REPORTING

Report Date:	APR-08-2024
Receipt Date:	APR-03-2024
Collection Date:	APR-02-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Chih-Hsueh Chen
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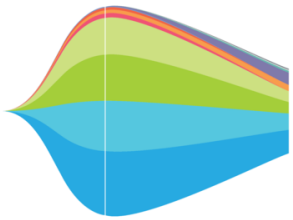
Address: F15., No 207-5 Sec 3, Beixin Rd, Xindian Dist, New Taipei City, 23143, Taiwan
Ph: +886 963 820 633 | Fax: N/A
Additional Recipient: N/A



Complete Tumor Response Map on page 3

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 5)	% cfDNA or Amplification
EGFR T790M	✓ Osimertinib ✗ Afatinib, Dacomitinib, Erlotinib, Erlotinib+ramucirumab, Gefitinib, Neratinib	Yes	2.1%
EGFR S768I	~ Osimertinib	Yes	3.0%
EGFR L747_T751del (Exon 19 deletion)	✓ Osimertinib	Yes	4.7%
TP53 P92fs	None	Yes	1.9%

Variants of Uncertain Clinical Significance
PDGFRA G898S (0.9%), *MET* K324N (0.2%), *AR* E804D (0.1%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
MTOR A849A (1.8%), *RHOA* R5R (0.1%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Comments

Reported by: JV4

Additional Biomarkers

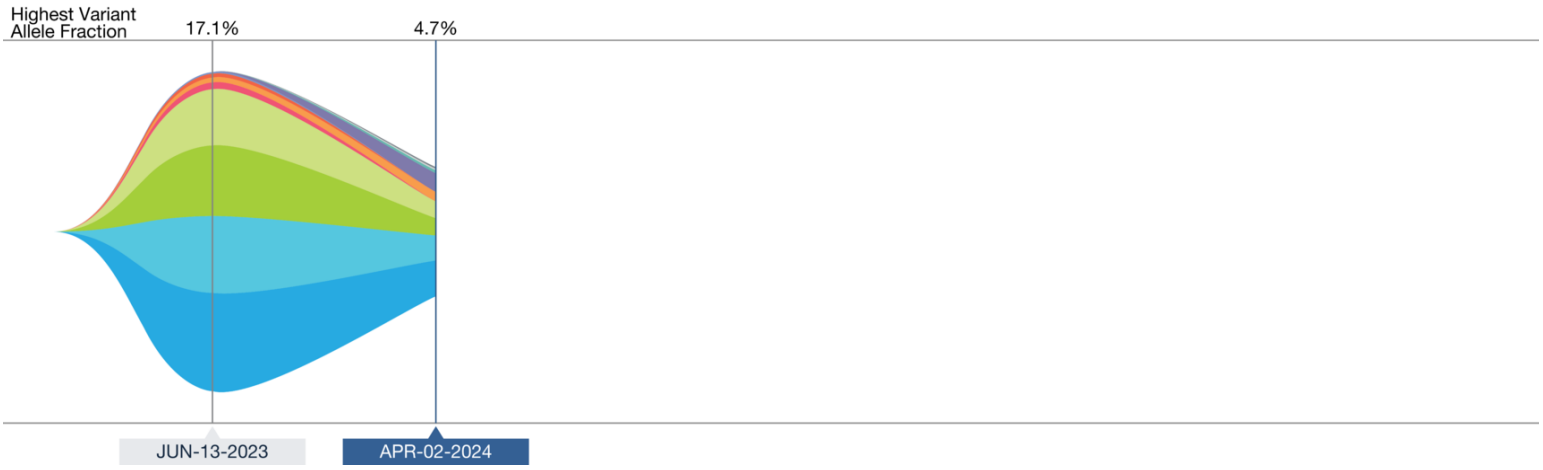
Biomarker	Additional Details
MSI-High	NOT DETECTED

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

EGFR(T790M and others)	*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	Alteration Trend	
EGFR L747_T751del (Exon 19 deletion)	4.7%	17.1% → 4.7%	
EGFR S768I	3.0%	12.6% → 3%	
EGFR T790M	2.1%	ND → 2.1%	
TP53 P92fs	1.9%	11.3% → 1.9%	
MTOR A849A	1.8%	8.5% → 1.8%	Synonymous Alteration §
PDGFRA G898S	0.9%	0.4% → 0.9%	Variants of Uncertain Clinical Significance §

Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend	
MET K324N	0.2%	ND → 0.2%	Variants of Uncertain Clinical Significance §
AR E804D	0.1%	ND → 0.1%	Variants of Uncertain Clinical Significance §
RHOA R5R	0.1%	ND → 0.1%	Synonymous Alteration §
TERT A651D	ND	0.6% → ND	
ATM R1619R	ND	0.1% → ND	
ATM Y2755C	ND	0.3% → ND	

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 A1008957 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
EGFR T790M	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
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Taipei City, Taiwan Tainan, Taiwan Taoyuan, Taiwan Taipei, Taiwan (3) Additional trial sites available
	NCT05526755 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study of 5 Years of Adjuvant Osimertinib in Completely Resected Epidermal Growth Factor Receptor Mutation (EGFRm) Non-small Cell Lung Carcinoma (NSCLC)	Phase 2	Kaohsiung City, Taiwan Kaohsiung, Taiwan Hualien, Taiwan Taipei, Taiwan (2) Additional trial sites available
	NCT05647122 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	First in Human Study of AZD9592 in Solid Tumors	Phase 1	Taipei City, Taiwan Taipei, Taiwan Taoyuan, Taiwan Taichung, Taiwan
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Yunlin, Taiwan Taipei City, Taiwan Kaohsiung, Taiwan (2) Taipei, Taiwan (2) Additional trial sites available
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			
EGFR S768I	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
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Taipei City, Taiwan Tainan, Taiwan Taoyuan, Taiwan Taipei, Taiwan (3) Additional trial sites available
	NCT05663866 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Premedication to Reduce Amivantamab Associated Infusion Related Reactions	Phase 2	ChangHua, Taiwan Kaohsiung, Taiwan Taipei City, Taiwan Tainan City, Taiwan Additional trial sites available
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Yunlin, Taiwan Taipei City, Taiwan Kaohsiung, Taiwan (2) Taipei, Taiwan (2) Additional trial sites available
	NCT06120140 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib	Phase 2	Taipei, Taiwan Taoyuan City, Taiwan Hsin Chu, Taiwan
	Visit **portal.guardanthealth.com** for trials not within the same state as the physician's office			

Alteration	Trial ID / Contact	Title	Phase	Site(s)
EGFR L747_T751del	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
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Taipei City, Taiwan Tainan, Taiwan Taoyuan, Taiwan Taipei, Taiwan (3) Additional trial sites available
	NCT05663866 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Premedication to Reduce Amivantamab Associated Infusion Related Reactions	Phase 2	ChangHua, Taiwan Kaohsiung, Taiwan Taipei City, Taiwan Tainan City, Taiwan Additional trial sites available
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Yunlin, Taiwan Taipei City, Taiwan Kaohsiung, Taiwan (2) Taipei, Taiwan (2) Additional trial sites available
	NCT06120140 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib	Phase 2	Taipei, Taiwan Taoyuan City, Taiwan Hsin Chu, Taiwan
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 P92fs	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

Somatic Alterations Not Detected (ND): Somatic alterations may be present that are below the limit of detection of this test. Certain sample or variant characteristics may result in reduced analytic sensitivity. The absence of detectable somatic alterations in circulating cell-free DNA does not preclude the presence of somatic alterations in the tumor.

Variants of Uncertain Clinical Significance: The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

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

Deletion (Del): The following alteration was detected in this patient: *EGFR* L747_T751del; *TP53* P92fs. 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.

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 A1008957 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 T790M	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)
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Louisville, KY; Fort Belvoir, VA; Newark, DE; Chicago, IL; Orange, CA; Morristown, NJ; San Francisco, CA; Los Angeles, CA; Houston, TX; Frederick, MD; Atlanta, GA; Grand Junction, CO; Lexington, KY; Anchorage, AK; NY (6); Argentina (8); Singapore (2); Romania (5); United Kingdom (7); Malaysia (4); Spain (5); Canada (3); Vietnam (3); Turkey (5); China (23); Taiwan (8); Poland (4); Brazil (7); Italy (10); Germany (7)
	NCT05401110 Clinical Trial Recruitment Navigator, cancer.trial.info@cshs.org,310-423-2133	Study of Osimertinib With Carotuximab in Advanced, EGFR-mutated Non-Small Cell Lung Cancer	Phase 1	CA (5)
	NCT05469022 In Ae Kim, MD. PhD.,20180618@kuh.ac.kr,+821035438353	Neoadjuvant Lazertinib Therapy in EGFR-Mutation Positive Lung Adenocarcinoma Detected by BALF Liquid Biopsy	Phase 2	Korea, Republic of
	NCT05507606 See https://clinicaltrials.gov/ct2/show/NCT05507606	Study of Osimertinib+Bevacizumab+Chemotherapy for EGFR+ Advanced Non-Small Cell Lung Cancer With Concurrent Mutations	Phase 2	China
	NCT05526755 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study of 5 Years of Adjuvant Osimertinib in Completely Resected Epidermal Growth Factor Receptor Mutation (EGFRm) Non-small Cell Lung Carcinoma (NSCLC)	Phase 2	Yuma, AZ; Rockville, MD; Las Vegas, NV; Santa Rosa, CA; White Plains, NY; Singapore; Hong Kong (2); Philippines (4); Taiwan (6); Korea, Republic of (15); United Kingdom (3); Italy (13); Malaysia (4); Thailand (2); Spain (8)
	NCT05647122 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	First in Human Study of AZD9592 in Solid Tumors	Phase 1	Providence, RI; Houston, TX; Duarte, CA; Mineola, NY; Milford, MA; Philadelphia, PA; Irvine, CA; Baltimore, MD; Fairfax, VA; North Haven, CT; New York, NY (3); Malaysia; Canada (2); Japan (2); China (4); Taiwan (4); Korea, Republic of (4); Italy (4); France (2); Australia (2); Spain (3)
	NCT05686434 chen chen,chen_checn@tmu.edu.cn, 13920761627	Osimertinib Therapy After Resection in High-risk Stage I EGFRm NSCLC (OSTAR)	Phase 2	China
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Canada (3); Singapore (3); Hong Kong (3); Taiwan (9); Korea, Republic of (7); Malaysia (6); Thailand (5)
	NCT06195189 Li Li, BA,tracy.li_2010@hotmail.com,	Sunvozertinib Combined With Chemotherapy for EGFRm After EGFR-TKI Treatment Failure#	Phase 1 /Phase 2	China

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	113880343287 x+86	Phase I/II		
EGFR S768I	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)
	NCT04197934 Clinical Trials Referral Office, mayocliniccancerstudies@mayo.edu,855-776-0015	WSD0922-FU for the Treatment of Glioblastoma, Anaplastic Astrocytoma, or Non-small Cell Lung Cancer With Central Nervous System Metastases	Phase 1	Rochester, MN; Scottsdale, AZ; Jacksonville, FL
	NCT05068024 Jo-Han Wang, Project Manager,jo-han.wang@wuxiapptec.com,+1-647-649-2850	A Study of FWD1509 in Adults With Non-Small Cell Lung Cancer	Phase 1 /Phase 2	Houston, TX; Canton, OH
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Louisville, KY; Fort Belvoir, VA; Newark, DE; Chicago, IL; Orange, CA; Morristown, NJ; San Francisco, CA; Los Angeles, CA; Houston, TX; Frederick, MD; Atlanta, GA; Grand Junction, CO; Lexington, KY; Anchorage, AK; NY (6); Argentina (8); Singapore (2); Romania (5); United Kingdom (7); Malaysia (4); Spain (5); Canada (3); Vietnam (3); Turkey (5); China (23); Taiwan (8); Poland (4); Brazil (7); Italy (10); Germany (7)
	NCT05326425 Jin Hyoung Kang,oncologykang@naver.com,82-2-2258-6043	Lazertinib in Patients With NSCLC With Asymptomatic or Mild Symptomatic Brain Metastases After Failure of EGFR TKI.	Phase 2	Korea, Republic of (6)
	NCT05469022 In Ae Kim, MD. PhD.,20180618@kuh.ac.kr,+821035438353	Neoadjuvant Lazertinib Therapy in EGFR-Mutation Positive Lung Adenocarcinoma Detected by BALF Liquid Biopsy	Phase 2	Korea, Republic of
	NCT05663866 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Premedication to Reduce Amivantamab Associated Infusion Related Reactions	Phase 2	Renton, WA; Fountain Valley, CA; Fairfax, VA; Taiwan (7); Korea, Republic of (6); France (6); Spain (14)
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Canada (3); Singapore (3); Hong Kong (3); Taiwan (9); Korea, Republic of (7); Malaysia (6); Thailand (5)
	NCT06120140 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib	Phase 2	Hinsdale, IL; Westbury, NY; W. Salem, WI; Reno, NV; Flemington, NJ; CA (5); Argentina; Turkey; China (3); Taiwan (3); Korea, Republic of (2); Malaysia (4); Spain (2)
	NCT06195189 Li Li, BA,tracy.li_2010@hotmail.com, 113880343287 x+86	Sunvozertinib Combined With Chemotherapy for EGFRm After EGFR-TKI Treatment Failure# Phase I/II	Phase 1 /Phase 2	China
EGFR L747_T751del	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);

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
				Korea, Republic of (4); Italy (5); France (7); Germany (8); Spain (8)
	NCT05120349 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Global Study to Assess the Effects of Osimertinib in Participants With EGFRm Stage IA2-IA3 NSCLC Following Complete Tumour Resection	Phase 3	Louisville, KY; Fort Belvoir, VA; Newark, DE; Chicago, IL; Orange, CA; Morristown, NJ; San Francisco, CA; Los Angeles, CA; Houston, TX; Frederick, MD; Atlanta, GA; Grand Junction, CO; Lexington, KY; Anchorage, AK; NY (6); Argentina (8); Singapore (2); Romania (5); United Kingdom (7); Malaysia (4); Spain (5); Canada (3); Vietnam (3); Turkey (5); China (23); Taiwan (8); Poland (4); Brazil (7); Italy (10); Germany (7)
	NCT05326425 Jin Hyoung Kang,oncologykang@naver.com,82-2-2258-6043	Lazertinib in Patients With NSCLC With Asymptomatic or Mild Symptomatic Brain Metastases After Failure of EGFR TKI.	Phase 2	Korea, Republic of (6)
	NCT05469022 In Ae Kim, MD. PhD.,20180618@kuh.ac.kr,+821035438353	Neoadjuvant Lazertinib Therapy in EGFR-Mutation Positive Lung Adenocarcinoma Detected by BALF Liquid Biopsy	Phase 2	Korea, Republic of
	NCT05663866 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Premedication to Reduce Amivantamab Associated Infusion Related Reactions	Phase 2	Renton, WA; Fountain Valley, CA; Fairfax, VA; Taiwan (7); Korea, Republic of (6); France (6); Spain (14)
	NCT05801029 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	A Study to Investigate Safety and Efficacy of Osimertinib and Amivantamab in Participants With Non-small Cell Lung Cancer With Common Epidermal Growth Factor Receptor Mutations	Phase 2	Canada (3); Singapore (3); Hong Kong (3); Taiwan (9); Korea, Republic of (7); Malaysia (6); Thailand (5)
	NCT05826483 Zhou Chengzhi, MD,doctorzcz@163.com,13560351186	Almonertinib in the First-line Treatment of Patients of NSCLC With Poor Performance Status	Phase 1	China
	NCT06043973 Degan Lu, Professor,deganlu@126.com,18753157623	Almonertinib Combined With Anlotinib as First-line Treatment for Advanced Non-small Cell Lung Cance	Phase 3	China
	NCT06120140 Study Contact,Participate-In-This-Study@its.jnj.com,844-434-4210	Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib	Phase 2	Hinsdale, IL; Westbury, NY; W. Salem, WI; Reno, NV; Flemington, NJ; CA (5); Argentina; Turkey; China (3); Taiwan (3); Korea, Republic of (2); Malaysia (4); Spain (2)
	NCT06195189 Li Li, BA,tracy.li_2010@hotmail.com,113880343287 x+86	Sunvozertinib Combined With Chemotherapy for EGFRm After EGFR-TKI Treatment Failure# Phase I/II	Phase 1 /Phase 2	China
TP53 P92fs	NCT02769962 Danielle F Pinkiert, R.N.,danielle.pinkiert@nih.gov,(240) 858-7566	Trial of EP0057, a Nanoparticle Camptothecin With Olaparib in People With Relapsed /Refractory Small Cell Lung Cancer	Phase 1 /Phase 2	Bethesda, MD
	NCT03968653 Debiopharm International S.A, clinicaltrials@debiopharm.com,+41 21 321 01 11	Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors	Phase 1	Spain; Netherlands (3)
	NCT04768868 Jian Wang,Jian.wang@impacttherapeutics.com,+86 18613056501	The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients With Advanced Solid Tumors	Phase 1	Louisville, KY; Boston, MA; Atlanta, GA; Dallas, TX; Fairway, KS; San Antonio, TX; China (4); Taiwan (5)
	NCT04869475 Min Shi, MD & Ph. D,sm11998@rjh.com.	Arsenic Trioxide in Refractory Solid Tumors With Rescuable p53 Mutation	Phase 2	China

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
	cn,+86-21-64370045			
	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)
	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

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
EGFR S768I T790M L747_T751del (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))
	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)
	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))
	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-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 (L858R, T790M, exon 19 deletion, exon 20 insertion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	ERAS-601		Shp-2 inhibitor.	Phase 2 (Solid Tumor)
	ET0038		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	Furmonertinib		Third generation mutation-specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	FWD1509		Egfr/Her2 kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	H002		Fourth generation Egfr inhibitor targeting exon 19del/L858R, T790M, and C797S mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	HBI-2376		Shp-2 inhibitor.	Phase 1 (Solid Tumor)
	Hemay022		Egfr tyrosine kinase inhibitor.	Phase 1 (Breast carcinoma (HER2+))
	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	Phase 2 (Non-small cell lung carcinoma (NSCLC))

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
			Egfr tyrosine kinase inhibitor.	
	Lifirafenib		Dual Braf/Egfr inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	MCLA-129		Anti-EGFR/c-Met bispecific antibody.	Phase 2 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Gastric carcinoma, Head and neck squamous cell carcinoma (HNSCC), Esophageal squamous cell carcinoma)
	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)
	Modotuximab		Anti-EGFR antibody.	Phase 1 (Gastric carcinoma, Colorectal carcinoma (CRC))
	Naquotinib		EGFR mutant-specific inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Solid Tumor)
	NX-019		Egfr inhibitor.	Phase 1 (Solid Tumor)
	Osimertinib	Tagrisso	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)
	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.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	TAVO412		Anti-c-Met/anti-EGFR/anti-VEGF trispecific antibody.	Phase 1 (Solid Tumor)
	Varlitinib		Egfr/Her2 kinase inhibitor.	Phase 2 (Gastric carcinoma, Hepatocellular carcinoma (HCC), Pancreatic carcinoma, Cholangiocarcinoma)
	ZN-e4		Egfr T790M inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
TP53 P92fs	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

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				(CMML), 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))
EGFR T790M L747_T751del (Exon 19 deletion)	Aumolertinib		Egfr T790M inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC))
	CM93		Third generation mutation-specific (T790M, L858R, exon 19 deletion) Egfr tyrosine kinase inhibitor.	Phase 1 (Glioblastoma)
	Nazartinib		Third generation EGFR mutant-specific (T790M, L858R, exon 19 deletion) tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	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

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
				(NSCLC))
	PF-06747775		Egfr T790M-specific inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC))
EGFR S768I L747_T751del (Exon 19 deletion)	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)
	BLU-701		Fourth generation Egfr inhibitor targeting exon 19del, L858R, and C797X resistance mutations.	Phase 2 (Non-small cell lung carcinoma (NSCLC))
	Icotinib	Conmana	Egfr inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC)) Phase 2 (Esophageal carcinoma)
	WSD0922-FU		Blood-brain barrier penetrable EGFR /EGFRvIII inhibitor.	Phase 1 (Non-small cell lung carcinoma (NSCLC)) Phase 1 (Glioblastoma, Anaplastic astrocytoma)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
EGFR T790M	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 EGFR T790M mutation has typically been reported as a secondary resistance mutation to the Egfr inhibitors erlotinib, gefitinib and afatinib, but has also been reported as a rare germline variant in de novo non-small cell lung cancer, particularly in lung adenocarcinoma. [2,3]. Several studies have reported the presence of the T790M mutation in the germline in 0-1% of NSCLC cases, although one study did detect this mutation in 50% (5/10) of cases; in addition, T790M was associated with a 31% risk of lung cancer in never smokers in one study. [4-7].	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. [8-11]. The EGFR T790M mutation reported here has been described as a "gatekeeper" mutation that confers resistance to the tyrosine kinase inhibitors erlotinib and gefitinib. [12,13]. Studies have also reported the emergence of EGFR T790M upon resistance to afatinib monotherapy. [3,15]. Third generation irreversible Egfr TKIs that target the EGFR T790M mutation have shown efficacy in T790M-mutant NSCLC and are under clinical investigation. Osimertinib has received approval by the FDA, EMA, and PMDA for the treatment of EGFR T790M-mutant metastatic NSCLC as well as EGFR-mutated NSCLC that has not been exposed to previous TKI treatment. [16-21]. However, this EGFR mutation has been associated with resistance to erlotinib; thus, the relevance of ramucirumab plus erlotinib is uncertain.	A Phase 2 study has reported no clinical responses in 12 non-small cell lung cancer (NSCLC) patients who harbored EGFR T790M and were treated with neratinib. [22]. In addition, Phase 2 studies have reported limited clinical activity with dacomitinib in NSCLC patients who harbored EGFR T790M, with 2/32 patients having shown a partial response. [23-25]. 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 the gene MET. [26-28]. 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. [29-32].
EGFR S768I	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. [8-11]. 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. [8,11,16,33-37]. Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations. [3]. The combination of erlotinib and ramucirumab as well as osimertinib plus platinum-based chemotherapy have been FDA-approved for the treatment of metastatic NSCLC patients with	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. [26-28,49]. 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. [17-21]. 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. [29-32]. 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. [50-52].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		tumors harboring an EGFR exon 19 deletion or the exon 21 L858R mutation. [38-40]. Amivantamab has been approved by the FDA for NSCLC patients with EGFR exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy and as frontline therapy in combination with carboplatin and pemetrexed. The accelerated FDA approval of mobocertinib for NSCLC patients with EGFR exon 20 insertions has been withdrawn due to lack of progression-free survival benefit in the confirmatory Phase 3 trial. [41-44]. 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. [8,11,16,33,38,45]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors. [46]. However, EGFR T790M, also detected in this tumor, has been associated with resistance to the Egfr tyrosine kinase inhibitors erlotinib, gefitinib, afatinib, and dacomitinib. [3,12,15,15-25,27,47].	
EGFR L747_T751del	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. [8-11]. 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. [8,11,16,33-37]. Afatinib has additionally been FDA-approved for the treatment of NSCLC with S768I, L861Q, and/or G719X mutations. [3]. The combination of erlotinib and ramucirumab as well as osimertinib plus platinum-based chemotherapy have been FDA-approved for the treatment of metastatic NSCLC patients with tumors harboring an EGFR exon 19 deletion or the exon 21 L858R	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. [26-28,49]. 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. [17-21]. 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. [29-32]. 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. [50-52].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
		mutation. [38-40]. Amivantamab has been approved by the FDA for NSCLC patients with EGFR exon 20 insertions, whose disease has progressed on or after platinum-based chemotherapy and as frontline therapy in combination with carboplatin and pemetrexed. The accelerated FDA approval of mobocertinib for NSCLC patients with EGFR exon 20 insertions has been withdrawn due to lack of progression-free survival benefit in the confirmatory Phase 3 trial. [41-44]. 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. [8,11,16,33,38,45]. Less common activating EGFR mutations have variable sensitivity to EGFR tyrosine kinase inhibitors. [46]. However, one of the EGFR mutations in the report has been associated with resistance to erlotinib; thus, the relevance of ramucirumab plus erlotinib is uncertain. However, EGFR T790M, also detected in this tumor, has been associated with resistance to the Egfr tyrosine kinase inhibitors erlotinib, gefitinib, afatinib, and dacomitinib. [3,12,15,15-25,27,47].	
TP53 P92fs	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers. [53]. 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. [54-56]. 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. [57-61]. TP53 alterations are believed to be early events in NSCLC, preceding lymph node metastasis. [62]. 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	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. [73-75]. 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. [76-78]. 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. [79-84].	Mutations in TP53 may increase resistance to ionizing radiation therapy. [85,86].

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
	with disease stage and higher grade tumors. [63-66]. TP53 mutation has been associated with PD-L1 expression and T-cell infiltration in lung adenocarcinoma samples. [67-71]. TP53 mutations have been significantly associated with the development of distant metastases after diagnosis in early-stage NSCLC in a cohort of 759 patients. [72].		

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