25933055, Fei (A0858567)

Patient MRN: N/A | DOB: NOV-01-1967 | Gender: Male Diagnosis: Lung adenocarcinoma | Test Number 1



Therapy Finder Page

REPORTING

Report Date: OCT-02-2023
Receipt Date: SEP-25-2023

Collection Date: SEP-23-2023

Specimen: Blood Status: FINAL **PHYSICIAN**

Chih-Hsueh Chen

Account: Genconn Biotech Co., LTD

Address: F15., No 207-5 Sec 3, Beixin Rd, Xindian

Dist, New Taipei City, 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

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 3)	% cfDNA or Amplification
EGFR E746_A750del (Exon 19 deletion)	Afatinib, Dacomitinib, Erlotinib, Erlotinib+ramucirumab, Gefitinib, Osimertinib	Yes	1.2%
<i>TP</i> 53 R248L	None	Yes	1.2%

Comments

Reported by: JV4

Additional Biomarkers

Biomarker	Additional Details
MSI-High	NOT DETECTED

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

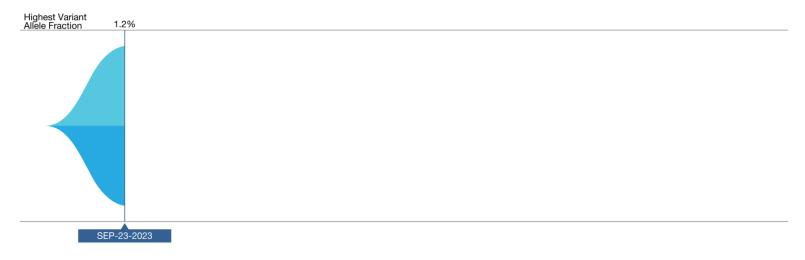
EGFR(T790M and others)	ROS1 BRAF	MET ERBB2(HER2)	RET	NTRK	KRAS
------------------------	-----------	-----------------	-----	------	------



Tumor Biology Page

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
	EGFR E746_A750del (Exon 19 deletion)	1.2%
	<i>TP53</i> R248L	1.2%

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order. § See definitions section for more detail



Clinical Trial Page

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 A0858567 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)			
EGFR E746_A750del	NCT04077463 Study Contact, Participate-In-This- Study@its.jnj.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			
	NCT05388669 Study Contact,Participate-In-This- Study@its.jnj.com,844-434-4210	A Study of Lazertinib With Subcutaneous Amivantamab Compared With Intravenous Amivantamab in Participants With Epidermal Growth Factor Receptor (EGFR)-Mutated Advanced or Metastatic Non-small Cell Lung Cancer	Phase 3	Kaohsiung City, Taiwan Kaohsiung, Taiwan Taipei City, Taiwan Taipei, Taiwan Additional trial sites available			
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office						
<i>TP53</i> R248L	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	s not within the same state as the physician's office					

More clinical trial options available at portal.guardanthealth.com

25933055, Fei (A0858567)

DOB: NOV-01-1967 | Test Number 1



Definitions

Deletion (Del): The following alteration was detected in this patient: *EGFR* E746_A750del. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

Interpretation

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





Method and Limitations

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

Table 1: Genes on the Guardant360 Panel

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

NTRK1 [#] NTRK3 PDGFRA [†] PIK3CA [†] PTEN PTPN11 RAF1 [†] RB1 RET [#] RHEB RHOA RIT1 ROS1 [#] SMAD4 SMO STK11 TERT [‡] TP53 TSC1 VHL	RHEB	RHOA							
--	------	------	--	--	--	--	--	--	--

 $[\]ensuremath{\ddagger}$ Guardant360 reports alterations in the promoter region 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



[#] Guardant360 reports fusion events involving this gene.

[†] Guardant360 reports amplifications of this gene.

25933055, Fei (A0858567)

DOB: NOV-01-1967 | Test Number 1



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 A0858567 in the subject line of the email for:

Additional clinical trials

- Relevance of Detected Alterations

Detailed Therapy Results

- 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 E746_A750del	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)
	NCT03944772 AstraZeneca Clinical Study Information Center,information.center@astrazeneca. com,1-877-240-9479	Phase 2 Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy (ORCHARD)	Phase 2	Seattle, WA; Houston, TX; Grand Rapids, MI; Pittsburgh, PA; Chicago, IL; New Haven, CT; Baltimore, MD; Portland, OR; Boston, MA (2); New York, NY (2); CA (5); Sweden; Netherlands (4); Norway (3); Japan (6); Korea, Republic of (4); Italy (5); Spain (6)
	NCT04077463 Study Contact, Participate-In-This- Study@its.jnj.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; Portland, OR; Salt Lake City, UT; Tampa, FL; Fairfax, VA; Boston, MA (3); New York, NY (2); CA (5); Puerto Rico; Japan (7); China (13); Taiwan (4); Korea, Republic of (4); Italy (5); France (7); Germany (8); Spain (8)
	NCT05388669 Study Contact, Participate-In-This- Study@its.jnj.com,844-434-4210	A Study of Lazertinib With Subcutaneous Amivantamab Compared With Intravenous Amivantamab in Participants With Epidermal Growth Factor Receptor (EGFR)-Mutated Advanced or Metastatic Non-small Cell Lung Cancer	Phase 3	Denver, CO; Orlando, FL; Philadelphia, PA; East Brunswick, NJ; New York, NY; New Brunswick, NJ; Bronx, NY; Boca Raton, FL; Kansas City, KS; Duarte, CA; Long Beach, CA; Irvine, CA; Charleston, SC; Fairfax, VA; Ann Arbor, MI; Portland, OR (2); Argentina (6); Japan (18); United Kingdom (4); Malaysia (6); Thailand (3); Portugal (4); Spain (16); Canada (2); Turkey (11); China (32); Taiwan (8); Poland (5); Korea, Republic of (9); Brazil (16); Italy (9); Israel (5); France (4); Australia (6); Germany (5)
	NCT05498428 Study Contact, Participate-In-This- Study@its.jnj.com,844-434-4210	A Study of Amivantamab in Participants With Advanced or Metastatic Solid Tumors Including Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small Cell Lung Cancer	Phase 2	Orlando, FL; Saint Louis, MO; Stanford, CA; Winston-Salem, NC; New Brunswick, NJ; Boca Raton, FL; Hackensack, NJ; Miami Beach, FL; Seattle, WA; Washington, DC; East Syracuse, NY; Warrensville Heights, OH; Fairfax, VA; Mayfield Heights, OH; Cleveland, OH (2); Japan (6); China (18); Korea, Republic of (5); Brazil (9); United Kingdom (6); Italy (3); Malaysia (4); Israel (5); France (6); Germany (5); Spain (14)
<i>TP53</i> R248L	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; Canton, OH; Chicago, IL; Dallas, TX; New Brunswick, NJ
	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)



Additional Information

List of Available Clinical Trials

Alteration Trial ID / Contact		Title	Phase	Site (number in parenthesis is count of trial sites)
	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)
	NCT05489731 li zhang, professor,zhangli6@mail.sysu. edu.cn,13902282893	VIC-1911 Combined With Osimertinib for EGFR -Mutant Non-small Cell Lung Cancer	Phase 1	China



Alteration	Drug	Trade Name	Target	Curre	ent Status
EGFR E746_A750del (Exon 19 deletion)	ABT-101			Egfr/Her2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Head and neck squamous cell carcinoma (HNSCC))
	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	Rybrev	ant	Bispecific anti-Met/Egfr antibody.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (NSCLC with EGFR exon 20 insertion)
	Aumolertinib			Egfr T790M inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC))
	Avitinib			Irreversible mutation-specific Egfr kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Non-Hodgkin lymphoma (NHL))
	AZD3759			Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BAY2927088			Egfr/Her2 kinase inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
	BBP-398			Shp-2 inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	BBT-176			Fourth generation Egfr inhibitor targeting exon 19del /L858R, T790M, and C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BDTX-1535			Irreversible brain-penetrant fourth generation Egfr inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Glioma)
	BDTX-189			Irreversible Egfr/Her2 inhibitor.	Phase 2 (Solid Tumor)
	Befotertinib			Third generation mutation- specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC))
	BLU-451			Egfr inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	BLU-701			Fourth generation Egfr inhibitor targeting exon 19del, L858R, and C797X resistance mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BLU-945			Fourth generation Egfr inhibitor targeting T790M and T790M/C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BPI-361175			Fourth generation Egfr inhibitor targeting T790M and T790M/C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	BPI-7711			Egfr T790M inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	CLN-081			Covalent mutation-specific	Phase 2 (Non-small cell lung carcinoma



Alteration	Drug Trade	Name Target	Current Status		
			(L858R, T790M, exon 19 deletion, exon 20 insertion) Egfr tyrosine kinase inhibitor.	(NSCLC))	
	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)	
	ERAS-601		Shp-2 inhibitor.	Phase 1 (Solid Tumor)	
	Erlotinib	Tarceva	Egfr 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, NSCLC with EGFR exon 19 del/L858R, Pancreatic carcinoma, EGFR-mutant NSCLC)	
	Erlotinib+bevacizumab	Tarceva+Avastin		Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Lung cancer)	
	Erlotinib+ramucirumab	Tarceva+Cyramza	Egfr tyrosine kinase inhibitor + anti-VEGFR-2 monoclonal antibody combination.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (NSCLC with EGFR exon 19 de /L858R)	
	Furmonertinib		Third generation mutation- specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))	
	Gefitinib	Iressa	Egfr 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)	
	H002		Fourth generation Egfr inhibitor targeting exon 19del /L858R, T790M, and C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))	
	Hemay022		Egfr tyrosine kinase inhibitor.	Phase 1 (Breast carcinoma (HER2+))	
	Icotinib	Conmana	Egfr inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Esophageal carcinoma)	
	JIN-A02		Fourth generation Egfr inhibitor targeting T790M and T790M/C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))	
	Lazertinib		Third generation mutation- specific Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))	
	Lifirafenib		Dual Braf/Egfr inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)	
	Mobocertinib	Exkivity	Mutation-specific Egfr/Her2 inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (NSCLC with EGFR exon 20 insertion)	



Alteration	Drug	Trade Name	Target	Current Status			
	Naquotinib			EGFR mutant-specific inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)		
	Nazartinib			Third generation EGFR mutant- specific (T790M, L858R, exon 19 deletion) tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))		
	Neratinib	Nerlynx	(Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) FDA Approved in other indications (Breast carcinoma (HER2+))		
	NX-019			Egfr inhibitor.	Phase 1 (Solid Tumor)		
	Olafertinib			Third generation mutation- specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)		
	Olmutinib			Egfr inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))		
	Osimertinib	Tagriss	60	Egfr T790M 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)		
	PF-06747775			Egfr T790M-specific inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))		
	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)		
	SKLB1028			Egfr/Flt3/c-Abl inhibitor.	Phase 2 (Acute myeloid leukemia (AML))		
	Sunvozertinib			Bispecific anti-Egfr/Her2 monoclonal antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Non-Hodgkin lymphoma (NHL))		
	TAS2940			Egfr/Her2 kinase inhibitor.	Phase 1 (Solid Tumor)		
	TAS3351			Fourth generation Egfr inhibitor targeting T790M and T790M/C797S mutations.			
	Varlitinib			Egfr/Her2 kinase inhibitor.	Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Cholangiocarcinoma)		
	WSD0922-FU			Blood-brain barrier penetrable EGFR/EGFRvIII inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Glioblastoma, Anaplastic astrocytoma)		
	ZN-e4			Egfr T790M inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))		



Alteration	Drug	Trade Name	Target	Current Status
<i>TP53</i> R248L	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 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 3 (Peripheral T-cell lymphoma (PTCL))
	AMG 900		Aurora A/B/C 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 (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)
	IMP7068		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	Kevetrin		Blocks Mdm2-p53 interaction, restoring transcriptional activity of p53.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma)
	LY3295668		Aurora A kinase 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 A/B kinase inhibitor.	Phase 1 (Solid Tumor)
	SY-4835		Wee1 tyrosine kinase inhibitor.	Phase 1 (Solid Tumor)
	TAS-119		Aurora A kinase inhibitor.	Phase 1 (Solid Tumor)
	TT-00420		Aurora A/B kinase 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

EGFR E746_A750del 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. ⁽¹⁾.

The presence of a sensitizing EGFR mutation in a tumor is the strongest biological predictor of sensitivity to an Egfr tyrosine kinase inhibitor (TKI). Compared with conventional chemotherapy, Egfr TKIs have been shown to improve progression-free survival in non-small cell lung cancer patients whose tumors harbor EGFR mutations. ⁽²⁻⁵⁾. The Egfr TKIs erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib have been approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR mutations; osimertinib has additionally been approved for the treatment of NSCLC with EGFR T790M. (2,5-11). Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations. (12). The combination of erlotinib and ramucirumab has been FDA-approved for the treatment of metastatic NSCLC patients with tumors harboring an EGFR exon 19 deletion or the exon 21 L858R mutation. ⁽¹³⁾. Amivantamab and mobocertinib have been approved by the FDA for NSCLC patients with EGFR exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy. (14-17). 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. (2,5-7,11,13,18). Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors. (19).

Some patients with EGFR-mutant NSCLC exhibit resistance to Egfr inhibition; resistance has been associated with insertions in EGFR exon 20, the T790M mutation in EGFR, and amplification of either MET or ERBB2. ⁽²⁰⁻²⁴⁾. Third generation irreversible Egfr TKIs that target the EGFR T790M mutation have shown efficacy in T790M-mutant NSCLC, including osimertinib, which has received approval by the FDA, EMA and PMDA for the treatment of EGFR T790M-mutant metastatic NSCLC. (25-²⁹⁾. Several studies have reported that resistance to Egfr TKIs in NSCLC is mediated by the transformation of NSCLC cell types to those of SCLC with neuroendocrine features. (30-33). Preclinical studies have reported increased Smo expression in NSCLC cell lines resistant to first, second, and third generation Egfr inhibitors as compared with sensitive ones; treatment with Smo inhibitors was observed to restore sensitivity in the resistant cell lines. (34-36).

TP53 R248L

Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. (37). 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. (38-40). 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

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. (57-59). 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. (60-62). Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients with solid tumors and hematologic

Mutations in TP53 may increase resistance to ionizing radiation therapy. (69,70)





Effect on Drug Resistance

Additional Information

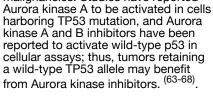
Relevance of Detected Alterations

Alteration Role in Disease

> malignancies. Studies have reported harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in

Effect on Drug Sensitivity

shown that it may have oncogenic gainof-function effects. (41-45). TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. ⁽⁴⁶⁾. 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. (47-50). TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. (51-55). TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients. ⁽⁵⁶⁾.







Additional Information

References

- 1. Ciardiello F, Tortora G "EGFR antagonists in cancer treatment." The New England journal of medicine (2008): 1160-74
- 2. Mok T, Wu Y, Thongprasert S, Yang C, Chu D, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang J, Chewaskulyong B, Jiang H, Duffield E, Watkins C, Armour A, Fukuoka M "Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma." The New England journal of medicine(2009): 947-57
- 3. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, Majem M, Lopez-Vivanco G, Isla D, Provencio M, Insa A, Massuti B, Gonzalez-Larriba J, Paz-Ares L, Bover I, Garcia-Campelo R, Moreno M, Catot S, Rolfo C, Reguart N, Palmero R, Sánchez J, Bastus R, Mayo C, Bertran-Alamillo J, Molina M, Sanchez J, Taron M "Screening for epidermal growth factor receptor mutations in lung cancer." The New England journal of medicine(2009): 958-67
- 4. Tsao M, Sakurada A, Cutz J, Zhu C, Kamel-Reid S, Squire J, Lorimer I, Zhang T, Liu N, Daneshmand M, Marrano P, da Cunha Santos G, Lagarde A, Richardson F, Seymour L, Whitehead M, Ding K, Pater J, Shepherd F "Erlotinib in lung cancer molecular and clinical predictors of outcome." The New England journal of medicine (2005): 133-44
- 5. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez J, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno M, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez J, Sanchez J, Molina M, Taron M, Paz-Ares L "Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial." The Lancet. Oncology(2012): 239-46
- 6. Soria J, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee K, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho B, Cheng Y, Cho E, Voon P, Planchard D, Su W, Gray J, Lee S, Hodge R, Marotti M, Rukazenkov Y, Ramalingam S "Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer." The New England journal of medicine(2018): 113-125
- 7. Wu Y, Cheng Y, Zhou X, Lee K, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J, Migliorino M, Pluzanski A, Sbar E, Wang T, White J, Nadanaciva S, Sandin R, Mok T "Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial." The Lancet. Oncology(2017): 1454-1466
- 8. Mok T, Cheng Y, Zhou X, Lee K, Nakagawa K, Niho S, Lee M, Linke R, Rosell R, Corral J, Migliorino M, Pluzanski A, Sbar E, Wang T, White J, Wu Y "Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations." Journal of clinical oncology: official journal of the American Society of Clinical Oncology(2018): 2244-2250
- Shepherd F, Rodrigues Pereira J, Ciuleanu T, Tan E, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L "Erlotinib in previously treated non-small-cell lung cancer." The New England journal of medicine(2005): 123-32
- 10. Sequist L, Yang J, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater S, Orlov S, Tsai C, Boyer M, Su W, Bennouna J, Kato T, Gorbunova V, Lee K, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M "Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations." Journal of clinical oncology: official journal of the American Society of Clinical Oncology(2013): 3327-34
- 11. Douillard J, Ostoros G, Cobo M, Ciuleanu T, McCormack R, Webster A, Milenkova T "First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study." British journal of cancer(2014): 55-62
- 12. Yang J, Sequist L, Geater S, Tsai C, Mok T, Schuler M, Yamamoto N, Yu C, Ou S, Zhou C, Massey D, Zazulina V, Wu Y "Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6." The Lancet. Oncology(2015): 830-8
- 13. Nakagawa K, Garon E, Seto T, Nishio M, Ponce Aix S, Paz-Ares L, Chiu C, Park K, Novello S, Nadal E, Imamura F, Yoh K, Shih J, Au K, Moro-Sibilot D, Enatsu S, Zimmermann A, Frimodt-Moller B, Visseren-Grul C, Reck M "Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial." The Lancet. Oncology(2019): 1655-1669
- 14. Cho B, Lee K, Cho E, et al. "Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd-generation tyrosine kinase inhibitor (TKI), in advanced EGFR NSCLC" Annals of Oncology(2020): Abstract 12580
- 15. Park K, John T, Kim S, et al. "Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC)." Journal of Clinical Oncology(2020)
- 16. Riely G, Neal J, Camidge D, Spira A, Piotrowska Z, Costa D, Tsao A, Patel J, Gadgeel S, Bazhenova L, Zhu V, West H, Mekhail T, Gentzler R, Nguyen D, Vincent S, Zhang S, Lin J, Bunn V, Jin S, Li S, Jänne P "Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non-Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations from a Phase I/II Trial." Cancer discovery(2021): 1688-1699
- 17. Zhou C, Ramalingam S, Li B, et al. "Mobocertinib in NSCLC With EGFR Exon 20 Insertions: Results From EXCLAIM and Pooled Platinum-Pretreated Patient Populations" Journal of Thoracic Oncology(2021)
- 18. Yang J, Wu Y, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu C, O'Byrne K, Feng J, Lu S, Huang Y, Geater S, Lee K, Tsai C, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su W, Lee K, Kato T, Massey D, Shahidi M, Zazulina V, Sequist L "Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials." The Lancet. Oncology (2015): 141-51
- 19. O'Kane G, Bradbury P, Feld R, Leighl N, Liu G, Pisters K, Kamel-Reid S, Tsao M, Shepherd F "Uncommon EGFR mutations in advanced non-small cell lung cancer." Lung cancer (Amsterdam, Netherlands)(2017): 137-144
- 20. Engelman J, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park J, Lindeman N, Gale C, Zhao X, Christensen J, Kosaka T, Holmes A, Rogers A, Cappuzzo F, Mok T, Lee C, Johnson B, Cantley L, Jänne P "MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling." Science (New York, N.Y.)(2007): 1039-43
- 21. Greulich H, Chen T, Feng W, Jänne P, Alvarez J, Zappaterra M, Bulmer S, Frank D, Hahn W, Sellers W, Meyerson M "Oncogenic transformation by inhibitor-sensitive and resistant EGFR mutants." PLoS medicine(2005): e313
- 22. Kwak E, Sordella R, Bell D, Godin-Heymann N, Okimoto R, Brannigan B, Harris P, Driscoll D, Fidias P, Lynch T, Rabindran S, McGinnis J, Wissner A, Sharma S, Isselbacher K, Settleman J, Haber D "Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib." Proceedings of the National Academy of Sciences of the United States of America(2005): 7665-70





Additional Information

References

- 23. Takezawa K, Pirazzoli V, Arcila M, Nebhan C, Song X, de Stanchina E, Ohashi K, Janjigian Y, Spitzler P, Melnick M, Riely G, Kris M, Miller V, Ladanyi M, Politi K, Pao W "HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation." Cancer discovery(2012): 922-33
- 24. Yu H, Arcila M, Rekhtman N, Sima C, Zakowski M, Pao W, Kris M, Miller V, Ladanyi M, Riely G "Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers." Clinical cancer research: an official journal of the American Association for Cancer Research(2013): 2240-7
- 25. Jänne P, Boss D, Camidge D, Britten C, Engelman J, Garon E, Guo F, Wong S, Liang J, Letrent S, Millham R, Taylor I, Eckhardt S, Schellens J "Phase I dose-escalation study of the pan-HER inhibitor, PF299804, in patients with advanced malignant solid tumors." Clinical cancer research: an official journal of the American Association for Cancer Research(2011): 1131-9
- 26. Jänne P, Yang J, Kim D, Planchard D, Ohe Y, Ramalingam S, Ahn M, Kim S, Su W, Horn L, Haggstrom D, Felip E, Kim J, Frewer P, Cantarini M, Brown K, Dickinson P, Ghiorghiu S, Ranson M "AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer." The New England journal of medicine(2015): 1689-99
- 27. Greig S "Osimertinib: First Global Approval." Drugs(2016): 263-73
- 28. Yang J, Ahn M, Kim D, Ramalingam S, Sequist L, Su W, Kim S, Kim J, Planchard D, Felip E, Blackhall F, Haggstrom D, Yoh K, Novello S, Gold K, Hirashima T, Lin C, Mann H, Cantarini M, Ghiorghiu S, Jänne P "Osimertinib in Pretreated T790M-Positive Advanced Non-Small-Cell Lung Cancer: AURA Study Phase II Extension Component." Journal of clinical oncology: official journal of the American Society of Clinical Oncology(2017): 1288-1296
- 29. Wang S, Cang S, Liu D "Third-generation inhibitors targeting EGFR T790M mutation in advanced non-small cell lung cancer." Journal of hematology & oncology(2016): 34
- 30. Watanabe S, Sone T, Matsui T, Yamamura K, Tani M, Okazaki A, Kurokawa K, Tambo Y, Takato H, Ohkura N, Waseda Y, Katayama N, Kasahara K "Transformation to small-cell lung cancer following treatment with EGFR tyrosine kinase inhibitors in a patient with lung adenocarcinoma." Lung cancer (Amsterdam, Netherlands)(2013): 370-2
- 31. Chang Y, Kim S, Choi Y, So K, Rho J, Kim W, Lee J, Chung J, Choi C "Neuroendocrine differentiation in acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitor." Tuberculosis and respiratory diseases(2013): 95-103
- 32. Popat S, Wotherspoon A, Nutting C, Gonzalez D, Nicholson A, O'Brien M "Transformation to "high grade" neuroendocrine carcinoma as an acquired drug resistance mechanism in EGFR-mutant lung adenocarcinoma." Lung cancer (Amsterdam, Netherlands)(2013): 1-4
- 33. Sequist L, Waltman B, Dias-Santagata D, Digumarthy S, Turke A, Fidias P, Bergethon K, Shaw A, Gettinger S, Cosper A, Akhavanfard S, Heist R, Temel J, Christensen J, Wain J, Lynch T, Vernovsky K, Mark E, Lanuti M, lafrate A, Mino-Kenudson M, Engelman J "Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors." Science translational medicine(2011): 75ra26
- 34. Della Corte C, Bellevicine C, Vicidomini G, Vitagliano D, Malapelle U, Accardo M, Fabozzi A, Fiorelli A, Fasano M, Papaccio F, Martinelli E, Troiani T, Troncone G, Santini M, Bianco R, Ciardiello F, Morgillo F "SMO Gene Amplification and Activation of the Hedgehog Pathway as Novel Mechanisms of Resistance to Anti-Epidermal Growth Factor Receptor Drugs in Human Lung Cancer." Clinical cancer research: an official journal of the American Association for Cancer Research(2015): 4686-97
- 35. Bai X, Zhang X, Yang S, An S, Chen Z, Su J, Xie Z, Gou L, Wu Y "Blockade of Hedgehog Signaling Synergistically Increases Sensitivity to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-Small-Cell Lung Cancer Cell Lines." PloS one(2016): e0149370
- **36.** Della Corte C, Malapelle U, Vigliar E, Pepe F, Troncone G, Ciaramella V, Troiani T, Martinelli E, Belli V, Ciardiello F, Morgillo F "Efficacy of continuous EGFR-inhibition and role of Hedgehog in EGFR acquired resistance in human lung cancer cells with activating mutation of EGFR." Oncotarget(2017): 23020-23032
- 37. Brown C, Lain S, Verma C, Fersht A, Lane D "Awakening guardian angels: drugging the p53 pathway." Nature reviews. Cancer(2009): 862-73
- **38.** Malkin D, Li F, Strong L, Fraumeni J, Nelson C, Kim D, Kassel J, Gryka M, Bischoff F, Tainsky M "Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms." Science (New York, N.Y.)(1990): 1233-8
- **39.** Srivastava S, Zou Z, Pirollo K, Blattner W, Chang E "Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome." Nature(1991): 747-9
- 40. Santibáñez-Koref M, Birch J, Hartley A, Jones P, Craft A, Eden T, Crowther D, Kelsey A, Harris M "p53 germline mutations in Li-Fraumeni syndrome." Lancet (London, England)(1991): 1490-1
- **41.** Wang Y, Lin R, Tan Y, Chen J, Chen C, Wang Y "Wild-type p53 overexpression and its correlation with MDM2 and p14ARF alterations: an alternative pathway to non-small-cell lung cancer." Journal of clinical oncology: official journal of the American Society of Clinical Oncology(2005): 154-64
- 42. Koga T, Hashimoto S, Sugio K, Yoshino I, Nakagawa K, Yonemitsu Y, Sugimachi K, Sueishi K "Heterogeneous distribution of P53 immunoreactivity in human lung adenocarcinoma correlates with MDM2 protein expression, rather than with P53 gene mutation." International journal of cancer(2001): 232-9
- 43. Kato S, Han S, Liu W, Otsuka K, Shibata H, Kanamaru R, Ishioka C "Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis." Proceedings of the National Academy of Sciences of the United States of America(2003): 8424-9
- 44. Houben R, Hesbacher S, Schmid C, Kauczok C, Flohr U, Haferkamp S, Müller C, Schrama D, Wischhusen J, Becker J "High-level expression of wild-type p53 in melanoma cells is frequently associated with inactivity in p53 reporter gene assays." PloS one(2011): e22096
- **45.** Olivier M, Petitjean A, Marcel V, Pétré A, Mounawar M, Plymoth A, de Fromentel C, Hainaut P "Recent advances in p53 research: an interdisciplinary perspective." Cancer gene therapy(2009): 1-12
- **46.** Chang Y, Wu C, Shih J, Lee Y "Comparison of p53 and epidermal growth factor receptor gene status between primary tumors and lymph node metastases in non-small cell lung cancers." Annals of surgical oncology(2011): 543-50
- 47. Jiang R, Zhang B, Teng X, Hu P, Xu S, Zheng Z, Liu R, Tang T, Ye F "Validating a targeted next-generation sequencing assay and profiling somatic variants in Chinese non-small cell lung cancer patients." Scientific reports(2020): 2070
- 48. Mattioni M, Soddu S, Prodosmo A, Visca P, Conti S, Alessandrini G, Facciolo F, Strigari L "Prognostic role of serum p53 antibodies in lung cancer." BMC cancer(2015): 148
- **49.** Bircan A, Bircan S, Kapucuoglu N, Songur N, Ozturk O, Akkaya A "Maspin, VEGF and p53 expression in small biopsies of primary advanced lung cancer and relationship with clinicopathologic parameters." Pathology oncology research: POR(2010): 553-61





Additional Information

References

- 50. Kim Y, Hammerman P, Kim J, Yoon J, Lee Y, Sun J, Wilkerson M, Pedamallu C, Cibulskis K, Yoo Y, Lawrence M, Stojanov P, Carter S, McKenna A, Stewart C, Sivachenko A, Oh I, Kim H, Choi Y, Kim K, Shim Y, Kim K, Song S, Na K, Choi Y, Hayes D, Kim J, Cho S, Kim Y, Ahn J, Ahn M, Getz G, Meyerson M, Park K "Integrative and comparative genomic analysis of lung squamous cell carcinomas in East Asian patients." Journal of clinical oncology: official journal of the American Society of Clinical Oncology(2014): 121-8
- 51. Dong Z, Zhong W, Zhang X, Su J, Xie Z, Liu S, Tu H, Chen H, Sun Y, Zhou Q, Yang J, Yang X, Lin J, Yan H, Zhai H, Yan L, Liao R, Wu S, Wu Y "Potential Predictive Value of TP53 and KRAS Mutation Status for Response to PD-1 Blockade Immunotherapy in Lung Adenocarcinoma." Clinical cancer research: an official journal of the American Association for Cancer Research(2017): 3012-3024
- 52. Scheel A, Ansén S, Schultheis A, Scheffler M, Fischer R, Michels S, Hellmich M, George J, Zander T, Brockmann M, Stoelben E, Groen H, Timens W, Perner S, von Bergwelt-Baildon M, Büttner R, Wolf J "PD-L1 expression in non-small cell lung cancer: Correlations with genetic alterations." Oncoimmunology(2016): e1131379
- 53. Albitar M, Sudarsanam S, Ma W, Jiang S, Chen W, Funari V, Blocker F, Agersborg S "Correlation of MET gene amplification and TP53 mutation with PD-L1 expression in non-small cell lung cancer." Oncotarget(2018): 13682-13693
- 54. Mansuet-Lupo A, Alifano M, Pécuchet N, Biton J, Becht E, Goc J, Germain C, Ouakrim H, Régnard J, Cremer I, Laurent-Puig P, Dieu-Nosjean M, Blons H, Damotte D "Intratumoral Immune Cell Densities Are Associated with Lung Adenocarcinoma Gene Alterations." American journal of respiratory and critical care medicine(2016): 1403-1412
- 55. Kadara H, Choi M, Zhang J, Parra E, Rodriguez-Canales J, Gaffney S, Zhao Z, Behrens C, Fujimoto J, Chow C, Yoo Y, Kalhor N, Moran C, Rimm D, Swisher S, Gibbons D, Heymach J, Kaftan E, Townsend J, Lynch T, Schlessinger J, Lee J, Lifton R, Wistuba I, Herbst R "Whole-exome sequencing and immune profiling of early-stage lung adenocarcinoma with fully annotated clinical follow-up." Annals of oncology: official journal of the European Society for Medical Oncology(2017): 75-82
- 56. Van Egeren D, Kohli K, Warner J, Bedard P, Riely G, Lepisto E, Schrag D, LeNoue-Newton M, Catalano P, Kehl K, Michor F "Genomic analysis of early-stage lung cancer reveals a role for TP53 mutations in distant metastasis." Scientific reports(2022): 19055
- 57. Schuler P, Harasymczuk M, Visus C, Deleo A, Trivedi S, Lei Y, Argiris A, Gooding W, Butterfield L, Whiteside T, Ferris R "Phase I dendritic cell p53 peptide vaccine for head and neck cancer." Clinical cancer research : an official journal of the American Association for Cancer Research(2014): 2433-44
- 58. Vermeij R, Leffers N, van der Burg S, Melief C, Daemen T, Nijman H "Immunological and clinical effects of vaccines targeting p53-overexpressing malignancies." Journal of biomedicine & biotechnology(2011): 702146
- 59. Saito H, Ando S, Morishita N, Lee K, Dator D, Dy D, Shigemura K, Adhim Z, Nibu K, Fujisawa M, Shirakawa T "A combined lymphokine-activated killer (LAK) cell immunotherapy and adenovirus-p53 gene therapy for head and neck squamous cell carcinoma." Anticancer research(2014): 3365-70
- 60. Ma C, Janetka J, Piwnica-Worms H "Death by releasing the breaks: CHK1 inhibitors as cancer therapeutics." Trends in molecular medicine(2011): 88-96
- 61. Hirai H, Arai T, Okada M, Nishibata T, Kobayashi M, Sakai N, Imagaki K, Ohtani J, Sakai T, Yoshizumi T, Mizuarai S, Iwasawa Y, Kotani H "MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil." Cancer biology & therapy(2010): 514-22
- 62. Bridges K, Hirai H, Buser C, Brooks C, Liu H, Buchholz T, Molkentine J, Mason K, Meyn R "MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells." Clinical cancer research: an official journal of the American Association for Cancer Research(2011): 5638-48
- 63. Vilgelm A, Pawlikowski J, Liu Y, Hawkins O, Davis T, Smith J, Weller K, Horton L, McClain C, Ayers G, Turner D, Essaka D, Stewart C, Sosman J, Kelley M, Ecsedy J, Johnston J, Richmond A "Mdm2 and aurora kinase a inhibitors synergize to block melanoma growth by driving apoptosis and immune clearance of tumor cells." Cancer research(2015): 181-93
- 64. Li Z, Sun Y, Chen X, Squires J, Nowroozizadeh B, Liang C, Huang J "p53 Mutation Directs AURKA Overexpression via miR-25 and FBXW7 in Prostatic Small Cell Neuroendocrine Carcinoma." Molecular cancer research : MCR(2015): 584-91
- 65. Katayama H, Sen S "Functional significance of Aurora kinase A regulatory interactions with p53-ERa complex in human breast cancer cells." Hormones & cancer(2011):
- 66. Tentler J, Ionkina A, Tan A, Newton T, Pitts T, Glogowska M, Kabos P, Sartorius C, Sullivan K, Espinosa J, Eckhardt S, Diamond J "p53 Family Members Regulate Phenotypic Response to Aurora Kinase A Inhibition in Triple-Negative Breast Cancer." Molecular cancer therapeutics(2015): 1117-29
- 67. Gully C, Velazquez-Torres G, Shin J, Fuentes-Mattei E, Wang E, Carlock C, Chen J, Rothenberg D, Adams H, Choi H, Guma S, Phan L, Chou P, Su C, Zhang F, Chen J, Yang T, Yeung S, Lee M "Aurora B kinase phosphorylates and instigates degradation of p53." Proceedings of the National Academy of Sciences of the United States of America(2012): E1513-22
- 68. Marxer M, Ma H, Man W, Poon R "p53 deficiency enhances mitotic arrest and slippage induced by pharmacological inhibition of Aurora kinases." Oncogene(2014): 3550-60
- 69. El-Deiry W "The role of p53 in chemosensitivity and radiosensitivity." Oncogene(2003): 7486-95
- 70. Miyasaka A, Oda K, Ikeda Y, Sone K, Fukuda T, Inaba K, Makii C, Enomoto A, Hosoya N, Tanikawa M, Uehara Y, Arimoto T, Kuramoto H, Wada-Hiraike O, Miyagawa K, Yano T, Kawana K, Osuga Y, Fujii T "PI3K/mTOR pathway inhibition overcomes radioresistance via suppression of the HIF1-α/VEGF pathway in endometrial cancer." Gynecologic oncology(2015): 174-80

