

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

Date: 23 Dec 2021 1 of 23

Sample Information

Patient Name: 陳欽玲 Gender: Female ID No.: J200033911 History No.: 22998738

Age: 72

Ordering Doctor: DOC8051A張千奕

Ordering REQ.: 0BQCHQV Signing in Date: 2021/12/22

Path No.: S110-94915 **MP No.:** F21112

Assay: Oncomine Focus Assay

Sample Type: FFPE Block No.: S110-62342A Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	EGFR p.(T790M) c.2369C>T, EGFR p.(G719S) c.2155G>A, EGFR amplification	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

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Date: 23 Dec 2021

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	EGFR p.(T790M) c.2369C>T epidermal growth factor receptor Allele Frequency: 45.55%	osimertinib ^{1, 2} osimertinib + chemotherapy	None	4
	Prognostic significance: None Diagnostic significance: None			
IA	EGFR p.(G719S) c.2155G>A epidermal growth factor receptor Allele Frequency: 63.30%	gefitinib* ² bevacizumab + erlotinib bevacizumab + gefitinib erlotinib + ramucirumab gefitinib + chemotherapy osimertinib osimertinib + chemotherapy	None	7
	Prognostic significance: None Diagnostic significance: None			
IIC	AR amplification androgen receptor Prognostic significance: None Diagnostic significance: None	None	hormone therapy	0

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

Public data sources included in prognostic and diagnostic significance: NCCN, 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



Alerts informed by public data sources: ⊘ Contraindicated, U Resistance

EGFR p.(T790M) c.2369C>T

DNA Sequence Variants

⊘ gefitinib*²

ofatinib, dacomitinib, erlotinib, gefitinib

Public data sources included in alerts: FDA1, NCCN, EMA2, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

EGFR amplification

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

Allele Gene Amino Acid Change Coding Variant ID Locus Frequency **Transcript** Variant Effect Coverage **EGFR** p.(G719S) c.2155G>A COSM6252 chr7:55241707 NM_005228.5 1970 63.30% missense p.(T790M) 2000 **EGFR** c.2369C>T COSM6240 chr7:55249071 45.55% NM_005228.5 missense p.(T726=) chr8:38271771 FGFR1 c.2178T>G 8.02% NM_001174067.1 synonymous 711

Copy Number Variations		
Gene	Locus	Copy Number
EGFR	chr7:55198956	23.15
AR	chrX:66776186	7.95

Biomarker Descriptions

AR (androgen receptor)

Background: The AR gene encodes the androgen receptor protein (AR), a ligand-activated transcription factor regulated by the binding of the hormones testosterone and dihydrotestosterone^{1,2}. Hormone binding to AR results in receptor dimerization, nuclear translocation, and target gene transcription, thus activating the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR signaling pathways, which promote cell proliferation and survival^{2,3,4}.

Alterations and prevalence: Alterations in AR function can result from overexpression, gene amplification, or mutations. AR mutations, including L702H, W742C/L, H875Y, and T878A, are commonly observed in 10-30% of castration-resistant prostate cancer and result in decreased ligand specificity, allowing other nuclear hormones to activate AR5. Androgen receptor splice variants have been reported in castration resistant prostate cancer^{6,7}. The androgen receptor splice variant 7 (AR-V7) is a result of aberrant mRNA splicing of AR exons 1-3 and a cryptic exon 3, resulting in the expression of a constitutively active protein⁷.

Potential relevance: The FDA has granted fast track designation (2016) to seviteronel for AR-positive triple-negative breast cancer (TNBC) patients⁸. Androgen deprivation therapy (ADT) such as abiraterone⁹ (2011) and enzalutamide¹⁰ (2011) are FDA approved for use in locally advanced and metastatic prostate cancers. Although many men initially respond to ADT, most will develop hormone resistance. Resistance to ADT is also associated with other aberrations of the AR gene including mutations within the ligand binding domain and gene amplification^{5,11,12}. The androgen receptor splice variant, AR-V7, lacks the ligand binding domain, resulting in constitutive activation and is associated with resistance to androgen deprivation therapy (ADT) in advanced prostate cancer⁶.

EGFR (epidermal growth factor receptor)

<u>Background:</u> The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the ERBB/human epidermal growth factor receptor (HER) family. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4¹³. 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^{14,15}.

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations 16,17,18,19. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21²⁰. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer. A second group of less prevalent activating mutations include E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{21,22,23,24}. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations²⁵. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V and are primarily observed in glioblastoma^{20,26}. Amplification of EGFR is observed in several cancer types including 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma^{17,18,19,26,27}. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRVIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma^{28,29,30}.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib³¹ (2004) and gefitinib³² (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations. Second-generation TKIs afatinib33 (2013) and dacomitinib34 (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies^{35,36,37,38}. However, in 2021, the irreversible tyrosine kinase inhibitor, mobocertinib³⁹was FDA approved for the treatment of NSCLC with EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance⁴⁰. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases²⁰. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib⁴¹ (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance. In this case, resistance is associated with the C797S mutation, and occurs in 22-44% of cases⁴⁰. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa⁴². T790M and C797S can occur in either cis or trans allelic orientation⁴². If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs⁴². If C797S co-occurs in trans with T790M following

Biomarker Descriptions (continued)

sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone^{42,43}. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs⁴². Fourth-generation TKIs are in development to overcome acquired C797S and T790M resistance mutations after osimertinib treatment. EGFR targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, amivantamab⁴⁴, targeting EGFR and MET was approved (2021) NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy quaratusugene ozeplasmid⁴⁵ in combination with osimertinib received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. BDTX-189⁴⁶ was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

Relevant Therapy Summary

EGFR p.(G719S) c.2155G>A

EGFR p.(T790M) c.2369C>T **Relevant Therapy** FDA **NCCN EMA ESMO Clinical Trials*** osimertinib × osimertinib + chemotherapy × × × × osimertinib + chemotherapy + surgical intervention × × × × durvalumab, chemotherapy (III) × × × DZD-9008 × × × × (I/II) amivantamah × × × × (I) lazertinib, amivantamab, chemotherapy (I) × × X ×

FDA NCCN **ESMO** Clinical Trials* **Relevant Therapy EMA** bevacizumab + erlotinib × × × erlotinib + ramucirumab × × × osimertinib × × osimertinib + chemotherapy × × × × osimertinib + chemotherapy + surgical intervention × × × × gefitinib (Mylan) × × × × bevacizumab + gefitinib × × × × gefitinib + carboplatin + pemetrexed × × × × durvalumab, chemotherapy × × × × **(III)** datopotamab deruxtecan × × × (II) × osimertinib, savolitinib (II) × × × ×

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

Relevant Therapy Summary (continued)

■ In this cancer type □ In other cancer type □ In this cancer type and other cancer types □ No evidence

EGFR p.(G719S) c.2155G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
DZD-9008	×	×	×	×	(/)
amivantamab	×	×	×	×	(I)
lazertinib, amivantamab, chemotherapy	×	×	×	×	(I)
TNO-155, nazartinib	×	×	×	×	(I)

AR amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
androgen receptor therapy	×	0	×	×	×
bicalutamide	×	0	×	×	×
leuprorelin	×	0	×	×	×

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

Relevant Therapy Details

Current FDA Information

In this cancer type
In other cancer type
In this cancer type and other cancer types

FDA information is current as of 2021-10-13. For the most up-to-date information, search www.fda.gov.

EGFR p.(T790M) c.2369C>T

osimertinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2021-07-26 Variant class: EGFR T790M mutation

Indications and usage:

TAGRISSO® is a kinase inhibitor indicated for:

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208065s022lbl.pdf

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Current NCCN Information

In this cancer type

O In other cancer type

In this cancer type and other cancer types

NCCN information is current as of 2021-10-01. 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.(T790M) c.2369C>T

osimertinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

osimertinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

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

osimertinib + chemotherapy

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Stage IIB, Stage IIIA, Stage IIIB (Adjuvant therapy)
- Stage IIIA; Resectable (Adjuvant therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

osimertinib + chemotherapy + surgical intervention

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Stage IIB (Adjuvant therapy)
- Stage IIIA; Resectable (Adjuvant therapy)

EGFR p.(G719S) c.2155G>A

osimertinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR G719 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR G719 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR G719 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

osimertinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR G719 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy);
 Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Leptomeningeal Metastases, Progression (Subsequent therapy); Consider

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EGFR p.(G719S) c.2155G>A (continued)

osimertinib + chemotherapy

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR G719 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

Stage IIB, Stage IIIA, Stage IIIB (Adjuvant therapy)

Stage IIIA; Resectable (Adjuvant therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

osimertinib + chemotherapy + surgical intervention

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR G719 mutation

NCCN Recommendation category: 2A Population segment (Line of therapy):

■ Stage IIB (Adjuvant therapy)

■ Stage IIIA; Resectable (Adjuvant therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

AR amplification

androgen receptor therapy

Cancer type: Head and Neck Cancer Variant class: AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

O bicalutamide

Cancer type: Head and Neck Cancer Variant class: AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

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AR amplification (continued)

O leuprorelin

Cancer type: Head and Neck Cancer Variant class: AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

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Current EMA Information

In this cancer type

O In other cancer type

In this cancer type and other cancer types

EMA information is current as of 2021-10-13. For the most up-to-date information, search www.ema.europa.eu/ema.

EGFR p.(T790M) c.2369C>T

osimertinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2021-07-01 Variant class: EGFR T790M mutation

Reference:

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

EGFR p.(G719S) c.2155G>A

gefitinib (Mylan)

Cancer type: Non-Small Cell Lung Cancer Label as of: 2021-10-05 Variant class: EGFR G719 mutation

Reference:

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

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Current ESMO Information

In this cancer type
In other cancer type
In this cancer type and other cancer types

ESMO information is current as of 2021-10-01. For the most up-to-date information, search www.esmo.org.

EGFR p.(T790M) c.2369C>T

osimertinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

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

Population segment (Line of therapy):

■ Stage IV (Second-line therapy); ESMO-MCBS v1.1 score: 4

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

EGFR p.(G719S) c.2155G>A

osimertinib

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

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

Population segment (Line of therapy):

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

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

bevacizumab + 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 (First-line therapy)

EGFR p.(G719S) c.2155G>A (continued)

bevacizumab + 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 (First-line therapy)

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

erlotinib + ramucirumab

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

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

Population segment (Line of therapy):

■ Stage IV (First-line therapy)

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

gefitinib + carboplatin + pemetrexed

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

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

Population segment (Line of therapy):

Stage IV (First-line therapy)

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

bevacizumab + erlotinib

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

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

Population segment (Line of therapy):

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

EGFR p.(G719S) c.2155G>A (continued)

bevacizumab + gefitinib

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):

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

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

erlotinib + ramucirumab

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

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

Population segment (Line of therapy):

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

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

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 (First-line therapy)

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

bevacizumab + erlotinib

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

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

Population segment (Line of therapy):

■ Stage IV (First-line therapy)

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EGFR p.(G719S) c.2155G>A (continued)

bevacizumab + 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 (First-line therapy)

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

erlotinib + ramucirumab

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

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

Population segment (Line of therapy):

■ Stage IV (First-line therapy)

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

gefitinib + carboplatin + pemetrexed

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

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

Population segment (Line of therapy):

Stage IV (First-line therapy)

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Clinical Trials in Taiwan region:

Clinical Trials Summary

EGFR p.(T790M) c.2369C>T

NCT ID	Title	Phase
NCTID	Title	Phase
NCT02609776	A Phase I, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer.	1
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) With EGFR or HER2 Mutation	1/11
NCT04077463	An Open-label Phase I/Ib Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer	I
NCT03800134	A Phase III, Double-blind, Placebo-controlled, Multi-center International Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III Non-small Cell Lung Cancer (AEGEAN)	III

EGFR p.(G719S) c.2155G>A

NCT ID	Title	Phase
NCT03778229	A Phase II, Single Arm Study Assessing Efficacy of Osimertinib With Savolitinib in Patients With EGFRm + MET+, Locally Advanced or Metastatic Non Small Cell Lung Cancer Who Have Progressed Following Osimertinib Treatment (SAVANNAH Study)	II
NCT02609776	A Phase I, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer.	I
NCT04484142	Phase II, Single-arm, Open-label Study of DS-1062a in Advanced or Metastatic Non-small Cell Lung Cancer With Actionable Genomic Alterations and Progressed On or After Applicable Targeted Therapy and Platinum Based Chemotherapy (TROPION-Lung05)	II
NCT03114319	An Open-label, Multi-center, Phase I, Dose Finding Study of Oral TNO155 in Adult Patients With Advanced Solid Tumors.	1
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) With EGFR or HER2 Mutation	1/11
NCT04077463	An Open-label Phase I/Ib Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer	I
NCT03800134	A Phase III, Double-blind, Placebo-controlled, Multi-center International Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III Non-small Cell Lung Cancer (AEGEAN)	III

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Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended



Resistance



Breakthrough



FDA information is current as of 2021-10-13. For the most up-to-date information, search www.fda.gov.

EGFR p.(T790M) c.2369C>T

A osimertinib + quaratusugene ozeplasmid

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Supporting Statement:

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

Reference:

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

EGFR p.(G719S) c.2155G>A

osimertinib + quaratusugene ozeplasmid

Cancer type: Non-Small Cell Lung Cancer

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Supporting Statement:

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Reference:

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

AR amplification

seviteronel

Cancer type: Triple Negative Breast Cancer

Variant class: AR positive

Supporting Statement:

The FDA has granted Fast Track Designation to the small-molecule CYP17 lyase-selective inhibitor, seviteronel, for:

- Androgen receptor (AR) positive advanced triple negative breast cancer (TNBC).
- Estrogen receptor (ER) positive advanced breast cancer.

https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA

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Current NCCN Information

Contraindicated

Not recommended

Resistance

Breakthrough

A Fast Track

NCCN information is current as of 2021-10-01. 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.(T790M) c.2369C>T

atezolizumab

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

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

nivolumab

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

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

pembrolizumab

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

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

afatinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

Summary:

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

■ "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

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EGFR p.(T790M) c.2369C>T (continued)

dacomitinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

Summary:

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

■ "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

erlotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

Summary:

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

■ "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

gefitinib

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR T790M mutation

Summary:

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

■ "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

EGFR p.(G719S) c.2155G>A

alectinib

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

Summary:

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

"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.(G719S) c.2155G>A (continued)

brigatinib

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

Summary:

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

"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 6.2021]

ceritinib

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

Summary:

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

"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 6.2021]

crizotinib

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

Summary:

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

"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 6.2021]

lorlatinib

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

Summary:

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

"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 6.2021]

atezolizumab

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

Summary:

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

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

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EGFR p.(G719S) c.2155G>A (continued)

nivolumab

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

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

pembrolizumab

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

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 6.2021]

Current EMA Information

Ocontraindicated Not recommended Resistance Preakthrough Fast Track

EMA information is current as of 2021-10-13. For the most up-to-date information, search www.ema.europa.eu/ema.

EGFR p.(T790M) c.2369C>T

gefitinib

Cancer type: Non-Small Cell Lung Cancer Label as of: 2021-03-05 Variant class: EGFR T790M mutation

Reference:

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

gefitinib (Mylan)

Cancer type: Non-Small Cell Lung Cancer Label as of: 2021-10-05 Variant class: EGFR T790M mutation

Reference:

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

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Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

Date: 23 Dec 2021

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