Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
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Sample Information

Patient Name: 韓鐘磊
Gender: Male
ID No.: C120260498
History No.: 46869232
Age: 50

Ordering Doctor: DOC1878G 沈佳儀
Ordering REQ.: 0BXNMHK
Signing in Date: 2022/07/21

Path No.: S111-99876
MP No.: F22072
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S111-26016A
Percentage of tumor cells: 60%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	***EML4-ALK fusion***	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	***MET amplification***		

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	**alectinib** [1, 2] **brigatinib** [1, 2] **ceritinib** [1, 2] **crizotinib** [1, 2] **lorlatinib** [1, 2] next-generation ALK inhibitor	brigatinib ceritinib crizotinib lorlatinib	4
IA	*MET amplification* MET proto-oncogene, receptor tyrosine kinase	capmatinib crizotinib tepotinib	None	1

Public data sources included in relevant therapies: FDA[1], 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.

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

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
EML4-ALK	EML4-ALK.E18A20.COSF487.1	chr2:42543190 - chr2:29446394	25783

Copy Number Variations

Gene	Locus	Copy Number
MET	chr7:116313480	5.1

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 kinases[1]. 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 genes[2]. 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), crizotinib[10], 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 IGF1R[15]. In order to overcome acquired resistance, second and third-generation ALK inhibitors including ceritinib[16] (2014), alectinib[17] (2015), brigatinib[18] (2017), and lorlatinib[19] (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 NSCLC[22].

MET (MET proto-oncogene, receptor tyrosine kinase)

Background: The MET proto-oncogene encodes a receptor tyrosine kinase for the hepatocyte growth factor (HGF) protein, which is expressed by mesenchymal cells. MET is expressed as multiple isoforms with transcript variant 1 (NM_001127500.3) encoding a

Biomarker Descriptions (continued)

1408 amino acid protein and transcript variant 2 (NM_000245.4) encoding a 1390 amino acid protein, both of which possess an intact protein kinase domain[23]. Ubiquitin-dependent proteolysis is responsible for regulating the steady state level of the MET protein via recognition of the tyrosine phosphorylation site Y1003(NM_000245.4), sometimes referred to as Y1021 (NM_001127500.3), in the MET Cbl-binding domain within the juxtamembrane region[24,25,26]. Growth factor signaling leads to MET dimerization and subsequent initiation of downstream effectors including those involved in the RAS/RAF/MEK/ERK and PI3K/AKT signaling pathways, which regulate cell migration, proliferation, and survival[27,28].

Alterations and prevalence: Somatic mutations in MET are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 8% of papillary renal cell carcinoma (PRCC), and 4% of lung adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[29,30]. Recurrent somatic MET alterations include activating mutations, gene amplification, and translocations generating MET gene fusions. Recurrent somatic mutations fall into two classes, mutations in the MET kinase domain, which are uncommon, and splice-site mutations affecting exon 14. Recurrent kinase domain mutations are observed in PRCC and include M1250T, H1094Y, and V1070E (NM_000245.4)[29,30]. Mutation of the Y1003 phosphorylation site is reported in approximately 2% of MET altered lung cancer[31]. In contrast, splice-site mutations flanking exon 14 are observed in 3-4% of all non-small cell lung cancer (NSCLC)[32]. These mutations include canonical splice site mutations affecting exon 14 and deletions that extend into the splicing motifs within intron 13[31,33]. Such mutations disrupt splicing leading to the formation of an alternative transcript that joins exon 13 directly to exon 15 and skips exon 14 entirely. The MET exon 14 skipping transcript lacks the juxtamembrane domain that contains the recognition motif for ubiquitin-dependent proteolysis and thus leads to a marked increase in the steady-state level of the MET protein[34]. MET exon 14 skipping mutations act as oncogenic drivers in lung cancer mutually exclusive to activating mutations in EGFR and KRAS and other oncogenic fusions such as ALK and ROS1[33,35,36]. MET is amplified in 2-5% of ovarian cancer, esophageal adenocarcinoma, stomach adenocarcinoma, glioblastoma, and lung adenocarcinoma[29,37,38]. Recurrent MET fusions, although infrequent, are observed in adult and pediatric glioblastoma, papillary renal cell carcinoma, lung cancer, liver cancer, thyroid cancer, and melanoma[39,40,41]. MET alterations are believed to be enriched in late-stage cancers where they drive tumor progression and metastasis[42,43,44].

Potential relevance: In 2020, the FDA granted accelerated approval to capmatinib[45] for NSCLC harboring MET exon 14 skipping positive as detected by an FDA-approved test. The kinase inhibitor, tepotinib[46], is also approved (2021) for MET exon 14 skipping mutations in NSCLC. MET exon 14 skipping mutations confer sensitivity to approved kinase inhibitors including crizotinib (2011), which is recommended for MET amplifications and exon 14 skipping mutations[22,33,35,36]. The FDA also granted breakthrough therapy designation (2018) to crizotinib for metastatic non-small cell lung cancer (NSCLC) with MET exon 14 alterations with disease progression on or after platinum-based chemotherapy[47]. Conversely, amplification of MET has been observed to mediate resistance to EGFR tyrosine kinase inhibitors (TKIs)[48,49,50,51,52]. However, the FDA has granted Fast Track designation (2021) to the MET/CSF1R/SRC small molecule inhibitor, TPX-0022[53], for MET amplified advanced or metastatic gastric cancer, including gastroesophageal junction adenocarcinoma (GEJ) after prior chemotherapy. Tepotinib has also been recommended for treatment of NSCLC with high-level MET amplification[22]. In a phase II trial testing the MET inhibitor savolitinib, patients with advanced PRCC exhibited median progression free survival (PFS) of 6.2 and 1.4 months for MET-driven and MET-independent PRCC, respectively[54].

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	●	◑	●	●	✖
lorlatinib	●	◑	●	●	✖
alectinib	●	●	●	●	✖
next-generation ALK inhibitor	✖	✖	✖	●	✖

* 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

EML4-ALK fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
brigatinib, alectinib	✖	✖	✖	✖	● (III)
repotrectinib	✖	✖	✖	✖	● (I/II)

MET amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capmatinib	✖	●	✖	✖	✖
crizotinib	✖	●	✖	✖	✖
tepotinib	✖	●	✖	✖	✖
HLX55	✖	✖	✖	✖	● (I)

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

Relevant Therapy Details

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2022-06-15. 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:** 2022-02-28 **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/2022/208772s013lbl.pdf

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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

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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

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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

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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 2022-06-01. 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 3.2022]

● 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 3.2022]

● 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 3.2022]

● 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 3.2022]

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 3.2022]

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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]

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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 3.2022]

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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 3.2022]

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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]

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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 3.2022]

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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 3.2022]

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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 3.2022]

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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]

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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 2.2022]

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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 2.2022]

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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 2.2022]

EML4-ALK fusion (continued)

lorlatinib

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 2.2022]

MET amplification

capmatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET amplification

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

crizotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET amplification

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

tepotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET amplification

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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 2022-06-15. 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:** 2022-05-18 **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:** 2022-02-21 **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:** 2022-02-25 **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:** 2022-04-07 **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 2022-06-01. 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.]

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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.]

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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.]

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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.]

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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.]

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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.]

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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.]

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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
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

MET amplification

NCT ID	Title	Phase
NCT04169178	A Phase I Dose Finding/Expansion Study of HLX55, A Monoclonal Antibody Targeting Tyrosine-Protein Kinase MET (C-MET) in Patients With Advanced Solide Tumors Refactory to Standard Therapy	I

Alerts Informed By Public Data Sources

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2022-06-01. 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 rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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 rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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 rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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