



Sample Information

Patient Name: 吳燦楠
Gender: Male
ID No.: J121107852
History No.: 46274242
Age: 62

Ordering Doctor: DOC3054C 陳奕廷
Ordering REQ.: 0CBMYCP
Signing in Date: 2022/10/27

Path No.: S111-97953
MP No.: F22112
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: C111-37091
Percentage of tumor cells: 60%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page
Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)	2
Biomarker Descriptions	2
Relevant Therapy Summary	4
Relevant Therapy Details	6
Clinical Trials Summary	26
Alert Details	27

Report Highlights
3 Relevant Biomarkers
17 Therapies Available
14 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	EGFR p.(L858R) c.2573T>G, EGFR p.(E709G) c.2126A>G	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	EGFR p.(L858R) c.2573T>G epidermal growth factor receptor Allele Frequency: 20.70%	afatinib ^{1, 2} bevacizumab* + erlotinib ² dacomitinib ^{1, 2} erlotinib ^{1, 2} erlotinib + ramucirumab ^{1, 2} gefitinib* ^{1, 2} osimertinib ^{1, 2} atezolizumab + bevacizumab + chemotherapy bevacizumab + gefitinib gefitinib + chemotherapy osimertinib + chemotherapy	None	13
IIC	PIK3CA p.(H1047R) c.3140A>G phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 17.10%	None	alpelisib + hormone therapy ^{1, 2}	1
IA	EGFR p.(E709G) c.2126A>G epidermal growth factor receptor Allele Frequency: 21.26%	afatinib dacomitinib erlotinib gefitinib osimertinib	None	6

Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO

Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

* Includes biosimilars

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
PIK3CA	p.(H1047R)	c.3140A>G	COSM775	chr3:178952085	17.10%	NM_006218.4	missense	2000
EGFR	p.(E709G)	c.2126A>G	COSM13009	chr7:55241678	21.26%	NM_005228.5	missense	1990
EGFR	p.(L858R)	c.2573T>G	COSM6224	chr7:55259515	20.70%	NM_005228.5	missense	1995

Biomarker Descriptions

EGFR (epidermal growth factor receptor)

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the ERBB/human epidermal growth factor receptor (HER) family. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4¹. EGFR ligand induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways. Activation of these pathways promote cell proliferation, differentiation, and survival^{2,3}.

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations^{4,5,6,7}. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21⁸. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer. A second group of less prevalent activating mutations include E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{9,10,11,12}. EGFR activating mutations in lung cancer

Biomarker Descriptions (continued)

tend to be mutually exclusive to KRAS activating mutations¹³. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V and are primarily observed in glioblastoma^{8,14}. Amplification of EGFR is observed in several cancer types including 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma^{5,6,7,14,15}. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma^{16,17,18}.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib¹⁹ (2004) and gefitinib²⁰ (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations. Second-generation TKIs afatinib²¹ (2013) and dacomitinib²² (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies^{23,24,25,26}. However, in 2021, the irreversible tyrosine kinase inhibitor, mobocertinib²⁷ was FDA approved for the treatment of NSCLC with EGFR exon 20 insertion mutations. Additionally, in 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)²⁸ and sunvozertinib²⁹, for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance³⁰. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases⁸. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib³¹ (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance. In this case, resistance is associated with the C797S mutation and occurs in 22-44% of cases³⁰. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa³². T790M and C797S can occur in either cis or trans allelic orientation³². If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs³². If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone^{32,33}. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs³². Fourth-generation TKIs are in development to overcome acquired C797S and T790M resistance mutations after osimertinib treatment. EGFR targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, amivantamab³⁴, targeting EGFR and MET was approved (2021) NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy quaratusugene ozeplasmid³⁵ in combination with osimertinib received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. BDTX-189³⁶ was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme³⁷. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases^{38,39}. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively³⁸. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction^{40,41}. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism^{40,41,42,43}. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability^{44,45,46}.

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers^{6,7}. Activating mutations in PIK3CA commonly cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase (codon H1047) domains, each having distinct mechanisms of activation^{47,48,49}. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers^{6,7}.

Potential relevance: The PI3K inhibitor, alpelisib⁵⁰, is FDA approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer, the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated

Biomarker Descriptions (continued)

tumors and 20% (2/20) in PIK3CA wild-type tumors⁵¹. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations⁵¹. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations⁵². Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers^{53,54}.

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ⓘ In this cancer type and other cancer types ✕ No evidence

EGFR p.(L858R) c.2573T>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	●	●	●	●	● (III)
afatinib	●	●	●	●	● (II)
dacomitinib	●	●	●	●	✕
erlotinib	●	●	●	●	✕
erlotinib + ramucirumab	●	●	●	●	✕
gefitinib	●	●	●	●	✕
bevacizumab + erlotinib	✕	●	●	●	✕
osimertinib + chemotherapy	✕	●	✕	✕	✕
bevacizumab (Allergan) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Fujifilm Kyowa Kirin Biologics) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Mabxience) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Pfizer) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Samsung Bioepis) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Stada) + erlotinib	✕	✕	●	✕	✕
gefitinib (Mylan)	✕	✕	●	✕	✕
atezolizumab + bevacizumab + carboplatin + paclitaxel	✕	✕	✕	●	✕
bevacizumab + gefitinib	✕	✕	✕	●	✕
gefitinib + carboplatin + pemetrexed	✕	✕	✕	●	✕
amivantamab, lazertinib, chemotherapy	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
patritumab deruxtecan	✕	✕	✕	✕	● (III)
atezolizumab, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

● In this cancer type
 ○ In other cancer type
 ● In this cancer type and other cancer types
 ✕ No evidence

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
durvalumab, tremelimumab, chemotherapy	✕	✕	✕	✕	● (II)
BLU-945	✕	✕	✕	✕	● (I/II)
sunvozertinib	✕	✕	✕	✕	● (I/II)
amivantamab, lazertinib	✕	✕	✕	✕	● (I)
lazertinib, amivantamab	✕	✕	✕	✕	● (I)
telisotuzumab vedotin, osimertinib	✕	✕	✕	✕	● (I)
TNO-155, nazartinib	✕	✕	✕	✕	● (I)

PIK3CA p.(H1047R) c.3140A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	○	○	✕
inavolisib	✕	✕	✕	✕	● (II)

EGFR p.(E709G) c.2126A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
afatinib	✕	●	✕	●	✕
gefitinib	✕	●	✕	●	✕
dacomitinib	✕	✕	✕	●	✕
erlotinib	✕	✕	✕	●	✕
osimertinib	✕	✕	✕	●	✕
atezolizumab, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
BLU-945	✕	✕	✕	✕	● (I/II)
sunvozertinib	✕	✕	✕	✕	● (I/II)
amivantamab	✕	✕	✕	✕	● (I)
lazertinib, amivantamab, chemotherapy	✕	✕	✕	✕	● (I)
TNO-155, nazartinib	✕	✕	✕	✕	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Details

Current FDA Information

☒ In this cancer type ☐ In other cancer type ☐ In this cancer type and other cancer types

FDA information is current as of 2022-08-17. For the most up-to-date information, search www.fda.gov.

EGFR p.(L858R) c.2573T>G

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-04-07

Variant class: EGFR L858R mutation

Indications and usage:

GILOTRIF® is a kinase inhibitor indicated for:

- First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.

Limitations of Use: Safety and efficacy of GILOTRIF® were not established in patients whose tumors have resistant EGFR mutations

- Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2020-12-18

Variant class: EGFR L858R mutation

Indications and usage:

VIZIMPRO® is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf

EGFR p.(L858R) c.2573T>G (continued)

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2016-10-18

Variant class: EGFR L858R mutation

Indications and usage:

TARCEVA® is a kinase inhibitor indicated for:

- The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

Limitations of Use:

- Safety and efficacy of TARCEVA® have not been established in patients with NSCLC whose tumors have other EGFR mutations.
- TARCEVA® is not recommended for use in combination with platinum-based chemotherapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-03-22

Variant class: EGFR L858R mutation

Indications and usage:

CYRAMZA® is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist indicated:

- as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- in combination with erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.
- in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA®.
- in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- as a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125477s042lbl.pdf

EGFR p.(L858R) c.2573T>G (continued)

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-05-05

Variant class: EGFR L858R mutation

Indications and usage:

IRESSA® is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of IRESSA® have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-01-19

Variant class: EGFR L858R mutation

Indications and usage:

TAGRISSO® is a kinase inhibitor indicated for:

- as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208065s025lbl.pdf

PIK3CA p.(H1047R) c.3140A>G

○ alpelisib + fulvestrant

Cancer type: Breast Cancer

Label as of: 2022-05-04

Variant class: PIK3CA H1047R mutation

Other criteria: ERBB2 negative, Hormone receptor positive

Indications and usage:

PIQRAY® is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212526s006lbl.pdf

Current NCCN Information

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types

NCCN information is current as of 2022-08-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

EGFR p.(L858R) c.2573T>G

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

EGFR p.(L858R) c.2573T>G (continued)**● osimertinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 1**Population segment (Line of therapy):**

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● afatinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● bevacizumab + erlotinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Non-squamous Cell; Advanced, Metastatic (First-line therapy); Other recommended intervention
- Non-squamous Cell; Advanced, Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● dacomitinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

EGFR p.(L858R) c.2573T>G (continued)**● erlotinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● erlotinib + ramucirumab****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Squamous Cell, Not otherwise specified (NOS), Adenocarcinoma, Large Cell; Advanced, Metastatic (First-line therapy); Other recommended intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● gefitinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● osimertinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Brain Metastases, Leptomeningeal Metastases, Spine Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

EGFR p.(L858R) c.2573T>G (continued)**● osimertinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Stage IB , Stage IIA, Stage IIB, Stage IIIA, Stage IIIB; Resected (Adjuvant therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Leptomeningeal Metastases, Progression (Subsequent therapy); Consider

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● osimertinib + chemotherapy****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Stage IB , Stage IIA, Stage IIB, Stage IIIA; Resected (Adjuvant therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**● erlotinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR L858R mutation**NCCN Recommendation category:** 2B**Population segment (Line of therapy):**

- Leptomeningeal Metastases, Spine Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]**● afatinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFRi sensitizing mutation**NCCN Recommendation category:** 2B**Population segment (Line of therapy):**

- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

EGFR p.(L858R) c.2573T>G (continued)**● gefitinib**

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

PIK3CA p.(H1047R) c.3140A>G**○ alpelisib + fulvestrant**

Cancer type: Breast Cancer

Variant class: PIK3CA activating mutation

Other criteria: ERBB2 negative, Hormone receptor positive

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

EGFR p.(E709G) c.2126A>G**● afatinib**

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

Current EMA Information

☒ In this cancer type ☐ In other cancer type ☒ In this cancer type and other cancer types

EMA information is current as of 2022-08-17. For the most up-to-date information, search www.ema.europa.eu/ema.

EGFR p.(L858R) c.2573T>G

☒ afatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-04-21

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/giotrif-epar-product-information_en.pdf

☒ bevacizumab (Allergan) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-14

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/mvasi-epar-product-information_en.pdf

☒ bevacizumab (Fujifilm Kyowa Kirin Biologics) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-06-23

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/equidacent-epar-product-information_en.pdf

☒ bevacizumab (Mabxience) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-06

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/alymsys-epar-product-information_en.pdf

☒ bevacizumab (Pfizer) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-26

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/zirabev-epar-product-information_en.pdf

☒ bevacizumab (Samsung Bioepis) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-21

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/onbevzi-epar-product-information_en.pdf

EGFR p.(L858R) c.2573T>G (continued)**● bevacizumab (Samsung Bioepis) + erlotinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-21

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/aybintio-epar-product-information_en.pdf**● bevacizumab (Stada) + erlotinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-05

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/oyavas-epar-product-information_en.pdf**● bevacizumab + erlotinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-04-11

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/abevmy-epar-product-information_en.pdf**● bevacizumab + erlotinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-01

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf**● dacomitinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-07-21

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vizimpro-epar-product-information_en.pdf**● erlotinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-08-18

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/tarceva-epar-product-information_en.pdf

EGFR p.(L858R) c.2573T>G (continued)**● erlotinib + ramucirumab**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-08-04

Variant class: EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

Reference:

https://www.ema.europa.eu/en/documents/product-information/cyramza-epar-product-information_en.pdf**● gefitinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-05

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/iressa-epar-product-information_en.pdf**● gefitinib (Mylan)**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-06-16

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/gefitinib-mylan-epar-product-information_en.pdf**● osimertinib**

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-04-07

Variant class: EGFR L858R mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf**PIK3CA p.(H1047R) c.3140A>G****○ alpelisib + fulvestrant**

Cancer type: Breast Cancer

Label as of: 2021-10-11

Variant class: PIK3CA H1047R mutation

Other criteria: ERBB2 negative, Hormone receptor positive

Reference:

https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf

Current ESMO Information

- ☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types

ESMO information is current as of 2022-08-01. For the most up-to-date information, search www.esmo.org.

EGFR p.(L858R) c.2573T>G

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● bevacizumab + gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(L858R) c.2573T>G (continued)

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(L858R) c.2573T>G (continued)

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IB , Stage IIA, Stage IIB, Stage IIIA; Resected (Adjuvant therapy); ESMO-MCBS v1.1 score: A

Reference: ESMO Clinical Practice Guidelines - ESMO-Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer [Ann Oncol (2017) 28 (suppl 4): iv1–iv21. (eUpdate: 01 September 2021, 04 May 2020)]

● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● bevacizumab + gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(L858R) c.2573T>G (continued)

● gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

- Advanced (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● atezolizumab + bevacizumab + carboplatin + paclitaxel

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Non-squamous Cell; Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 3
- Metastatic (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(L858R) c.2573T>G (continued)

● bevacizumab + gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(L858R) c.2573T>G (continued)

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

- Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(L858R) c.2573T>G (continued)

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

- Advanced (First-line therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: III / B

Population segment (Line of therapy):

- Non-squamous Cell (Maintenance therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

PIK3CA p.(H1047R) c.3140A>G

○ alpelisib + fulvestrant

Cancer type: Breast Cancer

Variant class: PIK3CA exon 20 mutation

Other criteria: ERBB2 negative, ER positive

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

- Luminal A; Advanced, Metastatic (Second-line therapy); ESMO-MCBS v1.1 score: 2

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Breast Cancer [Ann Oncol (2021) VOLUME 32, ISSUE 12, P1475-1495, DECEMBER 01, 2021; DOI:<https://doi.org/10.1016/j.annonc.2021.09.019>]

EGFR p.(E709G) c.2126A>G

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

EGFR p.(E709G) c.2126A>G (continued)

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Advanced (First-line therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

- Advanced (First-line therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

ESMO Level of Evidence/Grade of Recommendation: III / B

Population segment (Line of therapy):

- Non-squamous Cell (Maintenance therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

Clinical Trials in Taiwan region:

Clinical Trials Summary

EGFR p.(L858R) c.2573T>G

NCT ID	Title	Phase
NCT04988295	A Phase III, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure	III
NCT05120349	A Phase III, Double-blind, Randomised, Placebo-Controlled, International Study to Assess the Efficacy and Safety of Adjuvant Osimertinib Versus Placebo in Participants With EGFR Mutation-positive Stage IA2-IA3 Non-small Cell Lung Cancer, Following Complete Tumour Resection	III
NCT04351555	A Phase III, Randomised, Controlled, Multi-center, 3-Arm Study of Neoadjuvant Osimertinib as Monotherapy or in Combination With Chemotherapy Versus Standard of Care Chemotherapy Alone for the Treatment of Patients With Epidermal Growth Factor Receptor Mutation Positive, Resectable Non-small Cell Lung Cancer	III
NCT05338970	A Phase III Clinical Trial of U3-1402 in Patients With EGFR Mutated Non Small Cell Lung Cancer	III
NCT05215548	A Phase II Study of Primary Tumor Resection for Stage IV Non-small-cell Lung Cancer Without Progression After First-line Epidermal Growth Factor Receptor-tyrosine Kinase Inhibitor	II
NCT04147351	A Phase II Study of Atezolizumab in Combination With Bevacizumab, Carboplatin or Cisplatin, and Pemetrexed for EGFR-mutant Metastatic Non-small Cell Lung Cancer Patients After Failure of EGFR Tyrosine Kinase Inhibitors.	II
NCT03994393	A Phase II Trial of Durvalumab (MEDI4736) and Tremelimumab With Chemotherapy in Metastatic EGFR Mutant Non-squamous Non-small Cell Lung Cancer (NSCLC) Following Progression on EGFR Tyrosine Kinase Inhibitors (TKIs)	II
NCT02609776	A Phase I, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer.	I
NCT04077463	An Open-label Phase I/Ib Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer	I
NCT02099058	A Multicenter, Phase I/Ib, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors	I
NCT04862780	A Phase I/II Study Targeting Acquired Resistance Mechanisms in Patients With EGFR Mutant Non-Small Cell Lung Cancer.	I/II
NCT03114319	An Open-label, Multi-center, Phase I, Dose Finding Study of Oral TNO155 in Adult Patients With Advanced Solid Tumors.	I
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation	I/II

PIK3CA p.(H1047R) c.3140A>G

NCT ID	Title	Phase
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II

Clinical Trials Summary (continued)

EGFR p.(E709G) c.2126A>G

NCT ID	Title	Phase
NCT02609776	A Phase I, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer.	I
NCT04147351	A Phase II Study of Atezolizumab in Combination With Bevacizumab, Carboplatin or Cisplatin, and Pemetrexed for EGFR-mutant Metastatic Non-small Cell Lung Cancer Patients After Failure of EGFR Tyrosine Kinase Inhibitors.	II
NCT04862780	A Phase I/II Study Targeting Acquired Resistance Mechanisms in Patients With EGFR Mutant Non-Small Cell Lung Cancer.	I/II
NCT03114319	An Open-label, Multi-center, Phase I, Dose Finding Study of Oral TNO155 in Adult Patients With Advanced Solid Tumors.	I
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation	I/II
NCT04077463	An Open-label Phase I/Ib Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer	I

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

FDA information is current as of 2022-08-17. For the most up-to-date information, search www.fda.gov.

EGFR p.(L858R) c.2573T>G

patritumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation

Supporting Statement:

The FDA has granted Breakthrough Therapy Designation to a potential first-in-class HER3 directed antibody-drug conjugate, patritumab deruxtecan, for metastatic or locally advanced, EGFR-mutant non-small cell lung cancer.

Reference:

<https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-status-to-patritumab-deruxtecan-for-egfr-metastatic-nsclc>

EGFR p.(L858R) c.2573T>G (continued)

osimertinib + quaratusugene ozeplasmid

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Supporting Statement:

The FDA has granted Fast Track Designation to the immunogene therapy, quaratusugene ozeplasmid, in combination with EGFR inhibitor osimertinib for the treatment of non-small cell lung cancer (NSCLC) with EFGR mutations that progressed after treatment with osimertinib alone.

Reference:

<https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>

EGFR p.(E709G) c.2126A>G

patritumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation

Supporting Statement:

The FDA has granted Breakthrough Therapy Designation to a potential first-in-class HER3 directed antibody-drug conjugate, patritumab deruxtecan, for metastatic or locally advanced, EGFR-mutant non-small cell lung cancer.

Reference:

<https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-status-to-patritumab-deruxtecan-for-egfr-metastatic-nsclc>

osimertinib + quaratusugene ozeplasmid

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation


Supporting Statement:


The FDA has granted Fast Track Designation to the immunogene therapy, quaratusugene ozeplasmid, in combination with EGFR inhibitor osimertinib for the treatment of non-small cell lung cancer (NSCLC) with EFGR mutations that progressed after treatment with osimertinib alone.

Reference:


<https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>


Current NCCN Information

 Contraindicated

 Not recommended

 Resistance

 Breakthrough

 Fast Track

NCCN information is current as of 2022-08-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

EGFR p.(L858R) c.2573T>G

atezolizumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

nivolumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

pembrolizumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

EGFR p.(E709G) c.2126A>G**— atezolizumab****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR mutation**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**— nivolumab****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR mutation**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]**— pembrolizumab****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR mutation**Summary:**

NCCN Guidelines® include the following supporting statement(s):

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

References

1. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985 Sep 6;229(4717):974-6. PMID: 2992089
2. Zhixiang. ErbB Receptors and Cancer. *Methods Mol. Biol.* 2017;1652:3-35. PMID: 28791631
3. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
4. Pines et al. Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. *FEBS Lett.* 2010 Jun 18;584(12):2699-706. PMID: 20388509
5. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
8. da et al. EGFR mutations and lung cancer. *Annu Rev Pathol.* 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
9. Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol. Cancer Ther.* 2013 Feb;12(2):220-9. PMID: 23371856
10. Kobayashi et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. *Clin Cancer Res.* 2015 Dec 1;21(23):5305-13. doi: 10.1158/1078-0432.CCR-15-1046. Epub 2015 Jul 23. PMID: 26206867
11. Yasuda et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med.* 2013 Dec 18;5(216):216ra177. PMID: 24353160
12. Chiu et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment Response in Advanced Lung Adenocarcinomas with G719X/L861Q/S768I Mutations. *J Thorac Oncol.* 2015 May;10(5):793-9. PMID: 25668120
13. Karachaliou et al. KRAS mutations in lung cancer. *Clin Lung Cancer.* 2013 May;14(3):205-14. PMID: 23122493
14. Brennan et al. The somatic genomic landscape of glioblastoma. *Cell.* 2013 Oct 10;155(2):462-77. PMID: 24120142
15. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015 Jan 29;517(7536):576-82. PMID: 25631445
16. Mitsudomi et al. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *FEBS J.* 2010 Jan;277(2):301-8. PMID: 19922469
17. Gazdar. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene.* 2009 Aug;28 Suppl 1:S24-31. PMID: 19680293
18. Gan et al. The EGFRvIII variant in glioblastoma multiforme. *J Clin Neurosci.* 2009 Jun;16(6):748-54. PMID: 19324552
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf
23. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]
24. Naidoo et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. *Cancer.* 2015 Sep 15;121(18):3212-3220. PMID: 26096453
25. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther.* 2019;4:5. PMID: 30854234
26. Yi et al. A comparison of epidermal growth factor receptor mutation testing methods in different tissue types in non-small cell lung cancer. *Int J Mol Med.* 2014 Aug;34(2):464-74. PMID: 24891042
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215310s000lbl.pdf
28. <https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncology>
29. <https://www.prnewswire.com/news-releases/fda-grants-breakthrough-therapy-designation-for-dizal-pharmaceuticals-dzd9008-in-patients-with-locally-advanced-or-metastatic-non-small-cell-lung-cancer-harboring-egfr-exon20-insertion-301469692.html>
30. Madic et al. EGFR C797S, EGFR T790M and EGFR sensitizing mutations in non-small cell lung cancer revealed by six-color crystal digital PCR. *Oncotarget.* 2018 Dec 21;9(100):37393-37406. PMID: 30647840

References (continued)

31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208065s025lbl.pdf
32. Niederst et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. *Clin. Cancer Res.* 2015 Sep 1;21(17):3924-33. PMID: 25964297
33. Wang et al. Lung Adenocarcinoma Harboring EGFR T790M and In Trans C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance. *J Thorac Oncol.* 2017 Nov;12(11):1723-1727. PMID: 28662863
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s001lbl.pdf
35. <https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>
36. <https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda>
37. Volinia et al. Molecular cloning, cDNA sequence, and chromosomal localization of the human phosphatidylinositol 3-kinase p110 alpha (PIK3CA) gene. *Genomics.* 1994 Dec;24(3):472-7. PMID: 7713498
38. Whale et al. Functional characterization of a novel somatic oncogenic mutation of PIK3CB. *Signal Transduct Target Ther.* 2017;2:17063. PMID: 29279775
39. Osaki et al. PI3K-Akt pathway: its functions and alterations in human cancer. *Apoptosis.* 2004 Nov;9(6):667-76. PMID: 15505410
40. Cantley. The phosphoinositide 3-kinase pathway. *Science.* 2002 May 31;296(5573):1655-7. PMID: 12040186
41. Fruman et al. The PI3K Pathway in Human Disease. *Cell.* 2017 Aug 10;170(4):605-635. PMID: 28802037
42. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat. Rev. Genet.* 2006 Aug;7(8):606-19. PMID: 16847462
43. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. *Nat. Rev. Mol. Cell Biol.* 2012 Feb 23;13(3):195-203. PMID: 22358332
44. Yuan et al. PI3K pathway alterations in cancer: variations on a theme. *Oncogene.* 2008 Sep 18;27(41):5497-510. PMID: 18794884
45. Liu et al. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat Rev Drug Discov.* 2009 Aug;8(8):627-44. PMID: 19644473
46. Hanahan et al. Hallmarks of cancer: the next generation. *Cell.* 2011 Mar 4;144(5):646-74. PMID: 21376230
47. Miled et al. Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit. *Science.* 2007 Jul 13;317(5835):239-42. PMID: 17626883
48. Burke et al. Synergy in activating class I PI3Ks. *Trends Biochem. Sci.* 2015 Feb;40(2):88-100. PMID: 25573003
49. Burke et al. Oncogenic mutations mimic and enhance dynamic events in the natural activation of phosphoinositide 3-kinase p110α (PIK3CA). *Proc. Natl. Acad. Sci. U.S.A.* 2012 Sep 18;109(38):15259-64. PMID: 22949682
50. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212526s006lbl.pdf
51. Mayer et al. A Phase Ib Study of Alpelisib (BYL719), a PI3Kα-Specific Inhibitor, with Letrozole in ER+/HER2- Metastatic Breast Cancer. *Clin. Cancer Res.* 2017 Jan 1;23(1):26-34. PMID: 27126994
52. Mayer et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). *Clin. Cancer Res.* 2019 Feb 5. PMID: 30723140
53. Jung et al. Pilot study of sirolimus in patients with PIK3CA mutant/amplified refractory solid cancer. *Mol Clin Oncol.* 2017 Jul;7(1):27-31. PMID: 28685070
54. Janku et al. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. *Mol. Cancer Ther.* 2011 Mar;10(3):558-65. PMID: 21216929