7); MN (38); MO (30); OR (11); IL (49); MT (8); KS (9); AK (9); VA (7); CO (40); KY (10); PA (22); NC (5); LA (6); NE (12)
	NCT04394624 Trial Transparency email recommended (Toll free number for US & Canada), Contact-US@sanofi.com,800-633-1610 xoption 6	SAR408701 in Combination With Ramucirumab in Pre-treated Patients With Non Squamous Non-small Cell Lung Cancer (NSQ NSCLC)	Phase 2	Detroit, MI; Whittier, CA; Buffalo, NY; Waco, TX; Czechia (3); Korea, Republic of (2); Bulgaria (2); Portugal (2); Spain (5)
	NCT04606381 Study Contact,JNJ.CT@sylogent.com, 844-434-4210	A Study of Amivantamab Subcutaneous (SC) Administration for the Treatment of Advanced Solid Malignancies	Phase 1	West Hollywood, CA; Indianapolis, IN; New York, NY; Portland, OR; Nashville, TN; Canada; Korea, Republic of (2); United Kingdom (2)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	NCT04965090 Helena Yu, MD,yuh@mskcc.org,646-608-3912	A Study of Amivantamab and Lazertinib in People With Non-Small Cell Lung Cancer (NSCLC)	Phase 2	Basking Ridge, NJ; Uniondale, NY; Harrison, NY; Montvale, NJ; Commack, NY; New York, NY; Middletown, NJ
TP53 P278L	NCT04383938 Eyal Attar, MD,info@aprea.com,+1 617 804 6947	Phase 1/2 Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies	Phase 1 /Phase 2	Houston, TX; Saint Louis, MO; Rochester, MN; Phoenix, AZ; Jacksonville, FL; Nashville, TN; Boston, MA (2)
	NCT04555837 Faye M. Johnson,fmjohns@mdanderson.org,713-792-6363	Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer	Phase 1 /Phase 2	Houston, TX
	NCT04695223 See https://clinicaltrials.gov/show/NCT04695223	Arsenic Trioxide for Structural p53 Mutations	Phase 2	China
	NCT04742959 Peng Peng, Ph.D., peng_peng@transtherabio.com,86-25-86901107	Study of TT-00420 Tablet as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Houston, TX; Duarte, CA; New Brunswick, NJ
	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
TP53 H179R	NCT04383938 Eyal Attar, MD,info@aprea.com,+1 617 804 6947	Phase 1/2 Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies	Phase 1 /Phase 2	Houston, TX; Saint Louis, MO; Rochester, MN; Phoenix, AZ; Jacksonville, FL; Nashville, TN; Boston, MA (2)
	NCT04555837 Faye M. Johnson,fmjohns@mdanderson.org,713-792-6363	Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer	Phase 1 /Phase 2	Houston, TX
	NCT04695223 See https://clinicaltrials.gov/show/NCT04695223	Arsenic Trioxide for Structural p53 Mutations	Phase 2	China
	NCT04742959 Peng Peng, Ph.D., peng_peng@transtherabio.com,86-25-86901107	Study of TT-00420 Tablet as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Houston, TX; Duarte, CA; New Brunswick, NJ
	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

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
EGFR Amplification	ABBV-221		Anti-Egfr antibody drug conjugate.	Phase 1 (Solid Tumor)
	ABBV-321		Anti-Egfr antibody conjugated to monomethyl auristatin F.	Phase 1 (Solid Tumor) Phase 1 (Glioblastoma, Head and neck squamous cell carcinoma (HNSCC), Brain and Central Nervous System Tumors, Lung squamous cell carcinoma)
	ABT806		Anti-Egfr and EGFRvIII antibody.	Phase 1 (Solid Tumor) Phase 2 (Gastroesophageal junction carcinoma)
	Afatinib	Gilotrif	Irreversible pan-ErbB kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Lung squamous cell carcinoma, EGFR-mutant NSCLC)
	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)
	ASP-1929		An antibody-dye conjugate comprised of cetuximab and IRDye700DX acting as photoimmunotherapy.	Phase 3 (Head and neck carcinoma)
	AVID100		Anti-Egfr antibody-drug conjugate with DM1.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Breast carcinoma (triple negative))
	BDTX-189		Irreversible Egfr/Her2 inhibitor.	Phase 2 (Solid Tumor)
	BLU-945		Fourth generation Egfr inhibitor targeting T790M and T790M /C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	CPGJ602		Recombinant human-mouse chimeric anti-Egfr monoclonal antibody.	Phase 2 (Colorectal carcinoma (CRC))
	D2C7-IT		Immunotoxin targeting both wild-type Egfr and Egfr-vIII.	Phase 1 (Glioblastoma)
	Depatuxizumab mafodotin		Anti-Egfr monoclonal antibody drug conjugate.	Phase 1 (Solid Tumor) Phase 3 (Glioblastoma, Glioma)
	DZD9008		Bispecific anti-Egfr/Her2 monoclonal antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Non-Hodgkin lymphoma (NHL))
	EGFR(V)-EDV-Dox		Doxorubicin-loaded EGFR-targeting nanocells.	Phase 1 (Glioblastoma)
	GC1118		Anti-Egfr monoclonal antibody.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, Glioblastoma, Gastroesophageal junction carcinoma)
	Hemay022		Egfr tyrosine kinase inhibitor.	Phase 1 (Breast carcinoma (HER2+))
	Lifirafenib		Dual Braf/Egfr inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	MM-151		Anti-Egfr monoclonal antibody mixture.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	Neratinib	Nerlynx	Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				(Breast carcinoma (HER2+))
	Nimotuzumab	Theraloc	Anti-Egfr monoclonal antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Gastric carcinoma, Glioblastoma, Glioma, Pancreatic carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Esophageal carcinoma, Cervical carcinoma)
	Pirotinib		ErbB family inhibitor.	Phase 1 (Solid Tumor)
	Poziotinib		Egfr/Her2/ErbB4 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Head and neck squamous cell carcinoma (HNSCC), Breast carcinoma, Esophageal squamous cell carcinoma, Colorectal carcinoma (CRC))
	Pyrotinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	Ramucirumab	Cyramza	anti-VEGFR-2 monoclonal antibody.	FDA Approved in this indication (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Gastric carcinoma, Hepatocellular carcinoma (HCC), Gastroesophageal junction carcinoma, Colorectal carcinoma (CRC))
	SKLB1028		Egfr/Flt3/c-Abl inhibitor.	Phase 2 (Acute myeloid leukemia (AML))
	Sym004		Anti-Egfr antibody mixture.	Phase 2 (Glioma, Head and neck squamous cell carcinoma (HNSCC), Colorectal carcinoma (CRC))
	SYN004		Anti-Egfr monoclonal antibody.	Phase 1 (Solid Tumor) Phase 1 (Lung squamous cell carcinoma)
	Varlitinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Cholangiocarcinoma)
TP53 P278L H179R	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 A small molecule kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	ALT-801		p53-targeted T-cell receptor-IL2 fusion.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Urothelial carcinoma, Bladder carcinoma, Urethral melanoma, Urethral carcinoma, Multiple myeloma (MM))
	AMG 900		Aurora A, B, C small molecule kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	AT9283		Aurora A, B, Jak2, Jak3, Bcr-Abl kinase 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

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				(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 A kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Fibrolamellar hepatocellular carcinoma, Ovarian carcinoma, Breast carcinoma, Fallopian tube adenocarcinoma, Sarcoma)
	Eprenetapopt		Reactivates mutant p53.	Phase 3 (Myelodysplastic Syndrome (MDS))
	Kevetrin		Blocks Mdm2-p53 interaction, restoring transcriptional activity of p53.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma)
	LY3295668		Aurora kinase A-specific 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)
	TAS-119		Selective Aurora A kinase 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
TP53 P278L	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [1]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias. [2-4]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects. [5-9]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. [10]. 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. [11-14]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. [15-19].	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. [20-22]. 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. [23-25]. Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors. [26-31].	Mutations in TP53 may increase resistance to ionizing radiation therapy. [32,33].
TP53 H179R	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [1]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias. [2-4]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects. [5-9]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. [10]. 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	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. [20-22]. 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. [23-25]. Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors. [26-31].	Mutations in TP53 may increase resistance to ionizing radiation therapy. [32,33].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	tumors. [11-14]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. [15-19].		
EGFR Amplification	The presence of an EGFR abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Egfr protein, which can lead to excessive proliferation. [34]. EGFR mutations in NSCLC have been reported to occur more frequently in women, never-smokers, and in patients with adenocarcinoma histology. [35-44].	EGFR amplification or increased copy number may result in elevated Egfr protein expression and thus predict sensitivity to Egfr targeted therapies. The Egfr tyrosine kinase inhibitors (TKIs) erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib have been FDA approved for the treatment of non-small cell lung carcinoma (NSCLC) with specific EGFR mutations; however, only modest clinical benefit for gefitinib or erlotinib has been reported in patients harboring EGFR amplification without concurrent sensitizing mutations. [45-52]. Anti-Egfr monoclonal antibodies are also approved in some indications, including cetuximab, which is an approved therapy for head and neck and colorectal cancer, and panitumumab, which is approved in colorectal cancer. [53-55]. However, molecular analyses of tumor samples from a Phase 3 study in head and neck squamous cell carcinoma revealed that neither Egfr expression nor EGFR amplification predicted response to cetuximab. [56,57]. Studies have reported non-squamous NSCLC patients with metastatic disease and tumors harboring an EGFR exon 19 deletion or L858R mutation to be sensitive to osimertinib, erlotinib, afatinib, gefitinib, dacomitinib, and the combination of erlotinib plus ramucirumab. [45,58-63]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors. [64].	EGFR amplification has been reported as an acquired alteration in 15.5% (16 /103) of EGFR exon19del or L858R-mutant NSCLC patients who were treated with Egfr TKI and in 9.7% (3 /31) of patients treated with Egfr TKI in combination with bevacizumab. [65].

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