REPORTING

Report Date:	JUN-15-2024
Receipt Date:	JUN-08-2024
Collection Date:	JUN-06-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Chi-Lu Chiang
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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
ERBB2 A775_G776insYVMA (Exon 20 insertion)	✓ Trastuzumab deruxtecan ~ Ado-trastuzumab emtansine	Yes	0.4%
TP53 E285K	None	Yes	0.5%

Comments

Reported by: JW11

Additional Biomarkers

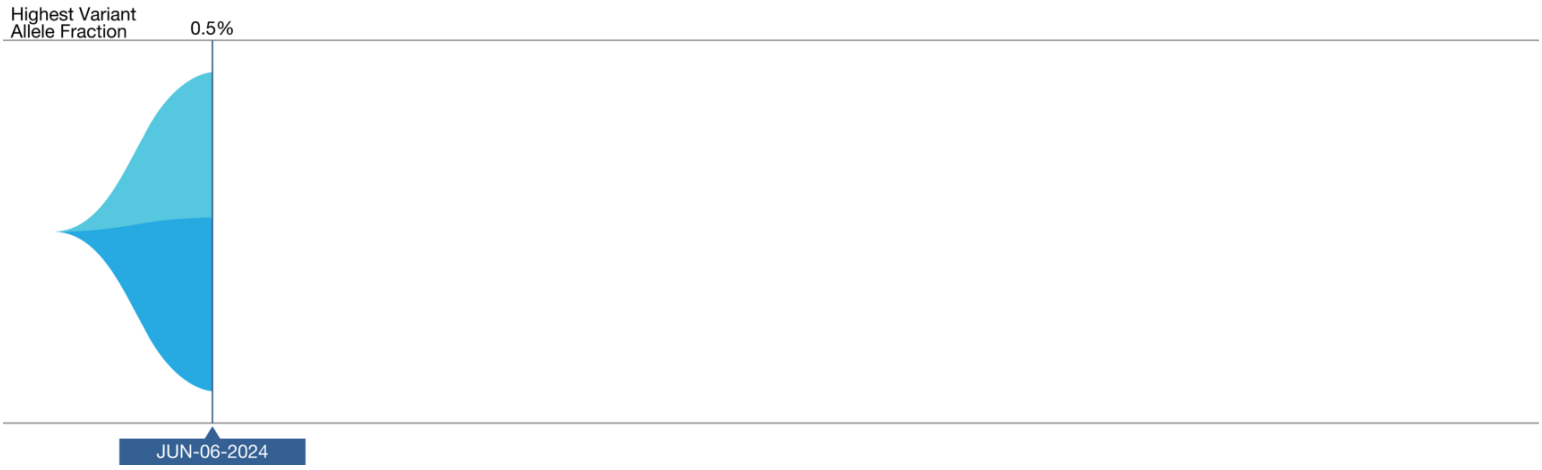
Biomarker	Additional Details
MSI-High	NOT DETECTED

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
TP53 E285K	0.5%
ERBB2 A775_G776insYVMA (Exon 20 insertion)	0.4%

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 A1065257 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
ERBB2 A775_G776insYVMA	NCT04446260 Sherry Zhu, MD, PhD,xiaoyu.zhu@hengrui.com,+86 021-61053363	A Study of SHR-A1811 in Subjects With Advanced Malignant Solid Tumors	Phase 1	Tainan, Taiwan Taoyuan, Taiwan Taichung, Taiwan
	NCT04686305 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Phase Ib Study of the Safety of T-DXd and Immunotherapy Agents With and Without Chemotherapy in Advanced or Metastatic HER2+, Non-squamous NSCLC	Phase 1	Tainan, Taiwan Kaohsiung city, Taiwan Taoyuan, Taiwan Taipei, Taiwan (3) Additional trial sites available
	NCT05099172 Bayer Clinical Trials Contact,clinical-trials-contact@bayer.com,(+)1-888-84 22937	First in Human Study of BAY2927088 in Participants Who Have Advanced Non-small Cell Lung Cancer (NSCLC) With Mutations in the Genes of Epidermal Growth Factor Receptor (EGFR) and/or Human Epidermal Growth Factor Receptor 2 (HER2)	Phase 1 /Phase 2	Taoyuan, Taiwan Taipei, Taiwan (2) Tainan, Taiwan (2) Taichung, Taiwan (2)
	NCT05650879 Helen L Collins, MD,helen.collins@enliventherapeutics.com,707 799-3272	ELVN-002 in HER2 Mutant Non-Small Cell Lung Cancer	Phase 1	Taipei City, Taiwan Tainan, Taiwan Taichung City, Taiwan
	NCT06151574 Boehringer Ingelheim,clintriage.rdg@boehringer-ingelheim.com,1-800-243-0127	Beamion LUNG-2: A Study to Test Whether Zongertinib (BI 1810631) Helps People With Advanced Non-small Cell Lung Cancer With HER2 Mutations Compared With Standard Treatment	Phase 3	Taichung, Taiwan
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
TP53 E285K	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

Insertion (Ins): The following alteration was detected in this patient: *ERBB2* A775_G776insYVMA. Guardant360 detects short insertions in exons of certain genes (see Table 1).

Interpretation

Somatic alterations were detected in the circulating cell-free DNA isolated from this patient's blood specimen. These genomic alterations are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatments. The percentage of altered cell-free DNA circulating (% cfDNA) in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn over, size, heterogeneity, vascularization, disease progression, and treatment.

Method and Limitations

Guardant360 sequences 74 cancer-associated genes to identify somatic alterations. Cell-free DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using the Illumina platform and hg19 as the reference genome. All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Guardant360 include single nucleotide variants, gene amplifications, fusions, short insertions/deletions (longest detected, 70 base pairs), and splice site disrupting events (see Table 1). Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Guardant360 panel. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue. MSI status is currently not reported for earlier panel versions. This version of the Guardant360 test is not validated for the detection of other types of genomic alterations, such as complex rearrangements or gene deletions. Certain sample or variant characteristics, such as low cfDNA concentration, may result in reduced analytic sensitivity. Guardant360 cannot discern the source of circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot easily distinguish germline variants from somatic alterations. Guardant360 is not validated for the detection of germline or de novo variants that are associated with hereditary cancer risk. Tissue genotyping should be considered when plasma genotyping is negative, if clinically appropriate.

Table 1: Genes on the Guardant360 Panel

Guardant360 reports single nucleotide variants, splice site mutations, and insertion and deletion variants (indels) in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

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

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

† Guardant360 reports amplifications of this gene.

Guardant360 reports fusion events involving this gene.

About the Test

The Guardant360 assay was developed and its performance characteristics were determined by Guardant Health, Inc. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test may be used for clinical purposes and should not be regarded as investigational or for research only. Guardant Health's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing. The laboratory report should be interpreted in the context of other clinical information and laboratory, pathology, and imaging studies by a qualified medical professional prior to initiating or changing a patient's treatment plan. The selection of any, all, or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) is entirely at the discretion of the treating medical professional. Drug and trial information are based on the diagnosis written on the submitted test request form; this information is not based on any supplemental information provided by the requesting medical professional, including pathology reports or other molecular studies. Some drugs listed in this report may not be approved or cleared by the FDA for the indicated use. Guardant Health makes no endorsement, express or implied, of any product, physician, or procedure contained in this report. This report makes no promises or guarantees that a particular medication will affect (or not affect) the clinical outcome of any patient.

Testing Performed at: Guardant Health

Laboratory Director: Martina Lefterova, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, USA

Additional information is available

Any therapeutic annotations are based on publicly available information. This information is described in the "Detailed Therapy Results" and "Relevance of Detected Alterations" sections.

Visit **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A1065257 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)
ERBB2 A775_G776insYVMA	NCT03574402 Yi-Long Wu, Professor,syylwu@live.cn, 862083827812	Phase II Umbrella Study Directed by Next Generation Sequencing	Phase 2	China
	NCT04446260 Sherry Zhu, MD, PhD,xiaoyu.zhu@hengrui.com,+86 021-61053363	A Study of SHR-A1811 in Subjects With Advanced Malignant Solid Tumors	Phase 1	Greenville, SC; Dallas, TX; Bronx, NY; China (18); Taiwan (3); Korea, Republic of (3); Australia (4)
	NCT04686305 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Phase Ib Study of the Safety of T-DXd and Immunotherapy Agents With and Without Chemotherapy in Advanced or Metastatic HER2+, Non-squamous NSCLC	Phase 1	Tacoma, WA; Houston, TX; Orange, CA; Baltimore, MD; Buffalo, NY; Fairfax, VA; Canada; Netherlands; Singapore (3); Philippines (4); Malaysia (4); Thailand (5); Turkey (3); Taiwan (8); Poland (5); Korea, Republic of (5); Italy (5); Israel (2); France (5); Australia (2)
	NCT04886804 Boehringer Ingelheim,clintriage.rdg@boehringer-ingelheim.com,1-800-243-0127	A Study to Test Different Doses of Zongertinib in People With Different Types of Advanced Cancer (Solid Tumours With Changes in the HER2 Gene)	Phase 1	Seattle, WA; New York, NY; Dallas, TX; Washington, DC; Birmingham, AL; Nashville, TN; Fairfax, VA; Durham, NC; CA (7); Sweden; Austria; Belgium; Singapore (2); Hong Kong (2); Japan (7); United Kingdom (3); Portugal (2); Spain (6); Netherlands (2); China (16); Korea, Republic of (5); Italy (3); Israel (4); France (6); Australia (2); Germany (5)
	NCT05099172 Bayer Clinical Trials Contact,clinical-trials-contact@bayer.com,(+)1-888-84 22937	First in Human Study of BAY2927088 in Participants Who Have Advanced Non-small Cell Lung Cancer (NSCLC) With Mutations in the Genes of Epidermal Growth Factor Receptor (EGFR) and/or Human Epidermal Growth Factor Receptor 2 (HER2)	Phase 1 /Phase 2	Houston, TX; Detroit, MI; Bethesda, MD; Boston, MA; Atlanta, GA; Nashville, TN; Fairfax, VA; Gilbert, AZ; Duarte, CA (2); Singapore (3); Hong Kong (3); Japan (11); Portugal (2); Spain (7); Netherlands (3); Belgium (2); China (14); Taiwan (7); Poland (2); Korea, Republic of (7); Brazil (3); Italy (8); Israel (2); France (7)
	NCT05650879 Helen L Collins, MD,helen.collins@enliventherapeutics.com,707 799-3272	ELVN-002 in HER2 Mutant Non-Small Cell Lung Cancer	Phase 1	Orlando, FL; Boston, MA; Plantation, FL; Aurora, CO; Fairfax, VA; Taiwan (3); Korea, Republic of (6); Italy (6); France (7); Australia (3); Spain (9)
	NCT06151574 Boehringer Ingelheim,clintriage.rdg@boehringer-ingelheim.com,1-800-243-0127	Beamion LUNG-2: A Study to Test Whether Zongertinib (BI 1810631) Helps People With Advanced Non-small Cell Lung Cancer With HER2 Mutations Compared With Standard Treatment	Phase 3	Glendale, CA; Rock Hill, SC; Canton, OH; Springfield, MO; Beverly Hills, CA; Wilson, NC; Bridgeton, MO; Singapore; Hong Kong; Taiwan; Japan (14); China (11); Korea, Republic of (8); Australia (3)
TP53 E285K	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)

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	NCT05109975 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	A Study to Evaluate Safety and Preliminary Anti-tumor Activity of Debio 0123 as Monotherapy in Adult Participants With Advanced Solid Tumors	Phase 1	Grand Rapids, MI; San Antonio, TX; Switzerland; Spain (7)
	NCT05253053 Caixia Sun, Ph.D., clinicaltrial@transtherabio.com,025-58216298	To Evaluate Efficacy and Safety of TT-00420 (Tinengotinib) as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors	Phase 1 /Phase 2	China (9)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
ERBB2 A775_G776insYVMA (Exon 20 insertion)	ABP 980	Kanjinti	Anti-Her2 monoclonal antibody.	FDA Approved in other indications (HER2+ Gastric carcinoma, HER2+ Gastroesophageal junction carcinoma, Breast carcinoma (HER2+))
	ABT-101		Egfr/Her2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Head and neck squamous cell carcinoma (HNSCC))
	Ado-trastuzumab emtansine	Kadcyla	Anti-Her2 monoclonal antibody trastuzumab conjugated to the maytansinoid DM1.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HER2+))
	ADXS31-164		Her2 vaccine.	Phase 1 (Solid Tumor)
	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)
	AMX-818		Anti-Her2 protease-activated T-cell-engager.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Anbenitamab		Anti-Her2 bispecific monoclonal antibody.	Phase 1 (Solid Tumor) Phase 3 (Gastric carcinoma, Breast carcinoma)
	ARX788		Anti-Her2 monoclonal antibody conjugated to monomethyl auristatin F.	Phase 1 (Solid Tumor)
	BAY2701438		Anti-Her2 monoclonal antibody.	Phase 1 (Solid Tumor)
	BAY2927088		Egfr/Her2 kinase inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	BL-M07D1		Anti-HER2 antibody-drug conjugate.	Phase 1 (Endometrial carcinoma, Ovarian carcinoma, Urothelial carcinoma, Cervical carcinoma, Cholangiocarcinoma)
	Bmab 200	Ogivri	Anti-Her2 monoclonal antibody.	FDA Approved in other indications (HER2+ Gastric carcinoma, HER2+ Gastroesophageal junction carcinoma, Breast carcinoma (HER2+))
	CT-P6	Herzuma	Anti-Her2 monoclonal antibody.	FDA Approved in other indications (HER2+ Gastric carcinoma, HER2+ Gastroesophageal junction carcinoma, Breast carcinoma (HER2+))
	Dacomitinib	Vizimpro	Pan-ErbB family tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (EGFR-mutant lung carcinoid, EGFR-mutant lung large cell neuroendocrine carcinoma, EGFR-mutant NSCLC)
	DB-1303		Anti-HER2 antibody-drug conjugate.	Phase 2 (Solid Tumor) Phase 3 (Breast carcinoma)
	Disitamab vedotin		Anti-Her2 antibody-drug conjugate.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Urothelial carcinoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	DZD1516		Her2 kinase inhibitor.	Phase 1 (Breast carcinoma)
	ELVN-002		Her2 kinase inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	GQ1001		Anti-HER2-DM1 antibody-drug conjugate.	Phase 1 (Solid Tumor)
	IAM1363		Her2 kinase inhibitor.	Phase 1 (Solid Tumor)
	IBI315		Anti-PD-1/Her2 bispecific antibody.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, Gastroesophageal junction carcinoma)
	Inetetamab	Cipterbin	Anti-Her2 antibody.	
	Lapatinib	Tykerb	Egfr/Her2 dual kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HER2+))
	Margetuximab	Margenza	Anti-Her2 monoclonal antibody.	Phase 1 (Solid Tumor) FDA Approved in other indications (Breast carcinoma (HER2+))
	Mobocertinib	Exkivity	Mutation-specific Egfr/Her2 inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (NSCLC with EGFR exon 20 insertion, Lung cancer)
	Neratinib	Nerlynx	Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HER2+))
	ORM-5029		Anti-HER2 GSPT1 degrader.	Phase 1 (Breast carcinoma (HER2+))
	Pertuzumab	Perjeta	Anti-Her2 monoclonal antibody.	Phase 2 (Lung adenocarcinoma) Phase 3 (Solid Tumor)
	PF-05280014	Trazimera	Anti-Her2 monoclonal antibody.	FDA Approved in other indications (HER2+ Gastric carcinoma, HER2+ Gastroesophageal junction carcinoma, Breast carcinoma (HER2+))
	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))
	PRS-343		Anti-Her2 monoclonal antibody/anti-CD137 anticalin bispecific fusion protein.	Phase 1 (Solid Tumor) Phase 1 (Brain and Central Nervous System Tumors)
	Pyrotinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)
	SB3	Ontruzant	Anti-Her2 monoclonal antibody.	FDA Approved in other indications (HER2+ Gastric carcinoma, HER2+ Gastroesophageal junction carcinoma, Breast carcinoma (HER2+))
	SHR-A1811		Anti-Her2 antibody-drug conjugate.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Breast carcinoma)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	TAS0728		Covalent Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Urothelial carcinoma, Breast carcinoma, Cholangiocarcinoma, Colorectal carcinoma (CRC))
	TAS2940		Egfr/Her2 kinase inhibitor.	Phase 1 (Solid Tumor)
	Trastuzumab	Herceptin	Anti-Her2 monoclonal antibody.	Phase 2 (Lung adenocarcinoma) FDA Approved in other indications (HER2+ Gastric carcinoma, HER2+ Gastroesophageal junction carcinoma, Breast carcinoma (HER2+))
	Trastuzumab deruxtecan	Enhertu	Anti-Her2 antibody conjugated with a TopoI inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (HER2+ Gastric carcinoma, HER2+ Gastroesophageal junction carcinoma, Breast carcinoma (HER2-low), Non-small cell lung carcinoma with ERBB2 mutation, Solid Tumor (HER2+ IHC3+), Breast carcinoma (HER2+))
	Trastuzumab duocarmazine		Anti-Her2 antibody conjugated with duocarmycin via a cleavable linker.	Phase 1 (Solid Tumor) Phase 3 (Breast carcinoma)
	Trastuzumab+pertuzumab	Herceptin+Perjeta	Anti-Her2 monoclonal antibody + anti-Her2 monoclonal antibody combination.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HER2+))
	Tucatinib	Tukysa	Her2 kinase inhibitor.	Phase 3 (Gastric carcinoma, Gastroesophageal junction carcinoma, Breast carcinoma, Colorectal carcinoma (CRC))
	Varlitinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Cholangiocarcinoma)
	Zanidatamab		Anti-Her2 bispecific antibody.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, Gastroesophageal junction carcinoma, Esophageal carcinoma, Breast carcinoma)
	Zenocutuzumab		Anti-Her2/anti-ErbB3 bispecific monoclonal antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Solid Tumor)
	ZN-A-1041		Her2 kinase inhibitor.	Phase 1 (Solid Tumor)
	Zongertinib		Her2 kinase inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
TP53 E285K	Adavosertib		Wee1 tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Lymphoma, Embryonal tumor with multi-layered rosettes (ETMR), Medulloblastoma, Small cell lung carcinoma (SCLC), Solid Tumor, Primary myelofibrosis (PMF), Ovarian carcinosarcoma, Acute myeloid leukemia (AML), MDS/MPN, unclassifiable, Chronic myelomonocytic leukemia (CMML),

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				Peritoneal papillary serous carcinoma, Myelodysplastic Syndrome (MDS))
	AL8326		Aurora kinase B/VEGFRs/Fgfr multi-kinase inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Small cell lung carcinoma (SCLC))
	Alisertib		Aurora kinase A inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	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))
	Azenosertib		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (High-grade serous ovarian carcinoma, Uterine serous/clear cell carcinoma, Osteosarcoma, Ovarian epithelial carcinoma, Colorectal adenocarcinoma, Acute myeloid leukemia (AML), Fallopian tube carcinoma, Peritoneal carcinoma, Pancreatic adenocarcinoma)
	Debio 0123		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	EP0042		Aurora kinase A/B and Flt3 inhibitor.	Phase 2 (Acute myeloid leukemia (AML), Chronic myelomonocytic leukemia (CMML), Myelodysplastic Syndrome (MDS))
	IMP7068		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	JAB-2485		Aurora kinase A inhibitor.	Phase 2 (Solid Tumor)
	LY3295668		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Head and neck squamous cell carcinoma (HNSCC), Small cell lung carcinoma (SCLC), Breast carcinoma (triple negative), Breast carcinoma (hormone receptor +, HER2-))
	SGT-53		TP53 gene therapy delivered via transferrin-targeted nanoparticles.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma, Pancreatic carcinoma)
	SY-4835		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	TAS-119		Aurora kinase A inhibitor.	Phase 1 (Solid Tumor)
	Tinengotinib		Aurora kinase A/B inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Breast carcinoma (triple negative))

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
ERBB2 A775_G776insYVMA	Activation of ERBB2 by amplification or mutation has been reported to play a role in several types of cancer. [1]. ERBB2 mutation has been reported to be mutually exclusive with EGFR, KRAS, and BRAF mutations and ALK and ROS rearrangements in NSCLC, and to be significantly correlated with smaller tumor size and never-smokers. [2-9].	Activating ERBB2 alterations may predict sensitivity to Her-targeted drug therapies.A number of therapies, including antibodies, small molecule inhibitors, and tyrosine kinase inhibitors, have been approved in various indications, including ado-trastuzumab emtansine, lapatinib, neratinib, pertuzumab, tucatinib, margetuximab, trastuzumab deruxtecan, and trastuzumab as well as several biosimilars, which have been approved by the EMA, PMDA, and/or FDA for use in Her2-overexpressing or ERBB2-amplified breast cancer. [10-21]. In addition, trastuzumab deruxtecan has been approved for the treatment of patients with unresectable or metastatic Her2 low breast cancer as well as adult patients with unresectable or metastatic ERBB2-mutant non–small cell lung cancer, as detected by an FDA-approved test, who have received previous systemic therapy. [22,23]. Fam-trastuzumab deruxtecan-nxki has also been FDA-approved for the treatment of adult patients with unresectable or metastatic Her2 positive solid tumors who have received prior systemic therapy and have no satisfactory alternative treatment options. [23-28]. Trastuzumab, alone and in combination with pembrolizumab, fluoropyrimidine- and platinum-containing chemotherapy, and trastuzumab deruxtecan have additionally been approved for the treatment of Her2 positive gastric and gastroesophageal junction adenocarcinoma, with the trastuzumab plus pembrolizumab approval restricted to PD-L1 positive disease. [15,29-31]. Trastuzumab in combination with tucatinib has been approved by the FDA for the treatment of advanced RAS wild-type /Her2 positive colorectal cancer patients following progression on standard-of-care chemotherapy. [32]. Her2-directed chimeric antigen receptor (CAR) T-cell therapies are additionally being investigated in glioblastoma and other diseases expressing ERBB2/Her2. [33,34]. Response to poziotinib has been reported in several NSCLC patient cases with ERBB2 exon 20 insertion	Several preclinical studies in various tumor types have reported an association between Her2 and chemo- and radio-resistance; similar results have been reported from clinical trials in some tumor types. [41-44].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		mutations as well as in NSCLC preclinical mouse models with ERBB2 exon 20 insertion mutations. [35-37]. Preclinical studies have also reported efficacy of Hsp90 inhibitors in NSCLC cell lines and xenograft models harboring ERBB2 mutations, specifically exon 20 mutations and the ERBB2 YVMA mutation. [38,39]. One retrospective study of 75 ERBB2-mutated NSCLC patients, including 65 with inframe insertion mutations, has reported increased median overall survival in patients treated with chemotherapy as compared with ERBB2 TKI therapy (5.5 vs. 3.7 months in the first-line setting and 4.2 vs. 2.0 months in the second-line setting). [40].	
TP53 E285K	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [45]. 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. [46-48]. 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. [49-53]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. [54]. 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. [55-58]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. [59-63]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients. [64].	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. [65-67]. 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. [68-70]. 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. [71-76].	Mutations in TP53 may increase resistance to ionizing radiation therapy. [77,78].

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