



Sample Information

Patient Name: 張斐萍
Gender: Female
ID No.: A223500935
History No.: 46317946
Age: 49

Ordering Doctor: DOC3064F 陳育民
Ordering REQ.: D6M463N
Signing in Date: 2022/01/05

Path No.: S111-98035
MP No.: F22002
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-40870A
Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page
Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)	2
Biomarker Descriptions	2
Relevant Therapy Summary	3
Relevant Therapy Details	3
Clinical Trials Summary	14
Alert Details	14

Report Highlights
1 Relevant Biomarkers
6 Therapies Available
6 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	<i>EML4-ALK fusion</i>	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	EML4-ALK fusion EMAP like 4 - ALK receptor tyrosine kinase Prognostic significance: None Diagnostic significance: None	alectinib ^{1,2} brigatinib ^{1,2} ceritinib ^{1,2} crizotinib ^{1,2} lorlatinib ^{1,2} next-generation ALK inhibitor	brigatinib ceritinib crizotinib	6

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.

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

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
EML4-ALK	EML4-ALK.E13A20.COSF408.1	chr2:42522656 - chr2:29446394	41821

Biomarker Descriptions

ALK (ALK receptor tyrosine kinase)

Background: The ALK gene encodes the ALK receptor tyrosine kinase (RTK) with sequence similarity to the insulin receptor subfamily of kinases¹. ALK is the target of recurrent alterations in cancer, the most common being chromosomal rearrangements that generate fusion genes containing the intact ALK tyrosine kinase domain combined with multiple partner genes². ALK fusion kinases are constitutively activated and drive oncogenic transformation via activation of downstream STAT3, PI3K/AKT/MTOR, and RAS/RAF/MEK/ERK pathways^{2,3,4,5}.

Alterations and prevalence: ALK was discovered by positional cloning of translocations involving nucleophosmin (NPM) on 5q35 with a previously unidentified RTK on 2p23 (ALK), which occur in over 50% of anaplastic large cell lymphoma cases^{1,6}. In contrast, about 5% of non-small cell lung cancer (NSCLC) cases generate recurrent ALK fusions with EML4, KIF5B, and HIP1^{7,8,9}.

Potential relevance: The first generation small molecule tyrosine kinase inhibitor (TKI), crizotinib¹⁰, was FDA approved (2011) for the treatment of ALK positive advanced NSCLC. Kinase domain mutations including L1196M, G1269A, F1174L, G1202R, as well as other variants have been shown to confer acquired resistance to crizotinib in ALK positive NSCLC^{11,12,13,14}. Other mechanisms of acquired resistance involve amplification of the ALK fusion gene and activation of alternate or bypass signaling pathways involving EGFR, KIT, MET, and IGF1R¹⁵. In order to overcome acquired resistance, second and third-generation ALK inhibitors including ceritinib¹⁶ (2014), alectinib¹⁷ (2015), brigatinib¹⁸ (2017), and lorlatinib¹⁹ (2018) were developed and approved by the FDA. Two phase III trials evaluating crizotinib and alectinib as first line therapy in NSCLC, including patients with asymptomatic central nervous system (CNS) disease, were conducted and both studies showed consistent higher objective response rates (ORR) with alectinib relative to crizotinib^{20,21}. For this reason, alectinib is a preferred first-line treatment of ALK positive NSCLC²².

Relevant Therapy Summary

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

EML4-ALK fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ceritinib	●	●	●	●	● (IV)
brigatinib	●	●	●	●	×
crizotinib	●	●	●	●	×
alectinib	●	●	●	●	● (III)
lorlatinib	●	●	●	●	×
next-generation ALK inhibitor	×	×	×	●	×
brigatinib, alectinib	×	×	×	×	● (III)
entrectinib	×	×	×	×	● (II)
repotrectinib	×	×	×	×	● (I/II)

* 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 2021-11-17. For the most up-to-date information, search www.fda.gov.

EML4-ALK fusion

● alectinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-09-03

Variant class: ALK fusion or ALK overexpression

Indications and usage:

ALECENSA® is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208434s012lbl.pdf

EML4-ALK fusion (continued)

● brigatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-09-24

Variant class: ALK fusion

Indications and usage:

ALUNBRIG® is a kinase inhibitor indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208772s012lbl.pdf

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-10-07

Variant class: ALK fusion or ALK overexpression

Indications and usage:

ZYKADIA® is a kinase inhibitor indicated for the treatment of adults with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-09-22

Variant class: ALK fusion

Indications and usage:

XALKORI® is a kinase inhibitor indicated for the treatment of

- patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test.
- pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.
 - Limitations of Use: The safety and efficacy of XALKORI® have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202570s031lbl.pdf

● lorlatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-03-03

Variant class: ALK fusion or ALK overexpression

Indications and usage:

LORBRENA® is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf

Current NCCN Information

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

NCCN information is current as of 2021-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

EML4-ALK fusion

● alectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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 7.2021]

● brigatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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 7.2021]

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

EML4-ALK fusion (continued)

● lorlatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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 7.2021]

● alectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion or ALK overexpression

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

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

● alectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

● brigatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

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

EML4-ALK fusion (continued)

● brigatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

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

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

● lorlatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion or ALK overexpression

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

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

EML4-ALK fusion (continued)

● lorlatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- Brain Metastases (Line of therapy not specified)

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

○ brigatinib

Cancer type: Inflammatory Myofibroblastic Tumor Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2021]

○ ceritinib

Cancer type: Inflammatory Myofibroblastic Tumor Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2021]

○ crizotinib

Cancer type: Inflammatory Myofibroblastic Tumor Variant class: ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2021]

Current EMA Information

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

EMA information is current as of 2021-11-17. For the most up-to-date information, search www.ema.europa.eu/ema.

EML4-ALK fusion

☒ alectinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-10-11

Variant class: ALK fusion or ALK overexpression

Reference:

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

☒ brigatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-10-15

Variant class: ALK fusion

Reference:

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

☒ crizotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-07-21

Variant class: ALK fusion

Reference:

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

☒ ceritinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-10-11

Variant class: ALK positive

Reference:

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

☒ lorlatinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-11-05

Variant class: ALK positive

Reference:

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

Current ESMO Information

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

ESMO information is current as of 2021-11-01. For the most up-to-date information, search www.esmo.org.

EML4-ALK fusion

● alectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 4
- Advanced, Progression (Second-line therapy, Subsequent 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.]

● brigatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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.]

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Advanced, Progression (Second-line therapy, Subsequent 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.]

EML4-ALK fusion (continued)

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 4
- (Second-line therapy, Subsequent 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.]

● next-generation ALK inhibitor

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Advanced (Second-line therapy, Subsequent 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.]

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Stage IV (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.]

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Stage IV (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.]

EML4-ALK fusion (continued)

● next-generation ALK inhibitor

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Advanced, Progression (Second-line therapy, Subsequent 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.]

● alectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- (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.]

● brigatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Advanced (Second-line therapy, Subsequent 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.]

● lorlatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- Stage IV; Advanced, Progression (Second-line therapy, Subsequent 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.]

EML4-ALK fusion (continued)

● brigatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

ESMO Level of Evidence/Grade of Recommendation: III / 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.]

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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

Population segment (Line of therapy):

- (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.]

Clinical Trials in Taiwan region:

Clinical Trials Summary

EML4-ALK fusion

NCT ID	Title	Phase
NCT03596866	A Phase III Randomized Open-label Study of Brigatinib (Alunbrig) Versus Alectinib (Alecensa) in Advanced Anaplastic Lymphoma Kinase-Positive Non Small-Cell Lung Cancer Patients Who Have Progressed on Crizotinib (Xalkori)	III
NCT02584933	An Open-label, Multi-center, Phase IV Roll-over Study in Patients With ALK Positive Malignancies Who Have Completed a Novartis-sponsored Ceritinib (LDK378) Study and Are Judged by the Investigator to Benefit From Continued Treatment With Ceritinib	IV
NCT03456076	A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With Completely Resected Stage IB (Tumors Equal to or Larger Than 4cm) to Stage IIIA Anaplastic Lymphoma Kinase Positive Non-Small Cell Lung Cancer	III
NCT02568267	An Open-Label, Multicenter, Global Phase II Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements. Studies of Tumor Alterations Responsive to Targeting Receptor Kinases (STARTRK-2)	II
NCT03093116	A Phase I/II, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)	I/II
NCT04094610	A Phase I/II, Open-Label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects With Advanced or Metastatic Malignancies Harboring ALK, ROS1, NTRK1-3 Alterations	I/II

Alerts Informed By Public Data Sources

Current NCCN Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

NCCN information is current as of 2021-11-01. For the most up-to-date information, search www.nccn.org. For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

EML4-ALK fusion

atezolizumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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 7.2021]

EML4-ALK fusion (continued)

– nivolumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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 7.2021]

– pembrolizumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

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 7.2021]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

References

1. Webb et al. Anaplastic lymphoma kinase: role in cancer pathogenesis and small-molecule inhibitor development for therapy. *Expert Rev Anticancer Ther.* 2009 Mar;9(3):331-56. PMID: 19275511
2. Shaw et al. Tyrosine kinase gene rearrangements in epithelial malignancies. *Nat. Rev. Cancer.* 2013 Nov;13(11):772-87. PMID: 24132104
3. Chiarle et al. Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target. *Nat. Med.* 2005 Jun;11(6):623-9. PMID: 15895073
4. Bai et al. Nucleophosmin-anaplastic lymphoma kinase associated with anaplastic large-cell lymphoma activates the phosphatidylinositol 3-kinase/Akt antiapoptotic signaling pathway. *Blood.* 2000 Dec 15;96(13):4319-27. PMID: 11110708
5. Hrustanovic et al. RAS signaling in ALK fusion lung cancer. *Small GTPases.* 2016;7(1):32-3. PMID: 26901483
6. Morris et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science.* 1994 Mar 4;263(5151):1281-4. PMID: 8122112
7. Kwak et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N. Engl. J. Med.* 2010 Oct 28;363(18):1693-703. PMID: 20979469
8. Yu et al. Frequencies of ALK rearrangements in lung adenocarcinoma subtypes: a study of 2299 Chinese cases. *Springerplus.* 2016 Jun 27;5(1):894. doi: 10.1186/s40064-016-2607-5. eCollection 2016. PMID: 27386342
9. Dai et al. Incidence and patterns of ALK FISH abnormalities seen in a large unselected series of lung carcinomas. *Send to Mol Cytogenet.* 2012 Dec 3;5(1):44. doi: 10.1186/1755-8166-5-44. PMID: 23198868
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202570s031lbl.pdf
11. Choi et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N. Engl. J. Med.* 2010 Oct 28;363(18):1734-9. PMID: 20979473
12. Awad et al. ALK inhibitors in non-small cell lung cancer: crizotinib and beyond. *Clin Adv Hematol Oncol.* 2014 Jul;12(7):429-39. PMID: 25322323
13. Kim et al. Heterogeneity of genetic changes associated with acquired crizotinib resistance in ALK-rearranged lung cancer. *J Thorac Oncol.* 2013 Apr;8(4):415-22. PMID: 23344087
14. Katayama et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. *Sci Transl Med.* 2012 Feb 8;4(120):120ra17. doi: 10.1126/scitranslmed.3003316. Epub 2012 Jan 25. PMID: 22277784
15. Katayama. Drug resistance in anaplastic lymphoma kinase-rearranged lung cancer. *Cancer Sci.* 2018 Mar;109(3):572-580. PMID: 29336091
16. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf
17. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208434s012lbl.pdf
18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208772s012lbl.pdf
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf
20. Peters et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* 2017 Aug 31;377(9):829-838. PMID: 28586279
21. Hida et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet.* 2017 Jul 1;390(10089):29-39. PMID: 28501140
22. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]