



Sample Information

Patient Name: 陳坤地
Gender: Male
ID No.: F100284708
History No.: 17749278
Age: 77

Ordering Doctor: DOC2490H 游敦傑
Ordering REQ.: OCSKCUH
Signing in Date: 2023/10/26

Path No.: M112-00276
MP No.: F23078
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-52284B
Percentage of tumor cells: 50%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page	Report Highlights
Variant Details	2	1 Relevant Biomarkers
Biomarker Descriptions	2	12 Therapies Available
Relevant Therapy Summary	4	14 Clinical Trials
Relevant Therapy Details	5	
Clinical Trials Summary	20	
Alert Details	21	

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 exon 19 deletion	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 exon 19 deletion epidermal growth factor receptor Allele Frequency: 60.52%	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 gefitinib + chemotherapy	None	14

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/generics

Prevalent cancer biomarkers without relevant evidence based on included data sources

FGFR4 amplification

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
EGFR	p.(E746_A750del)	c.2236_2250delGAAT TAAGAGAAGCA	COSM6225	chr7:55242465	60.52%	NM_005228.5	nonframeshift Deletion	1958
JAK1	p.(P733=)	c.2199A>G	.	chr1:65310489	99.85%	NM_002227.4	synonymous	1998
ALK	p.(A1200=)	c.3600G>C	.	chr2:29443617	60.73%	NM_004304.5	synonymous	1971
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.65%	NM_213647.3	missense	2000
EGFR	p.(Q787=)	c.2361G>A	.	chr7:55249063	71.50%	NM_005228.5	synonymous	2000

Copy Number Variations

Gene	Locus	Copy Number
FGFR4	chr5:176517312	5.66

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

Biomarker Descriptions (continued)

E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{9,10,11,12}. EGFR activating mutations in lung cancer 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) for NSCLC tumors harboring EGFR exon 20 insertion mutations. CPO301³⁵ received a fast track designation (2023) from the FDA for EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid³⁶ 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-189³⁷ was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

FGFR4 (fibroblast growth factor receptor 4)

Background: The FGFR4 gene encodes fibroblast growth receptor 4, a member of the fibroblast growth-factor receptor (FGFR) family that also includes FGFR1, 2, and 3. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival^{38,39,40}. FGFR4 selectively binds the ligand FGF19, wherein FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma^{41,42}.

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions. The majority of these aberrations result in gain of function⁴³. FGFR4 exhibits amplification in up to 15% of clear-cell renal cell carcinomas, with somatic mutations observed in up to 6% of melanomas and uterine cancer^{6,7}.

Potential relevance: Currently, no targeted therapies are approved for FGFR4 aberrations. However, FDA-approved multi-kinase inhibitors known to inhibit FGFR family members, including regorafenib (2013), ponatinib (2012), lenvatinib (2015), nintedanib (2014), and pazopanib (2009), have demonstrated anti-tumor activity in select cancer types harboring FGFR alterations^{44,45,46,47,48,49,50}. Selective, irreversible FGFR4 inhibitors, including BLU-554, have underwent clinical trial evaluation. In a phase-I clinical study of BLU-554 in patients with FGF19-positive advanced hepatocellular carcinoma, the overall response rate was 17%⁵¹.

Relevant Therapy Summary

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ✕ No evidence

EGFR exon 19 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	●	●	●	●	● (III)
afatinib	●	●	●	●	● (II)
dacomitinib	●	●	●	●	✕
erlotinib	●	●	●	●	✕
erlotinib + ramucirumab	●	●	●	●	✕
gefitinib	●	●	●	●	✕
bevacizumab + erlotinib	✕	●	●	●	✕
bevacizumab (Allergan) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Celltrion) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Mabxience) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Pfizer) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Samsung Bioepis) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Stada) + erlotinib	✕	✕	●	✕	✕
atezolizumab + bevacizumab + carboplatin + paclitaxel	✕	✕	✕	●	✕
gefitinib + carboplatin + pemetrexed	✕	✕	✕	●	✕
amivantamab, lazertinib, chemotherapy	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
patritumab deruxtecan	✕	✕	✕	✕	● (III)
savolitinib, osimertinib	✕	✕	✕	✕	● (III)
erlotinib, OBI-833	✕	✕	✕	✕	● (II)
osimertinib, savolitinib	✕	✕	✕	✕	● (II)
BLU-451, chemotherapy	✕	✕	✕	✕	● (I/II)
BLU-945, osimertinib	✕	✕	✕	✕	● (I/II)
sunvozertinib	✕	✕	✕	✕	● (I/II)
ABBV 400	✕	✕	✕	✕	● (I)
BAY-2927088	✕	✕	✕	✕	● (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 2023-08-16. For the most up-to-date information, search www.fda.gov.

EGFR exon 19 deletion

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-04-07

Variant class: EGFR exon 19 deletion

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 exon 19 deletion

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 exon 19 deletion (continued)

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2016-10-18

Variant class: EGFR exon 19 deletion

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 exon 19 deletion

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 exon 19 deletion (continued)

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-05-05

Variant class: EGFR exon 19 deletion

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: 2023-06-21

Variant class: EGFR exon 19 deletion

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/2023/208065Orig1s028lbl.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 2023-08-01. For the most up-to-date information, search www.nccn.org. For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

EGFR exon 19 deletion

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

EGFR exon 19 deletion (continued)

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Non-squamous Cell; Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention
- Non-squamous Cell; Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

EGFR exon 19 deletion (continued)

● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Non-squamous Cell; Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

EGFR exon 19 deletion (continued)

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

EGFR exon 19 deletion (continued)

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Brain Metastases, Leptomeningeal Metastases (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

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, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)
- 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 3.2023]

EGFR exon 19 deletion (continued)

● 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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- Leptomeningeal Metastases (Line of therapy not specified); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

● 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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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 2023-08-16. For the most up-to-date information, search www.ema.europa.eu/ema.

EGFR exon 19 deletion

● afatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-06-21

Variant class: EGFR exon 19 deletion

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: 2023-01-05

Variant class: EGFR exon 19 deletion

Reference:

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

● bevacizumab (Celltrion) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-05-10

Variant class: EGFR exon 19 deletion

Reference:

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

● bevacizumab (Mabxience) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-07-26

Variant class: EGFR exon 19 deletion

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: 2023-01-05

Variant class: EGFR exon 19 deletion

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: 2023-04-11

Variant class: EGFR exon 19 deletion

Reference:

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

EGFR exon 19 deletion (continued)

● bevacizumab (Samsung Bioepis) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-04-11

Variant class: EGFR exon 19 deletion

Reference:

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

● bevacizumab (Stada) + erlotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-07-14

Variant class: EGFR exon 19 deletion

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: 2022-12-15

Variant class: EGFR exon 19 deletion

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: 2023-03-17

Variant class: EGFR exon 19 deletion

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 exon 19 deletion

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: 2023-05-16

Variant class: EGFR exon 19 deletion

Reference:

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

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-12-13

Variant class: EGFR exon 19 deletion

Other criteria: EGFR T790M mutation negative

Reference:

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

EGFR exon 19 deletion (continued)

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-07-27

Variant class: EGFR exon 19 deletion

Reference:

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

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-07-17

Variant class: EGFR exon 19 deletion

Reference:

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

● osimertinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-08-11

Variant class: EGFR exon 19 deletion

Reference:

https://www.ema.europa.eu/en/documents/product-information/tagrisso-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 2023-08-01. For the most up-to-date information, search www.esmo.org.

EGFR exon 19 deletion

● osimertinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR exon 19 deletion

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)]

● osimertinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

● afatinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 5

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

● bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 2

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

EGFR exon 19 deletion (continued)

● dacomitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

● erlotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

● erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

● gefitinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

EGFR exon 19 deletion (continued)

● gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

- Stage IV; Advanced, Metastatic (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

● atezolizumab + bevacizumab + carboplatin + paclitaxel

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

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

Population segment (Line of therapy):

- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

Clinical Trials in Taiwan region:

Clinical Trials Summary

EGFR exon 19 deletion

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	HERTHENA–Lung02: Phase III, Randomized, Open-label Study of Patritumab Deruxtecan Versus Platinum-Based Chemotherapy in Metastatic or Locally Advanced Non-Small Cell Lung Cancer (NSCLC) With Epidermal Growth Factor Receptor (EGFRm) Mutation After Failure treatment with epidermal growth factor (EGFR) tyrosine kinase inhibitors (TKIs)	III
NCT05261399	A Phase III, Randomised, Open-Label Study of Savolitinib in Combination With Osimertinib Versus Platinum-Based Doublet Chemotherapy in Participants With EGFR Mutated, MET-Overexpressed and/or Amplified, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed on Treatment With Osimertinib (SAFFRON).	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
NCT05442060	A Randomized, Open-Label, Phase 2 Study to Evaluate OBI-833/OBI-821 in Combination With First-Line Erlotinib in Patients With EGFR-Mutated, Globo H-Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer	II
NCT03778229	A Phase II Study Assessing the Efficacy of Osimertinib in Combination With Savolitinib in Patients With EGFRm+ and MET+, Locally Advanced or Metastatic Non Small Cell Lung Cancer Who Have Progressed Following Treatment With Osimertinib.	II
NCT04862780	A Phase I/II Study Targeting Acquired Resistance Mechanisms in Patients With EGFR Mutant Non-Small Cell Lung Cancer.	I/II
NCT05099172	An Open Label, First-in-human Study of BAY 2927088 in Participants With Advanced Non-small Cell Lung Cancer (NSCLC) Harboring an EGFR and/or HER2 Mutation	I
NCT03114319	An Open-label, Multi-center, Phase I, Dose Finding Study of Oral TNO155 in Adult Patients With Advanced Solid Tumors.	I
NCT05241873	Phase I/II Study of BLU-451 in Advanced Cancers With EGFR Exon 20 Insertion Mutations	I/II
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
NCT05029882	A Phase I First in Human Study Evaluating Safety, Pharmacokinetics and Efficacy of ABBV-400 in Adult Subjects With Advanced Solid Tumors	I

Alerts Informed By Public Data Sources


Current FDA Information

 Contraindicated

 Not recommended

 Resistance

 Breakthrough

 Fast Track

FDA information is current as of 2023-08-16. For the most up-to-date information, search www.fda.gov.

EGFR exon 19 deletion

patritumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFRi sensitizing mutation or EGFR exon 19 deletion

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-nscl>

CPO-301

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Supporting Statement:

The FDA has granted Fast Track Designation to a first-in-class antibody drug conjugate, CPO301, for EGFR mutations in patients with metastatic non-small cell lung cancer (NSCLC) who are relapsed/refractory to or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors including Osimertinib.

Reference:

<http://iis.aastocks.com/20230612/10770455-0.PDF>

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 EGFR mutations in non-small cell lung cancer (NSCLC) patients 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/>

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 3.2023]
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/2023/215310s002lbl.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/2023/208065Orig1s028lbl.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/2022/761210s002lbl.pdf
35. <http://iis.aastocks.com/20230612/10770455-0.PDF>
36. <https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>
37. <https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda>
38. Babina et al. Advances and challenges in targeting FGFR signalling in cancer. *Nat. Rev. Cancer.* 2017 May;17(5):318-332. PMID: 28303906
39. Ahmad et al. Mechanisms of FGFR-mediated carcinogenesis. *Biochim. Biophys. Acta.* 2012 Apr;1823(4):850-60. PMID: 22273505
40. Sarabipour et al. Mechanism of FGF receptor dimerization and activation. *Nat Commun.* 2016 Jan 4;7:10262. doi: 10.1038/ncomms10262. PMID: 26725515
41. Repana et al. Targeting FGF19/FGFR4 Pathway: A Novel Therapeutic Strategy for Hepatocellular Carcinoma. *Diseases.* 2015 Oct 28;3(4):294-305. PMID: 28943626
42. Lu et al. Fibroblast Growth Factor Receptor 4 (FGFR4) Selective Inhibitors as Hepatocellular Carcinoma Therapy: Advances and Prospects. *J. Med. Chem.* 2018 Nov 16. PMID: 30403487
43. Helsten et al. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. *Clin. Cancer Res.* 2016 Jan 1;22(1):259-67. PMID: 26373574
44. Cha et al. FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers in vitro. *Mol Oncol.* 2018 Jun;12(7):993-1003. PMID: 29573334
45. Chae et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. *Oncotarget.* 2017 Feb 28;8(9):16052-16074. PMID: 28030802
46. Porta et al. FGFR a promising druggable target in cancer: Molecular biology and new drugs. *Crit. Rev. Oncol. Hematol.* 2017 May;113:256-267. PMID: 28427515
47. Gozgit et al. Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. *Mol. Cancer Ther.* 2012 Mar;11(3):690-9. PMID: 22238366
48. Yamamoto et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell.* 2014 Sep 6;6:18. doi: 10.1186/2045-824X-6-18. eCollection 2014. PMID: 25197551
49. Kim et al. Pazopanib, a novel multitargeted kinase inhibitor, shows potent in vitro antitumor activity in gastric cancer cell lines with FGFR2 amplification. *Mol. Cancer Ther.* 2014 Nov;13(11):2527-36. PMID: 25249557
50. Hibi et al. FGFR gene alterations in lung squamous cell carcinoma are potential targets for the multikinase inhibitor nintedanib. *Cancer Sci.* 2016 Nov;107(11):1667-1676. PMID: 27581340
51. Kim et al. First-in-Human Phase I Study of Fisogatinib (BLU-554) Validates Aberrant FGF19 Signaling as a Driver Event in Hepatocellular Carcinoma. *Cancer Discov.* 2019 Dec;9(12):1696-1707. PMID: 31575541