Taipei Veterans General Hospital

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Sample Information

Patient Name:
Gender: Female
ID No.: A201816096
History No.: 44878195
Age: 72

Ordering Doctor: DOC3016D
Ordering REQ.: 0ASVFSM
Signing in Date: 2020/06/17

Path No.: S109-99595
MP No.: F20035
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-16723A
Percentage of tumor cells: 30%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

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13 Therapies Available
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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 exon 19 deletion***	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
EGFR exon 19 deletion epidermal growth factor receptor Tier: IA Allele Frequency: 13.52%	**afatinib** [1, 2] **dacomitinib** [1, 2] **erlotinib** [1, 2] **gefitinib** [1, 2] **osimertinib** [1, 2] **bevacizumab* + erlotinib** [2] **erlotinib + ramucirumab** [2] afatinib + cetuximab atezolizumab + bevacizumab + chemotherapy gefitinib + chemotherapy bevacizumab + gefitinib	None	188
PIK3CA p.(E545K) c.1633G>A phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Tier: IIC Allele Frequency: 15.15%	None	**alpelisib + fulvestrant** [1]	12

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, 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**

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
PIK3CA	p.(E545K)	c.1633G>A	COSM763	chr3:178936091	15.15%	NM_006218.3	missense	2000
EGFR	p.(E746_T751delinsA)	c.2237_2251delAATTAAGAGAAGCAA	COSM12678	chr7:55242466	13.52%	NM_005228.4	nonframeshift Deletion	1945
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	99.45%	NM_002227.3	synonymous	1990
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.95%	NM_004304.4	missense	1998
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.75%	NM_004304.4	missense	2000
ALK	p.(=)	c.3375C>A	.	chr2:29445458	42.05%	NM_004304.4	synonymous	1993
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.55%	NM_000142.4	synonymous	1990
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	99.40%	NM_006206.5	synonymous	1996
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.85%	NM_006206.5	synonymous	1997
PDGFRA	p.(=)	c.2472C>T	.	chr4:55152040	48.42%	NM_006206.5	synonymous	1995
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.50%	NM_213647.2	missense	2000

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	20.65%	NM_213647.2	synonymous	1995
RET	p.(=)	c.2307G>T	.	chr10:43613843	100.00%	NM_020975.4	synonymous	1988

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 family[1]. 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 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[4,5,6,7]. 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[8]. 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, S768I, L861Q, and short in-frame insertions in exon 20[9,10,11,12]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[13]. 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[8,14]. 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[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 which is frequently observed in glioblastoma and has been shown to lead to lung cancer development as well as sensitivity to TKIs[16,17,18].

Potential relevance: Erlotinib[19] (2004), afatinib[20] (2013), gefitinib[21] (2015), osimertinib[22] (2015), and dacomitinib[23] (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[8]. 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[24] (2004), panitumumab[25] (2006), and necitumumab[26] (2016) are also under investigation in combination with EGFR-targeting TKIs for efficacy against 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[27].

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

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[28]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples the p110α subunit (PI3K) to activated tyrosine protein kinases. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[29,30]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[29,30,31,32]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in activation of the PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[33,34,35].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[6,7]. Activating

Biomarker Descriptions (continued)

mutations in PIK3CA commonly cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase (codon H1047) domains, each having distinct mechanisms of activation[36,37,38]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[6,7].

Potential relevance: The PI3K inhibitor, alpelisib[39], is FDA approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer, the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[40]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[40]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[41]. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[42,43].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 19 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
afatinib	●	●	●	●	● (IV)
gefitinib	●	●	●	●	● (IV)
erlotinib	●	●	●	●	● (III)
osimertinib	●	●	●	●	● (III)
dacomitinib	●	●	●	●	● (I)
bevacizumab + erlotinib	✖	●	●	●	● (II)
erlotinib + ramucirumab	✖	●	●	●	✖
afatinib + cetuximab	✖	●	✖	✖	✖
bevacizumab (Allergan) + erlotinib	✖	✖	●	✖	✖
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	●	✖
bevacizumab + gefitinib	✖	✖	✖	●	✖
gefitinib + carboplatin + pemetrexed	✖	✖	✖	●	✖
anlotinib hydrochloride, toripalimab	✖	✖	✖	✖	● (IV)
apatinib + EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (IV)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
apatinib + gefitinib	✖	✖	✖	✖	● (IV)
bevacizumab + osimertinib, osimertinib	✖	✖	✖	✖	● (IV)
EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (IV)
erlotinib, gefitinib, icotinib hydrochloride, chemotherapy	✖	✖	✖	✖	● (IV)
gefitinib, radiation therapy	✖	✖	✖	✖	● (IV)
icotinib hydrochloride	✖	✖	✖	✖	● (IV)
icotinib hydrochloride, icotinib hydrochloride + chemotherapy	✖	✖	✖	✖	● (IV)
icotinib hydrochloride, radiation therapy	✖	✖	✖	✖	● (IV)
ASK120067, gefitinib	✖	✖	✖	✖	● (III)
bevacizumab (Shanghai Hengrui Pharmaceutical) + chemotherapy, bevacizumab + chemotherapy	✖	✖	✖	✖	● (III)
bevacizumab, atezolizumab, chemotherapy	✖	✖	✖	✖	● (III)
bevacizumab, erlotinib	✖	✖	✖	✖	● (III)
BPI-7711, gefitinib	✖	✖	✖	✖	● (III)
durvalumab, chemotherapy	✖	✖	✖	✖	● (III)
erlotinib, chemotherapy	✖	✖	✖	✖	● (III)
erlotinib, erlotinib + chemotherapy	✖	✖	✖	✖	● (III)
gefitinib + chemotherapy	✖	✖	✖	✖	● (III)
gefitinib, anlotinib hydrochloride	✖	✖	✖	✖	● (III)
gefitinib, apatinib	✖	✖	✖	✖	● (III)
gefitinib, chemotherapy	✖	✖	✖	✖	● (III)
gefitinib, erlotinib	✖	✖	✖	✖	● (III)
gefitinib, erlotinib, gefitinib + radiation therapy, erlotinib + radiation therapy	✖	✖	✖	✖	● (III)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
gefitinib, icotinib hydrochloride, erlotinib, gefitinib + radiation therapy, icotinib hydrochloride + radiation therapy, erlotinib + radiation therapy	✖	✖	✖	✖	● (III)
HS-10296, gefitinib	✖	✖	✖	✖	● (III)
icotinib hydrochloride, chemotherapy	✖	✖	✖	✖	● (III)
icotinib hydrochloride, icotinib hydrochloride + radiation therapy	✖	✖	✖	✖	● (III)
nivolumab, chemotherapy	✖	✖	✖	✖	● (III)
osimertinib, chemotherapy	✖	✖	✖	✖	● (III)
pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
AZD-3759, erlotinib, gefitinib	✖	✖	✖	✖	● (II/III)
afatinib + DFP-14323, erlotinib + DFP-14323, osimertinib + DFP-14323	✖	✖	✖	✖	● (II)
afatinib, bevacizumab	✖	✖	✖	✖	● (II)
afatinib, chemotherapy, radiation therapy	✖	✖	✖	✖	● (II)
anlotinib hydrochloride + icotinib hydrochloride	✖	✖	✖	✖	● (II)
anlotinib hydrochloride, erlotinib, icotinib hydrochloride, gefitinib	✖	✖	✖	✖	● (II)
atezolizumab, chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab + gefitinib + chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, erlotinib, chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, osimertinib	✖	✖	✖	✖	● (II)
bintrafusp alfa, chemoradiation therapy, durvalumab	✖	✖	✖	✖	● (II)
chemotherapy, atezolizumab, bevacizumab	✖	✖	✖	✖	● (II)
chemotherapy, durvalumab	✖	✖	✖	✖	● (II)
chemotherapy, ramucirumab	✖	✖	✖	✖	● (II)
crizotinib + chemotherapy	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
durvalumab, tremelimumab, chemotherapy	✖	✖	✖	✖	● (II)
EGFR tyrosine kinase inhibitor + chemotherapy	✖	✖	✖	✖	● (II)
EGFR tyrosine kinase inhibitor + chemotherapy, EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (II)
EGFR tyrosine kinase inhibitor, radiation therapy	✖	✖	✖	✖	● (II)
erlotinib + chemotherapy	✖	✖	✖	✖	● (II)
erlotinib + surgical intervention	✖	✖	✖	✖	● (II)
erlotinib, bevacizumab + erlotinib	✖	✖	✖	✖	● (II)
erlotinib, gefitinib	✖	✖	✖	✖	● (II)
erlotinib, gefitinib, icotinib hydrochloride, erlotinib + chemotherapy, gefitinib + chemotherapy, icotinib hydrochloride + chemotherapy	✖	✖	✖	✖	● (II)
erlotinib, radiation therapy	✖	✖	✖	✖	● (II)
famitinib, HS-10296	✖	✖	✖	✖	● (II)
gefitinib + fulvestrant	✖	✖	✖	✖	● (II)
gefitinib + nazartinib	✖	✖	✖	✖	● (II)
gefitinib, surgical intervention	✖	✖	✖	✖	● (II)
gefitinib, thalidomide	✖	✖	✖	✖	● (II)
icotinib hydrochloride + radiation therapy	✖	✖	✖	✖	● (II)
icotinib hydrochloride + radiation therapy, icotinib hydrochloride	✖	✖	✖	✖	● (II)
nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
osimertinib + radiation therapy	✖	✖	✖	✖	● (II)
osimertinib + selumetinib	✖	✖	✖	✖	● (II)
osimertinib, afatinib	✖	✖	✖	✖	● (II)
osimertinib, bevacizumab	✖	✖	✖	✖	● (II)
osimertinib, gefitinib + osimertinib	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib, radiation therapy	✖	✖	✖	✖	● (II)
osimertinib, ramucirumab	✖	✖	✖	✖	● (II)
osimertinib, savolitinib	✖	✖	✖	✖	● (II)
pembrolizumab + chemotherapy	✖	✖	✖	✖	● (II)
poziotinib	✖	✖	✖	✖	● (II)
ramucirumab, osimertinib	✖	✖	✖	✖	● (II)
tyrosine kinase inhibitors, radiation therapy	✖	✖	✖	✖	● (II)
zoledronic acid, gefitinib	✖	✖	✖	✖	● (II)
AZD-3759	✖	✖	✖	✖	● (I/II)
bevacizumab + erlotinib + chemotherapy	✖	✖	✖	✖	● (I/II)
CBT-502, anlotinib hydrochloride	✖	✖	✖	✖	● (I/II)
DZD-9008	✖	✖	✖	✖	● (I/II)
EMB01	✖	✖	✖	✖	● (I/II)
erlotinib + trametinib	✖	✖	✖	✖	● (I/II)
gefitinib + osimertinib	✖	✖	✖	✖	● (I/II)
icotinib hydrochloride + chemotherapy + radiation therapy	✖	✖	✖	✖	● (I/II)
KP-673	✖	✖	✖	✖	● (I/II)
lazertinib	✖	✖	✖	✖	● (I/II)
ningetinib, gefitinib	✖	✖	✖	✖	● (I/II)
oleclumab + osimertinib	✖	✖	✖	✖	● (I/II)
S-49076, gefitinib	✖	✖	✖	✖	● (I/II)
telaglenastat, osimertinib	✖	✖	✖	✖	● (I/II)
U3-1402	✖	✖	✖	✖	● (I/II)
afatinib, chemotherapy	✖	✖	✖	✖	● (I)
afatinib, immunostimulant	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
afatinib, osimertinib	✖	✖	✖	✖	● (I)
alisertib, osimertinib	✖	✖	✖	✖	● (I)
anlotinib hydrochloride + erlotinib	✖	✖	✖	✖	● (I)
CK-101	✖	✖	✖	✖	● (I)
dacomitinib, osimertinib	✖	✖	✖	✖	● (I)
DS-1205c, gefitinib	✖	✖	✖	✖	● (I)
DS-1205c, osimertinib	✖	✖	✖	✖	● (I)
EGFR tyrosine kinase inhibitor, anlotinib hydrochloride	✖	✖	✖	✖	● (I)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✖	✖	✖	✖	● (I)
genolimzumab, fruquintinib	✖	✖	✖	✖	● (I)
JNJ-61186372, lazertinib	✖	✖	✖	✖	● (I)
lazertinib, JNJ-61186372	✖	✖	✖	✖	● (I)
nazartinib + trametinib, nazartinib + ribociclib, LXH254 + nazartinib, capmatinib + nazartinib, gefitinib + nazartinib	✖	✖	✖	✖	● (I)
niraparib, osimertinib	✖	✖	✖	✖	● (I)
nivolumab, ipilimumab, radiation therapy	✖	✖	✖	✖	● (I)
osimertinib + radiation therapy, osimertinib	✖	✖	✖	✖	● (I)
osimertinib, necitumumab	✖	✖	✖	✖	● (I)
osimertinib, sapanisertib	✖	✖	✖	✖	● (I)
pirotinib	✖	✖	✖	✖	● (I)
SH-1028	✖	✖	✖	✖	● (I)
telisotuzumab vedotin, osimertinib	✖	✖	✖	✖	● (I)
TNO-155	✖	✖	✖	✖	● (I)
TP-0903	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tyrosine kinase inhibitors, tyrosine kinase inhibitors + chemotherapy	✖	✖	✖	✖	● (I)

PIK3CA p.(E545K) c.1633G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	✖	✖	✖
capivasertib	✖	✖	✖	✖	● (II)
erlotinib, gefitinib, icotinib hydrochloride, erlotinib + chemotherapy, gefitinib + chemotherapy, icotinib hydrochloride + chemotherapy	✖	✖	✖	✖	● (II)
paxalisib	✖	✖	✖	✖	● (II)
samotolisib	✖	✖	✖	✖	● (II)
sirolimus	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
atezolizumab + ipatasertib	✖	✖	✖	✖	● (I/II)
ARQ-751, fulvestrant, chemotherapy	✖	✖	✖	✖	● (I)
copanlisib, olaparib, durvalumab	✖	✖	✖	✖	● (I)
GDC-0077	✖	✖	✖	✖	● (I)
gedatolisib + palbociclib	✖	✖	✖	✖	● (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 ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

FDA information is current as of 2020-02-28. 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:** 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

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

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

EGFR exon 19 deletion (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

PIK3CA p.(E545K) c.1633G>A

○ alpelisib + fulvestrant

Cancer type: Breast Cancer **Label as of:** 2019-05-24 **Variant class:** PIK3CA E545K mutation

Other criteria: ERBB2 negative, Hormone receptor positive

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212526s000lbl.pdf

Current NCCN Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

NCCN information is current as of 2019-11-01. 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 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; 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 2.2020]

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; 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 2.2020]

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; 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 2.2020]

EGFR exon 19 deletion (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; 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 2.2020]

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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; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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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; 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; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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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 Non-Small Cell Lung Cancer; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

EGFR exon 19 deletion (continued)

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; 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; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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; 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; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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 first-line systemic therapy (First-line therapy) (Other Recommended)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Sensitizing EGFR mutation discovered during first-line systemic therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; 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; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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; 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 (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

bevacizumab + erlotinib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Non-Squamous Non-Small Cell Lung Cancer; Sensitizing EGFR mutation discovered prior to first-line systemic therapy (First-line therapy) (Useful in Certain Circumstances)
- Non-Squamous Non-Small Cell Lung Cancer; Sensitizing EGFR mutation discovered during first-line systemic therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

EGFR exon 19 deletion (continued)

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; Weekly pulse erlotinib (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

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afatinib

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; Recurrent disease; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

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afatinib + cetuximab

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

Other criteria: EGFR T790M negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Progression after receiving erlotinib, afatinib, dacomitinib, or gefitinib and systemic therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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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; Recurrent disease; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

EGFR exon 19 deletion (continued)

gefitinib

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; Recurrent disease; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

osimertinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Brain metastases; Newly diagnosed (Not specified)
- Non-Small Cell Lung Cancer; Leptomeningeal and Spine metastases (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

alectinib

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

brigatinib

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

EGFR exon 19 deletion (continued)

ceritinib

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

crizotinib

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

lorlatinib

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing EGFR mutations who relapse on EGFR TKI therapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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%."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

PIK3CA p.(E545K) c.1633G>A

alpelisib + fulvestrant

Cancer type: Breast Cancer **Variant class:** PIK3CA mutation

Other criteria: ERBB2 negative, ER positive, PR positive

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Recurrent or Stage IV Invasive Breast Cancer; Postmenopausal or Premenopausal receiving ovarian ablation or suppression (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 1.2020]

Current EMA Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

EMA information is current as of 2020-02-28. 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:** 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 (Allergan) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2019-11-12 **Variant class:** EGFR exon 19 deletion

Reference:

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

bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2020-02-20 **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

EGFR exon 19 deletion (continued)

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

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

Current ESMO Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

ESMO information is current as of 2019-11-01. For the most up-to-date information, search www.esmo.org.

EGFR exon 19 deletion

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 / 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)

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]

EGFR exon 19 deletion (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)

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]

EGFR exon 19 deletion (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)

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]

EGFR exon 19 deletion (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)

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]

EGFR exon 19 deletion (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 / 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]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

References

1. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974-6. PMID: 2992089
2. 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. 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
19. 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. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]
28. Volinia et al. Molecular cloning, cDNA sequence, and chromosomal localization of the human phosphatidylinositol 3-kinase p110 alpha (PIK3CA) gene. Genomics. 1994 Dec;24(3):472-7. PMID: 7713498

References (continued)

29. Cantley. The phosphoinositide 3-kinase pathway. Science. 2002 May 31;296(5573):1655-7. PMID: 12040186
30. Fruman et al. The PI3K Pathway in Human Disease. Cell. 2017 Aug 10;170(4):605-635. PMID: 28802037
31. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat. Rev. Genet. 2006 Aug;7(8):606-19. PMID: 16847462
32. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. Nat. Rev. Mol. Cell Biol. 2012 Feb 23;13(3):195-203. PMID: 22358332
33. Yuan et al. PI3K pathway alterations in cancer: variations on a theme. Oncogene. 2008 Sep 18;27(41):5497-510. PMID: 18794884
34. Liu et al. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. 2009 Aug;8(8):627-44. PMID: 19644473
35. Hanahan et al. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74. PMID: 21376230
36. Miled et al. Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit. Science. 2007 Jul 13;317(5835):239-42. PMID: 17626883
37. Burke et al. Synergy in activating class I PI3Ks. Trends Biochem. Sci. 2015 Feb;40(2):88-100. PMID: 25573003
38. Burke et al. Oncogenic mutations mimic and enhance dynamic events in the natural activation of phosphoinositide 3-kinase p110α (PIK3CA). Proc. Natl. Acad. Sci. U.S.A. 2012 Sep 18;109(38):15259-64. PMID: 22949682
39. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212526s000lbl.pdf
40. Mayer et al. A Phase Ib Study of Alpelisib (BYL719), a PI3Kα-Specific Inhibitor, with Letrozole in ER+/HER2- Metastatic Breast Cancer. Clin. Cancer Res. 2017 Jan 1;23(1):26-34. PMID: 27126994
41. Mayer et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). Clin. Cancer Res. 2019 Feb 5. PMID: 30723140
42. Jung et al. Pilot study of sirolimus in patients with PIK3CA mutant/amplified refractory solid cancer. Mol Clin Oncol. 2017 Jul;7(1):27-31. PMID: 28685070
43. Janku et al. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol. Cancer Ther. 2011 Mar;10(3):558-65. PMID: 21216929