Taipei Veterans General Hospital

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

Sample Information

Patient Name: 邱狄勇
Gender: Male
ID No.: 3309211979
History No.: 49387975
Age: 44

Ordering Doctor: DOC5354J 陳威志
Ordering REQ.: D75F3GC
Signing in Date: 2023/05/04

Path No.: M112-00086
MP No.: F23024
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-79179 From Linkou Chang Gung Memorial Hospital
Percentage of tumor cells: 40%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents

Report Highlights

1 Relevant Biomarkers
6 Therapies Available
4 Clinical Trials

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	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	**alectinib** [1, 2] **brigatinib** [1, 2] **ceritinib** [1, 2] **crizotinib** [1, 2] **lorlatinib** [1, 2] atezolizumab + bevacizumab + chemotherapy	**crizotinib** [1] alectinib brigatinib ceritinib lorlatinib	4

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

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

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
MTOR	p.(L1878M)	c.5632C>A	.	chr1:11189877	26.01%	NM_004958.4	missense	419
MTOR	p.(G1479=)	c.4437C>T	.	chr1:11217241	4.90%	NM_004958.4	synonymous	2000
JAK1	p.([G732=;P733=])	c.2196_2199delCCCAinsTCCG	.	chr1:65310489	11.58%	NM_002227.4	synonymous, synonymous	915
ALK	p.(V1541=)	c.4623C>T	.	chr2:29416330	6.85%	NM_004304.5	synonymous	2000
ALK	p.(L1221=)	c.3663G>A	.	chr2:29436930	49.14%	NM_004304.5	synonymous	869
IDH1	p.(W124R)	c.370T>C	.	chr2:209113137	7.05%	NM_005896.3	missense	2000
IDH1	p.(G105D)	c.314G>A	.	chr2:209113193	29.00%	NM_005896.3	missense	2000
CTNNB1	p.(T40=)	c.120T>C	.	chr3:41266123	7.88%	NM_001904.4	synonymous	165
PIK3CA	p.(W424*)	c.1272G>A	.	chr3:178927994	4.80%	NM_006218.4	nonsense	999
PIK3CA	p.(R537=)	c.1611A>G	.	chr3:178936069	13.00%	NM_006218.4	synonymous	1069
FGFR3	p.(C119=)	c.357C>T	.	chr4:1801228	5.80%	NM_000142.4	synonymous	2000
FGFR3	p.(L398P)	c.1193T>C	.	chr4:1806174	6.33%	NM_000142.4	missense	1438
PDGFRA	p.(L839=)	c.2517G>T	.	chr4:55152085	12.06%	NM_006206.6	synonymous	1999
KIT	p.(M425T)	c.1274T>C	.	chr4:55589792	18.28%	NM_000222.3	missense	1072
KIT	p.(V824L)	c.2470G>T	.	chr4:55599344	6.72%	NM_000222.3	missense	238
ROS1	p.(K1976=)	c.5928A>G	.	chr6:117641043	7.27%	NM_002944.2	synonymous	1031
ROS1	p.(V1965=)	c.5895G>A	.	chr6:117641076	5.39%	NM_002944.2	synonymous	1039
ROS1	p.(R1942Q)	c.5825G>A	.	chr6:117641146	8.14%	NM_002944.2	missense	1007
EGFR	p.(L778=)	c.2334G>T	.	chr7:55249036	6.75%	NM_005228.5	synonymous	415
EGFR	p.(R832=)	c.2496C>A	.	chr7:55259438	10.33%	NM_005228.5	synonymous	1355
MET	p.(Y71S)	c.212A>C	.	chr7:116339350	5.07%	NM_001127500.3	missense	710
MET	p.(V1084M)	c.3250G>A	.	chr7:116415102	25.77%	NM_001127500.3	missense	873
MET	p.(G1108V)	c.3323G>T	.	chr7:116417452	8.33%	NM_001127500.3	missense	96

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

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
BRAF	p.(V765=)	c.2295C>T	.	chr7:140434403	5.13%	NM_004333.6	synonymous	780
BRAF	p.(G563=)	c.1689C>A	.	chr7:140476717	11.35%	NM_004333.6	synonymous	1559
BRAF	p.(S432*)	c.1295C>A	.	chr7:140482840	6.15%	NM_004333.6	nonsense	374
BRAF	p.(S273=)	c.819T>C	.	chr7:140501253	8.65%	NM_004333.6	synonymous	347
FGFR1	p.(S269=)	c.807C>T	.	chr8:38283671	6.95%	NM_001174067.1	synonymous	2000
HRAS	p.(G60S)	c.178G>A	.	chr11:533878	5.74%	NM_001130442.2	missense	975
HRAS	p.(V7=)	c.21G>T	.	chr11:534302	5.00%	NM_001130442.2	synonymous	2000
CCND1	p.(V109L)	c.325G>T	.	chr11:69457925	7.62%	NM_053056.3	missense	1996
ERBB3	p.(V59M)	c.175G>A	.	chr12:56477627	8.92%	NM_001982.4	missense	1570
ERBB3	p.(L77=)	c.231G>C	.	chr12:56477683	4.68%	NM_001982.4	synonymous	1603
ERBB3	p.(V119F)	c.355G>T	.	chr12:56478899	7.95%	NM_001982.4	missense	1999
ERBB3	p.(Q225L)	c.674A>T	.	chr12:56481639	4.80%	NM_001982.4	missense	1999
ERBB3	p.(P307A)	c.919C>G	.	chr12:56482371	5.55%	NM_001982.4	missense	1999
CDK4	p.(K297=)	c.891G>A	.	chr12:58142329	11.95%	NM_000075.4	synonymous	2000
CDK4	p.(G224V)	c.671G>T	.	chr12:58143249	7.92%	NM_000075.4	missense	669
CDK4	p.(R210Q)	c.629G>A	.	chr12:58144442	15.41%	NM_000075.4	missense	1999
CDK4	p.(Y17=)	c.51T>C	.	chr12:58145450	6.22%	NM_000075.4	synonymous	1480
CDK4	p.(P8=)	c.24A>T	.	chr12:58145477	6.97%	NM_000075.4	synonymous	1477
CDK4	p.(?)	c.-463C>T	.	chr12:58145963	7.05%	NM_000075.4	unknown	1999
CDK4	p.(?)	c.-501C>T	.	chr12:58146001	7.70%	NM_000075.4	unknown	2000
AKT1	p.(P42=)	c.126G>T	.	chr14:105246474	7.45%	NM_001014431.2	synonymous	2000
NF1	p.(?)	c.-43C>T	.	chr17:29422285	6.55%	NM_001042492.3	unknown	2000
ERBB2	p.(G327E)	c.980G>A	.	chr17:37868259	47.67%	NM_004448.3	missense	623
ERBB2	p.(L841=)	c.2523C>T	.	chr17:37881331	14.95%	NM_004448.3	synonymous	1933
ERBB2	p.(L866P)	c.2597T>C	.	chr17:37881405	7.22%	NM_004448.3	missense	1953
BRCA1	p.(Y1769=)	c.5307T>C	.	chr17:41203105	4.93%	NM_007294.4	synonymous	203
BRCA1	p.(M1?)	c.3G>A	.	chr17:41276111	61.09%	NM_007294.4	missense	221
JAK3	p.(E567K)	c.1699G>A	.	chr19:17948743	8.71%	NM_000215.4	missense	1779
AR	p.(F877=)	c.2631C>T	.	chrX:66943551	21.13%	NM_000044.6	synonymous	956
MED12	p.(S1201F)	c.3602C>T	.	chrX:70349190	29.10%	NM_005120.3	missense	1938

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

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
EML4-ALK	EML4-ALK.E13A20.COSF408.1	chr2:42522656 - chr2:29446394	44926

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 (ALCL)[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 as well as ALK positive ALCL or inflammatory myofibroblastic tumor (IMT). 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].

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*
crizotinib	◑	◑	●	●	✖
ceritinib	●	◑	●	●	● (IV)
lorlatinib	●	◑	●	●	● (IV)
alectinib	●	◑	●	●	✖
brigatinib	●	◑	●	●	✖
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	●	✖
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 2023-03-15. For the most up-to-date information, search www.fda.gov.

EML4-ALK fusion

◑ crizotinib

Cancer type: Inflammatory Myofibroblastic Tumor, Non-Small Cell Lung Cancer

Label as of: 2022-07-14

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.
- adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/202570s033lbl.pdf

---

● 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

---

● 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

---

EML4-ALK fusion (continued)

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

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 2023-03-01. 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, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

● 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, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

● 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, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

● 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, Biomarker discovered prior to first line therapy (First-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

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, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

---

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 2.2022]

---

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); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

---

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 2.2022]

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); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

---

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 2.2022]

---

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, Biomarker discovered during first line therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

---

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, Biomarker discovered during first line therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

EML4-ALK fusion (continued)

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 2.2022]

---

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); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

---

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 2.2022]

---

alectinib

Cancer type: Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

EML4-ALK fusion (continued)

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]

---

brigatinib

Cancer type: Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

---

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]

---

ceritinib

Cancer type: Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

---

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)

crizotinib

Cancer type: Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

---

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]

---

lorlatinib

Cancer type: Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

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 2023-03-15. 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:** 2022-08-11 **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:** 2022-12-02 **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 2023-03-01. 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; Progression, Advanced, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

● lorlatinib

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

EML4-ALK fusion (continued)

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

---

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

---

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

---

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; Progression, Advanced, Metastatic (Subsequent therapy, Second-line therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

EML4-ALK fusion (continued)

atezolizumab + bevacizumab + carboplatin + paclitaxel

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):
- Stage IV; Progression, Advanced, Metastatic (Subsequent therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (pre-proof)]

Clinical Trials in Taiwan region:

Clinical Trials Summary

EML4-ALK fusion

NCT ID	Title	Phase
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
NCT05144997	Lorlatinib (PF-06463922) Continuation Protocol: An Open-Label, Single-Arm Continuation Study For Participants With ALK-Positive or ROS1-Positive Non-Small Cell Lung Cancer (NSCLC) Continuing From Pfizer Sponsored Lorlatinib Clinical Studies	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

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/2022/202570s033lbl.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/2022/208772s013lbl.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 2.2023]