

Department of Pathology and Laboratory Medicine No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan 11217, R.O.C. Tel: 02-2875-7449

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# **Sample Information**

Patient Name: 翟玉茹 Gender: Female ID No.: L201250551 History No.: 15084772

**Age:** 84

Ordering Doctor: DOC3109L 陳育民

Ordering REQ.: C223BD8 Signing in Date: 2020/10/28

**Path No.:** S109-89791 **MP No.:** F20091

Assay: Oncomine Focus Assay

Sample Type: FFPE Block No.: \$109-78250C Percentage of tumor cells: 60%

Note:

# Sample Cancer Type: Non-Small Cell Lung Cancer

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## Report Highlights

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# **Relevant Non-Small Cell Lung Cancer Findings**

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	EGFR p.(E746_A750del) c.2236_2250delGAATTAAGAGAAGCA (EGFR exon 19 deletion)	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		



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## **Relevant Biomarkers**

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	EGFR p.(E746_A750del) c.2236_2250delGAATTAAGAGAA GCA EGFR exon 19 deletion epidermal growth factor receptor Allele Frequency: 49.11%	afatinib 1,2 dacomitinib 1,2 erlotinib 1,2 gefitinib 1,2 osimertinib 1,2 afatinib + cetuximab bevacizumab + erlotinib 2 erlotinib + ramucirumab 2 atezolizumab + bevacizumab + chemotherapy gefitinib + chemotherapy bevacizumab + gefitinib	None	196

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.

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

DNA	DNA Sequence Variants									
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage		
EGFR	p.(E746_A750del)	c.2236_2250delGAA TTAAGAGAAGCA	COSM6225	chr7:55242465	49.11%	NM_005228.4	nonframeshift Deletion	1959		

## **Biomarker Descriptions**

#### EGFR (epidermal growth factor receptor)

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the human epidermal growth factor receptor (HER) family. Along with EGFR/ERBB1/HER1, ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family¹. 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 survival².³.

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain of EGFR are observed in approximately 10-20% of lung adenocarcinoma and at higher frequencies in never-smoker, female, and in Asian populations with lung cancer<sup>4,5,6,7</sup>. The most common mutations occur near the ATP-binding pocket of the kinase domain and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21<sup>8</sup>. These mutations constitutively activate the EGFR kinase resulting in downstream signaling and represent 80% of the EGFR mutations observed in lung cancer. A second group of recurrent activating mutations that are less common include E709K, G719X, S768l, L861Q, and short in-frame insertions in exon 20<sup>9,10,11,12</sup>. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations<sup>13</sup>. Although these variants are common in lung cancer, they are rare in other cancer types. In glioblastoma, recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V<sup>8,14</sup>. The recurrent focal amplification of the EGFR gene leads to an increase in expression in several cancer types. EGFR is amplified in up to 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma<sup>5,6,7,14,15</sup>. Deletion of exons 2-7 encoding the extracellular domain of EGFR (EGFRVIII) results in overexpression of a ligand-independent constitutively active protein which is frequently observed in glioblastoma and has been shown to lead to lung cancer development as well as sensitivity to TKIs<sup>16,17,18</sup>.



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# **Biomarker Descriptions (continued)**

Potential relevance: Erlotinib<sup>19</sup> (2004), afatinib<sup>20</sup> (2013), gefitinib<sup>21</sup> (2015), osimertinib<sup>22</sup> (2015), and dacomitinib<sup>23</sup> (2018) are small molecule TKIs that are FDA approved for non-small cell lung cancer (NSCLC) patients with sensitizing exon 19 deletions and exon 21 L858R mutations. Acquired secondary mutations often confer resistance to first line TKI therapy with the T790M amino acid substitution accounting for 50-60% of cases<sup>8</sup>. Osimertinib is also indicated for NSCLC patients harboring EGFR T790M mutations whose disease has progressed on or after treatment with a first line TKI. EGFR targeting antibodies including cetuximab<sup>24</sup> (2004), panitumumab<sup>25</sup> (2006), and necitumumab<sup>26</sup> (2016) are also under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, JNJ-61186372<sup>27</sup>, targeting EGFR and MET, and the tyrosine kinase inhibitor<sup>28</sup> each received a breakthrough designation from the FDA (2020) for NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy CNVN-202<sup>29</sup> in combination with the EGFR inhibitor, osimertinib, received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations. The use of cetuximab in combination with afatinib is currently recommended by the NCCN for patients who have progressed after receiving erlotinib, afatinib, dacomitinib, or gefitinib and chemotherapy<sup>30</sup>.

# **Relevant Therapy Summary**

In this cancer type  In other cancer	In this cancer type and	Contraindicated	A Both for use and	✗ No evidence
type	other cancer types		contraindicated	

EGFR p.(E746_A750del) c.2236_2250delGAATTAAGAGAAGCA						
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*	
afatinib	•	•	•		(IV)	
gefitinib	•		•	•	(IV)	
erlotinib	•	•	•	•	<b>(III)</b>	
osimertinib	•	•	•	•	<b>(III)</b>	
dacomitinib	•	•	•	•	<b>(II)</b>	
bevacizumab + erlotinib	×	•	•	•	<b>(II)</b>	
erlotinib + ramucirumab	×	•	•	•	×	
afatinib + cetuximab	×	•	×	×	×	
atezolizumab + bevacizumab + carboplatin + paclitaxel	×	×	×	•	×	
bevacizumab + gefitinib	×	×	×	•	×	
gefitinib + carboplatin + pemetrexed	×	×	×	•	×	
anlotinib hydrochloride, toripalimab	×	×	×	×	(IV)	
apatinib + EGFR tyrosine kinase inhibitor	×	×	×	×	(IV)	
apatinib, gefitinib	×	×	×	×	(IV)	
bevacizumab + osimertinib, osimertinib	×	×	×	×	(IV)	

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



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# **Relevant Therapy Summary (continued)**

In this cancer type In other cancer type

In this cancer type and other cancer types

Contraindicated

A Both for use and contraindicated

× No evidence

× × × ×	× × × ×	× × ×	×	(IV) (IV)
×	×	×	×	
×	×			(IV)
×		×		
	×		×	(IV)
×		×	×	(IV)
	×	×	×	(IV)
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
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×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
×	×	×	×	<b>(III)</b>
	X X X X X X X X X X X X X X X X X X X	<pre></pre>	X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X         X       X       X	X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       X       X       X         X       <

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



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# **Relevant Therapy Summary (continued)**

In this cancer type O In other cancer type

In this cancer type and O Contraindicated other cancer types

A Both for use and contraindicated

X No evidence

EGFR p.(E746_A750del) c.2236_2250delGAATTAAGAGAAGCA (continued)						
Relevant Therapy	FDA	NCCN	EMA			
Relevant Therapy	FDA	NCCN	LIVIA			

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
SH-1028, gefitinib	×	×	×	×	<b>(III)</b>
AZD-3759, erlotinib, gefitinib	×	×	×	×	<b>(</b>   /   )
D-0316, icotinib hydrochloride	×	×	×	×	<b>(</b> II/III)
afatinib, bevacizumab	×	×	×	×	<b>(II)</b>
afatinib, chemotherapy, radiation therapy	×	×	×	×	<b>(II)</b>
anlotinib hydrochloride	×	×	×	×	<b>(II)</b>
anlotinib hydrochloride, erlotinib, icotinib hydrochloride, gefitinib	×	×	×	×	<b>(II)</b>
anlotinib hydrochloride, gefitinib	×	×	×	×	<b>(II)</b>
anlotinib hydrochloride, icotinib hydrochloride	×	×	×	×	<b>(II)</b>
atezolizumab, chemotherapy	×	×	×	×	<b>(II)</b>
avitinib, AZD-3759	×	×	×	×	<b>(II)</b>
bevacizumab + gefitinib + chemotherapy	×	×	×	×	<b>(II)</b>
bevacizumab, erlotinib, chemotherapy	×	×	×	×	<b>(II)</b>
bevacizumab, osimertinib	×	×	×	×	<b>(II)</b>
bintrafusp alfa, chemoradiation therapy, durvalumab	×	×	×	×	<b>(II)</b>
chemotherapy, atezolizumab, bevacizumab	×	×	×	×	<b>(II)</b>
chemotherapy, durvalumab	×	×	×	×	<b>(II)</b>
crizotinib + chemotherapy	×	×	×	×	<b>(II)</b>
durvalumab, tremelimumab, chemotherapy	×	×	×	×	<b>(II)</b>
EGFR tyrosine kinase inhibitor + chemotherapy	×	×	×	×	<b>(II)</b>
EGFR tyrosine kinase inhibitor + chemotherapy, EGFR tyrosine kinase inhibitor	×	×	×	×	<b>(II)</b>
EGFR tyrosine kinase inhibitor, apatinib	×	×	×	×	<b>(II)</b>
EGFR tyrosine kinase inhibitor, radiation therapy	×	×	×	×	<b>(II)</b>
erlotinib + chemotherapy	×	×	×	×	<b>(II)</b>

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



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# **Relevant Therapy Summary (continued)**

In this cancer type O In other cancer

type

In this cancer type and other cancer types

Contraindicated

A Both for use and contraindicated

X No evidence

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
erlotinib, anlotinib hydrochloride	×	×	×	×	<b>(II)</b>
erlotinib, bevacizumab	×	×	×	×	<b>(II)</b>
erlotinib, gefitinib	×	×	×	×	<b>(II)</b>
erlotinib, gefitinib, icotinib hydrochloride, erlotinib + chemotherapy, gefitinib + chemotherapy, icotinib hydrochloride + chemotherapy	×	×	×	×	<b>(II)</b>
erlotinib, radiation therapy	×	×	×	×	<b>(II)</b>
famitinib, HS-10296	×	×	×	×	<b>(II)</b>
gefitinib, hormone therapy	×	×	×	×	<b>(II)</b>
gefitinib, surgical intervention	×	×	×	×	<b>(II)</b>
gefitinib, thalidomide	×	×	×	×	<b>(II)</b>
nazartinib, gefitinib	×	×	×	×	<b>(II)</b>
nivolumab, ipilimumab	×	×	×	×	<b>(II)</b>
osimertinib, afatinib	×	×	×	×	<b>(II)</b>
osimertinib, bevacizumab	×	×	×	×	<b>(II)</b>
osimertinib, gefitinib + osimertinib	×	×	×	×	<b>(II)</b>
osimertinib, radiation therapy	×	×	×	×	<b>(II)</b>
osimertinib, ramucirumab	×	×	×	×	<b>(II)</b>
osimertinib, savolitinib	×	×	×	×	<b>(II)</b>
osimertinib, selumetinib	×	×	×	×	<b>(II)</b>
poziotinib	×	×	×	×	<b>(II)</b>
ramucirumab, chemotherapy, cytokine	×	×	×	×	<b>(II)</b>
ramucirumab, osimertinib	×	×	×	×	<b>(II)</b>
SH-1028	×	×	×	×	<b>(II)</b>
tyrosine kinase inhibitors, radiation therapy	×	×	×	×	<b>(II)</b>
zoledronic acid, gefitinib	×	×	×	×	(II)

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



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# **Relevant Therapy Summary (continued)**

In this cancer type O In other cancer

type

In this cancer type and other cancer types

Contraindicated

A Both for use and contraindicated

X No evidence

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
anlotinib hydrochloride, chemotherapy	×	×	×	×	(I/II)
BDTX-189	×	×	×	×	<b>(</b> 1/11)
bevacizumab + erlotinib + chemotherapy	×	×	×	×	<b>(</b> 1/11)
CBT-502, anlotinib hydrochloride	×	×	×	×	<b>(</b> 1/11)
DZD-9008	×	×	×	×	<b>(</b> 1/11)
EMB01	×	×	×	×	<b>(</b> 1/11)
gefitinib + osimertinib	×	×	×	×	<b>(</b> I/II)
icotinib hydrochloride + chemotherapy	×	×	×	×	(I/II)
KP-673	×	×	×	×	<b>(</b> 1/11)
ningetinib, gefitinib	×	×	×	×	<b>(</b> 1/11)
telaglenastat, osimertinib	×	×	×	×	<b>(</b>  /  )
U3-1402	×	×	×	×	<b>(</b> I/II)
AB-928, zimberelimab, chemotherapy	×	×	×	×	(I)
afatinib, chemotherapy	×	×	×	×	(I)
afatinib, immunostimulant	×	×	×	×	<b>(</b> 1)
afatinib, osimertinib	×	×	×	×	(I)
alisertib, osimertinib	×	×	×	×	(I)
CK-101	×	×	×	×	(I)
dacomitinib, osimertinib	×	×	×	×	(I)
DS-1205c, osimertinib	×	×	×	×	<b>(</b> I)
EGFR tyrosine kinase inhibitor, anlotinib hydrochloride	×	×	×	×	<b>(</b> I)
genolimzumab, fruquintinib	×	×	×	×	(I)
JNJ-61186372, lazertinib	×	×	×	×	(I)
lazertinib, JNJ-61186372	×	×	×	×	(I)

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



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# **Relevant Therapy Summary (continued)**

In this cancer type In other cancer type

In this cancer type and other cancer types

Contraindicated

A Both for use and contraindicated

× No evidence

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nazartinib + trametinib, nazartinib + ribociclib, LXH254 + nazartinib, capmatinib + nazartinib, gefitinib + nazartinib	×	×	×	×	<b>(</b> 1)
neratinib, palbociclib, everolimus, trametinib	×	×	×	×	(I)
niraparib, osimertinib	×	×	×	×	<b>(</b> I)
osimertinib, necitumumab	×	×	×	×	<b>(</b> l)
pirotinib	×	×	×	×	<b>(</b> l)
ramucirumab, erlotinib, osimertinib	×	×	×	×	<b>(</b> l)
telisotuzumab vedotin, osimertinib	×	×	×	×	<b>(</b> I)
TNO-155	×	×	×	×	<b>(</b> I)
TP-0903	×	×	×	×	<b>(</b> I)
TQB 3804	×	×	×	×	<b>(</b> I)
tyrosine kinase inhibitors, tyrosine kinase inhibitors + chemotherapy	×	×	×	×	<b>(</b> 1)
WSD-0922	×	×	×	×	<b>(</b> I)

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



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## **Relevant Therapy Details**

## **Current FDA Information**

In this cancer type	O In other cancer type	In this cancer type and other cancer types	Ontraindicated	Ontirecommended	Resis	stance
7	9	other cancer types				

FDA information is current as of 2020-05-26. For the most up-to-date information, search www.fda.gov.

## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA

## afatinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2019-10-11 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.

Limitation 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/2019/201292s015lbl.pdf

## dacomitinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2018-09-27 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/2018/211288s000lbl.pdf



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (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

## gefitinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2018-08-22 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/2018/206995s003lbl.pdf



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

## osimertinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2019-12-19 Variant class: EGFR exon 19 deletion

### Indications and usage:

TAGRISSO® is a kinase inhibitor indicated for

- the first-line treatment of patients with metastatic 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 treatment of 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/2019/208065s013lbl.pdf



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#### **Current NCCN Information**

In this cancer type \(\Omega\) In other cancer type

In this cancer type and other cancer types

Contraindicated

Not recommended Resistance

NCCN information is current as of 2020-05-01. 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.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA

## 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Other Recommended)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

### 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Other Recommended)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

### 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Other Recommended)



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

## 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
 Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Other Recommended)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

### 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
 EGFR sensitizing mutation discovered prior to first-line systemic therapy (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

### 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Sensitizing EGFR mutation discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
   Progression on erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib; Asymptomatic or symptomatic with brain metastases or isolated lesions (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

#### afatinib + cetuximab

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

NCCN Recommendation category: 2A

### Population segment (Line of therapy):

 Non-Small Cell Lung Cancer; Progression on erlotinib, afatinib, dacomitinib, gefitinib, chemotherapy, or osimertinib; Systemic multiple lesions (Subsequent therapy)



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

#### bevacizumab + 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Progression on erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib; Asymptomatic or symptomatic with brain metastases or isolated lesions (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

### 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
   Sensitizing EGFR mutation discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy,
   including maintenance therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
   Progression on erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib; Asymptomatic or symptomatic with brain metastases or isolated lesions (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

#### 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
   Sensitizing EGFR mutation discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
   Progression on erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib; Asymptomatic or symptomatic with brain metastases or isolated lesions (Subsequent therapy)



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

#### 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Sensitizing EGFR mutation discovered prior to or during first-line systemic therapy (First-line therapy) (Other Recommended)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression on erlotinib +/(ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib; Asymptomatic or symptomatic with brain metastases or
  isolated lesions (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
   Sensitizing EGFR mutation discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy,
   including maintenance therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease;
   Progression on erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib; Asymptomatic or symptomatic with brain metastases or isolated lesions (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## osimertinib

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

NCCN Recommendation category: 2A

### Population segment (Line of therapy):

Non-Small Cell Lung Cancer; Leptomeningeal and spine metastases (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

### osimertinib

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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Sensitizing EGFR mutation discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy) (Preferred)
- Progression on osimertinib; Advanced or metastatic disease; Asymptomatic or symptomatic with brain or isolated lesions (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## bevacizumab + erlotinib

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

NCCN Recommendation category: 2B

### Population segment (Line of therapy):

 Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Sensitizing EGFR mutation discovered prior to or during first-line systemic therapy (First-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## erlotinib

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

NCCN Recommendation category: 2B

## Population segment (Line of therapy):

Non-Small Cell Lung Cancer; Leptomeningeal and spine metastases; Pulsatile erlotinib (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]

### erlotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

NCCN Recommendation category: 2A

### Population segment (Line of therapy):

Non-Small Cell Lung Cancer; Brain metastases; Use agents active against primary tumor; Pulsatile erlotinib (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]



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# EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

### afatinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

Non-Small Cell Lung Cancer; Brain metastases; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]

## gefitinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

Non-Small Cell Lung Cancer; Brain metastases; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]

## alectinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

Summary:

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

■ "Thus, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended as subsequent therapy for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## brigatinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

Summary:

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

■ "Thus, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended as subsequent therapy for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

## ceritinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

#### Summary:

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

"Thus, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended as subsequent therapy for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## crizotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

#### Summary:

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

"Thus, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended as subsequent therapy for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

### lorlatinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFRi sensitizing mutation

#### Summary:

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

"Thus, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended as subsequent therapy for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

### atezolizumab

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR mutation

#### Summary:

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

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



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

## nivolumab

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR mutation

#### Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## pembrolizumab

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR mutation

#### Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

## pembrolizumab

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR mutation

Other criteria: CD274 overexpression

#### Summary:

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

"A small study suggests that single-agent pembrolizumab is not effective as first-line therapy in patients with metastatic NSCLC and EGFR mutations, even those with PD-L1 levels more than 50%."



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## **Current EMA Information**

EMA information is current as of 2020-05-26. For the most up-to-date information, search www.ema.europa.eu/ema.

## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA

### afatinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2020-02-13 Variant class: EGFR exon 19 deletion

Reference:

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

#### bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2020-03-11 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: 2019-06-05 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: 2019-04-24 Variant class: EGFR exon 19 deletion

Reference:

 $https://www.ema.europa.eu/documents/product-information/tarceva-epar-product-information\_en.pdf\\$ 

#### erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer Label as of: 2020-02-25 Variant class: EGFR exon 19 deletion

Reference:

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



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# EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

gefitinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2019-05-28 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: 2020-02-25 Variant class: EGFR exon 19 deletion

Reference:

 $https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information\_en.pdf\\$ 



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#### **Current ESMO Information**

In this cancer type O In other cancer type

In this cancer type and other cancer types

Contraindicated

Not recommended Resistance

ESMO information is current as of 2020-05-01. For the most up-to-date information, search www.esmo.org.

## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA

## atezolizumab + bevacizumab + carboplatin + paclitaxel

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

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

Population segment (Line of therapy):

- Metastatic Non-Squamous; Magnitude of Clinical Benefit Scale Score version 1.1 score: 3 (First-line therapy)
- Metastatic; PS 0-1; Without contraindications to immunotherapy after targeted therapies have been exploited (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

### 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 stage (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

## 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 stage (First-line therapy)



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (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 stage (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

#### 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 stage; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

### 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):

Stage IV; Magnitude of Clinical Benefit Scale Version v1.1 Score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

## 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 (Maintenance therapy)



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

### afatinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Stage IV; PS 0-2 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

### erlotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Stage IV; PS 0-2 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

## gefitinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Stage IV; PS 0-2 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

## gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Advanced stage (First-line therapy)



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# EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

### bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Stage IV; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

## bevacizumab + gefitinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Stage IV; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

### erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

■ Stage IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

## afatinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Stage IV; PS 3-4 (First-line therapy)



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## EGFR p.(E746\_A750del) c.2236\_2250delGAATTAAGAGAAGCA (continued)

## dacomitinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

■ Stage IV; PS 3-4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

### erlotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

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

Population segment (Line of therapy):

Stage IV; PS 3-4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192-iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

## gefitinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR activating mutation

ESMO Level of Evidence/Grade of Recommendation: III /  ${\sf A}$ 

Population segment (Line of therapy):

Stage IV; PS 3-4 (First-line therapy)



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	<b>Dutc.</b> 27 00t 20	27 01 27
Signatures		
Testing Personnel:		
Laboratory Supervisor:		
Pathologist:		

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## 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. 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
- 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
- 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
- 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. Ji et al. Epidermal growth factor receptor variant III mutations in lung tumorigenesis and sensitivity to tyrosine kinase inhibitors. Proc. Natl. Acad. Sci. U.S.A. 2006 May 16;103(20):7817-22. PMID: 16672372
- 18. 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
- https://www.accessdata.fda.gov/drugsatfda\_docs/label/2016/021743s025lbl.pdf
- 20. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2019/201292s015lbl.pdf
- 21. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2018/206995s003lbl.pdf
- 22. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2019/208065s013lbl.pdf
- 23. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2018/211288s000lbl.pdf
- 24. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2019/125084s273lbl.pdf
- 25. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2017/125147s207lbl.pdf
- 26. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2015/125547s000lbl.pdf
- 27. https://www.jnj.com/janssen-announces-u-s-fda-breakthrough-therapy-designation-granted-for-jnj-6372-for-the-treatment-of-non-small-cell-lung-cancer
- 28. https://www.takeda.com/newsroom/newsreleases/2020/takeda-announces-u.s.-fda-breakthrough-therapy-designation-for-mobocertinib-tak-788-for-the-treatment-of-nsclc-patients-with-egfr-exon-20-insertion-mutations/



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**Date**: 29 Oct 2020 29 of 29

# **References (continued)**

- 29. https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/
- 30. NCCN Guidelines® NCCN-Non-Small Cell Lung Cancer [Version 4.2020]