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: 歐素萍
Gender: Female
ID No.: N223069387
History No.: 44757473
Age: 43

Ordering Doctor: DOC3016D 江起陸
Ordering REQ.: 0AVHFNM
Signing in Date: 2020/08/26

Path No.: S109-99923
MP No.: F20066
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-26726A
Percentage of tumor cells: 80%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Report Highlights
2 Relevant Biomarkers
7 Therapies Available
65 Clinical Trials

Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	***EML4-ALK fusion***	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not 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* echinoderm microtubule associated protein like 4 - ALK receptor tyrosine kinase	**brigatinib** [1, 2] **crizotinib** [1, 2] **lorlatinib** [1, 2]	ceritinib crizotinib	49

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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		alectinib [1, 2] **ceritinib** [1, 2] next-generation ALK inhibitor atezolizumab + bevacizumab + chemotherapy		
IA	*MET amplification* MET proto-oncogene, receptor tyrosine kinase	crizotinib	None	21

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.95%	NM_004304.4	missense	1996
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.90%	NM_004304.4	missense	1999
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.90%	NM_004304.4	synonymous	1992
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.62%	NM_000142.4	synonymous	1599
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.95%	NM_006206.5	synonymous	1999
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.35%	NM_213647.2	missense	2000
ESR1	p.(D564Y)	c.1690G>T	.	chr6:152420003	49.27%	NM_001122740.1	missense	1997

Gene Fusions (RNA)

Genes	Variant ID	Locus
EML4-ALK	EML4-ALK.E20A20.COSF409.1	chr2:42552694 - chr2:29446394

Copy Number Variations

Gene	Locus	Copy Number
MET	chr7:116313480	9.06

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

Biomarker Descriptions (continued)

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 the 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. Ubiquitin-dependent proteolysis regulates the steady state level of the MET protein via recognition of the tyrosine phosphorylation site Y1003 in the MET Cbl-binding domain within the juxtamembrane region[23,24,25]. 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[26,27].

Alterations and prevalence: 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 papillary renal cell carcinoma (PRCC) (1-2%) and include M1250T, H1094Y, and V1070E. Mutation of the Y1003 phosphorylation site is reported in lung cancer but is uncommon (<1%)[28,29]. In contrast, splice-site mutations flanking exon 14 are observed in 4% of non-small cell lung cancer (NSCLC). These mutations include canonical splice site mutations affecting exon 14 and deletions that extend into the splicing motifs within intron 13[30,31]. 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 steady-state level of the MET protein[32]. 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[30,33,34]. MET is amplified in 2-5% of ovarian cancer, esophageal adenocarcinoma, stomach adenocarcinoma, glioblastoma, and lung adenocarcinoma[28,29,35]. Recurrent MET fusions, although infrequent, are observed in adult and pediatric glioblastoma, papillary renal cell carcinoma, lung cancer, liver cancer, thyroid cancer, and melanoma[36,37,38]. MET alterations are believed to be enriched in late-stage cancers where they drive tumor progression and metastasis[39,40,41].

Potential relevance: In 2020, the FDA granted accelerated approval to capmatinib[42] for NSCLC harboring MET exon 14 skipping positive as detected by an FDA-approved test[22]. Tepotinib[43] has been granted FDA breakthrough designation (2019) for advanced MET exon 14 skipping 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[22,30,33,34]. Conversely, amplification of MET has been observed to mediate resistance to EGFR tyrosine kinase inhibitors (TKIs)[44,45,46,47,48]. 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[49].

Relevant Therapy Summary

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

EML4-ALK fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	●	◑	●	◑	● (IV)
ceritinib	●	◑	●	●	● (IV)
alectinib	●	●	●	●	● (IV)
brigatinib	●	●	●	●	● (II)
lorlatinib	●	●	●	●	● (II)
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	●	✖
next-generation ALK inhibitor	✖	✖	✖	●	✖
alectinib, crizotinib	✖	✖	✖	✖	● (III)
brigatinib, alectinib	✖	✖	✖	✖	● (III)
conteltinib, crizotinib	✖	✖	✖	✖	● (III)
toripalimab, chemotherapy	✖	✖	✖	✖	● (III)
TQ-B3139, crizotinib	✖	✖	✖	✖	● (III)
WX-0593, crizotinib	✖	✖	✖	✖	● (III)
bevacizumab + crizotinib	✖	✖	✖	✖	● (II)
bevacizumab, atezolizumab, chemotherapy	✖	✖	✖	✖	● (II)
bintrafusp alfa, chemoradiation therapy, durvalumab	✖	✖	✖	✖	● (II)
ensartinib	✖	✖	✖	✖	● (II)
entrectinib	✖	✖	✖	✖	● (II)
pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II)
TQ-B3139	✖	✖	✖	✖	● (II)
WX-0593	✖	✖	✖	✖	● (II)
alectinib, bevacizumab	✖	✖	✖	✖	● (I/II)
alectinib, cobimetinib	✖	✖	✖	✖	● (I/II)
CBT-502, anlotinib hydrochloride	✖	✖	✖	✖	● (I/II)

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

Relevant Therapy Summary (continued)

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

EML4-ALK fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ceritinib, trametinib	✖	✖	✖	✖	● (I/II)
foritinib	✖	✖	✖	✖	● (I/II)
repotrectinib	✖	✖	✖	✖	● (I/II)
U3-1402	✖	✖	✖	✖	● (I/II)
APG-2449	✖	✖	✖	✖	● (I)
binimetinib, brigatinib	✖	✖	✖	✖	● (I)
brigatinib, radiation therapy, surgical intervention	✖	✖	✖	✖	● (I)
ceritinib, everolimus	✖	✖	✖	✖	● (I)
conteltinib	✖	✖	✖	✖	● (I)
crizotinib, temsirolimus	✖	✖	✖	✖	● (I)
GSK3326595	✖	✖	✖	✖	● (I)
PLB1003	✖	✖	✖	✖	● (I)
RF-A089	✖	✖	✖	✖	● (I)
XZP-3621	✖	✖	✖	✖	● (I)

MET amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	✖	●	✖	✖	● (II)
bevacizumab + crizotinib	✖	✖	✖	✖	● (II)
cabozantinib	✖	✖	✖	✖	● (II)
capmatinib	✖	✖	✖	✖	● (II)
capmatinib + nivolumab	✖	✖	✖	✖	● (II)
ensartinib	✖	✖	✖	✖	● (II)
telisotuzumab vedotin	✖	✖	✖	✖	● (II)
glumetinib	✖	✖	✖	✖	● (I/II)

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

Relevant Therapy Summary (continued)

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

MET amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
REGN-5093	✖	✖	✖	✖	● (I/II)
GST-HG161	✖	✖	✖	✖	● (I)
HLX55	✖	✖	✖	✖	● (I)
metatinib	✖	✖	✖	✖	● (I)
TPX-0022	✖	✖	✖	✖	● (I)

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

Relevant Therapy Details

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⛔ Not recommended 🛡 Resistance

FDA information is current as of 2020-05-26. For the most up-to-date information, search www.fda.gov.

EML4-ALK fusion

● brigatinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2018-12-21 **Variant class:** ALK fusion

Indications and usage:
ALUNBRIG™ a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208772s004lbl.pdf

EML4-ALK fusion (continued)

crizotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2019-06-25 **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.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202570s028lbl.pdf

lorlatinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2018-11-02 **Variant class:** ALK fusion or ALK overexpression

Indications and usage:

LORBRENA® is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on

- crizotinib and at least one other ALK inhibitor for metastatic disease; or
- alectinib as the first ALK inhibitor therapy for metastatic disease; or
- ceritinib as the first ALK inhibitor therapy for metastatic disease.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210868s000lbl.pdf

alectinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2018-06-05 **Variant class:** ALK positive

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/2018/208434s004lbl.pdf

EML4-ALK fusion (continued)

ceritinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2019-03-05 **Variant class:** ALK positive

Indications and usage:

ZYKADIA® 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)-positive as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205755s016lbl.pdf

Current NCCN Information

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

NCCN information is current as of 2020-05-01. 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ALK rearrangement discovered prior to first-line systemic therapy (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

brigatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ALK rearrangement discovered prior to first-line systemic therapy (First-line therapy) (Other Recommended)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

ceritinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ALK rearrangement discovered prior to first-line systemic therapy (First-line therapy) (Other Recommended)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

EML4-ALK fusion (continued)

crizotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ALK rearrangement discovered prior to first-line systemic therapy (First-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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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):
- Non-Small Cell Lung Cancer; Brain metastases; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]

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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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ALK rearrangement discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression on first-line therapy or progression on/intolerant to crizotinib, if not previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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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):
- Non-Small Cell Lung Cancer; Brain metastases; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]

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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ALK rearrangement discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy) (Other Recommended)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression on first-line therapy or progression on/intolerant to crizotinib, if not previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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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):
- Non-Small Cell Lung Cancer; Brain metastases; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]

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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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ALK rearrangement discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy) (Other Recommended)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression on first-line therapy or progression on/intolerant to crizotinib, if not previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

EML4-ALK fusion (continued)

crizotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; ALK rearrangement discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy) (Useful in Certain Circumstances)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Progression after first-line therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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lorlatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression on first-line therapy with alectinib, brigatinib, or ceritinib (Subsequent therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression on subsequent therapy with crizotinib followed by alectinib, brigatinib, or ceritinib (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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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):
- Non-Small Cell Lung Cancer; Brain metastases; Use agents active against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2020]

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ceritinib

Cancer type: Soft Tissue Sarcoma **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Inflammatory Myofibroblastic Tumor (Not specified) (Preferred)

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2020]

EML4-ALK fusion (continued)

crizotinib

Cancer type: Soft Tissue Sarcoma **Variant class:** ALK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Inflammatory Myofibroblastic Tumor (Not specified) (Preferred)

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2020]

afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

atezolizumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:

NCCN Guidelines® include the following supporting statement(s):
- "Therefore, 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 4.2020]

cabozantinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

EML4-ALK fusion (continued)

capmatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

cetuximab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

dabrafenib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

EML4-ALK fusion (continued)

erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:

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

- "Therefore, 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 4.2020]

osimertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

EML4-ALK fusion (continued)

pembrolizumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:

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

- "Therefore, 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 4.2020]

pembrolizumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Other criteria: CD274 overexpression

Summary:

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

- "Patients with ALK-positive NSCLC and very high PD-L1 expression do not respond to pembrolizumab."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

selpercatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

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

- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

trametinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

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

- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

EML4-ALK fusion (continued)

vandetanib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ALK fusion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Specific targeted therapy for RET rearrangements, BRAF mutations, METex14 skipping mutations, and sensitizing EGFR mutations is not recommended as subsequent therapy in patients with ALK or ROS1 fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib"

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

MET amplification

crizotinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease; High-level MET amplification (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

Current EMA Information

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

EMA information is current as of 2020-05-26. For the most up-to-date information, search www.ema.europa.eu/ema.

EML4-ALK fusion

brigatinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2019-02-18 **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:** 2020-01-22 **Variant class:** ALK fusion

Reference:

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

alectinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2018-09-14 **Variant class:** ALK overexpression

Reference:

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

ceritinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2020-02-12 **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:** 2020-01-13 **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 | Contraindicated | Not recommended | Resistance

ESMO information is current as of 2020-05-01. 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)
- Advanced stage; Progression on or intolerant to crizotinib; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 4 (Second-line or greater)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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 stage; Progression on or intolerant to crizotinib; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 4 (Second-line or greater)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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; ESMO-Magnitude of Clinical Benefit Scale Score version 1.1 score: 4 (First-line therapy)
- If crizotinib not previously used (Second-line or greater)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

EML4-ALK fusion (continued)

brigatinib

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 Non-Small Cell Lung Cancer (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 4 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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 stage; Progressing on crizotinib; Central nervous system progression (Second-line or greater)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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):
- Central nervous system involvement (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

EML4-ALK fusion (continued)

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 stage; Crizotinib resistance; Progression on crizotinib; Magnitude of Clinical Benefit Scale Version v1.1 Score: 3 (Second-line or greater)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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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):
- Advanced stage; Progression on crizotinib (Second-line or greater)
- Stage IV; Progression after next-generation ALK TKI; Magnitude of Clinical Benefit Scale Version v1.1 Score: 3 (Second-line or greater)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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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):
- Metastatic Non-Squamous; Magnitude of Clinical Benefit Scale Score version 1.1 score: 3 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

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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 stage; Central nervous system involvement (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

EML4-ALK fusion (continued)

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):
- Central nervous system involvement (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

crizotinib

Cancer type: Soft Tissue Sarcoma **Variant class:** ALK fusion

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

Population segment (Line of therapy):
- Advanced or Metastatic Inflammatory Myofibroblastic Tumor (Not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-EUROCAN-Soft Tissue and Visceral Sarcomas [Ann Oncol (2018) 29 (Suppl 4): iv51–iv67. (eUpdate: 22 March 2019; 22 March 2019; Corrigendum: 03 OCT 2018)]

Signatures

Testing Personnel:

Shin-Ying Lin 2020.08.27 17:55:53 +08'00'

Laboratory Supervisor:

2020.08.27 17:56:07 +08'00'

Pathologist:

Yi-Chu Yeh 2020.08.27 17:56:22 +08'00'

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/2019/202570s028lbl.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/2019/205755s016lbl.pdf
17. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208434s004lbl.pdf
18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208772s004lbl.pdf
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210868s000lbl.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 4.2020]
23. Peschard et al. A conserved DpYR motif in the juxtamembrane domain of the Met receptor family forms an atypical c-Cbl/Cbl-b tyrosine kinase binding domain binding site required for suppression of oncogenic activation. J. Biol. Chem. 2004 Jul 9;279(28):29565-71. PMID: 15123609
24. Peschard et al. Mutation of the c-Cbl TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein. Mol. Cell. 2001 Nov;8(5):995-1004. PMID: 11741535
25. Abella et al. Met/Hepatocyte growth factor receptor ubiquitination suppresses transformation and is required for Hrs phosphorylation. Mol. Cell. Biol. 2005 Nov;25(21):9632-45. PMID: 16227611

References (continued)

26. Sierra et al. c-MET as a potential therapeutic target and biomarker in cancer. Ther Adv Med Oncol. 2011 Nov;3(1 Suppl):S21-35. PMID: 22128285
27. Mo et al. Targeting MET in cancer therapy. Chronic Dis Transl Med. 2017 Sep;3(3):148-153. PMID: 29063069
28. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
29. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
30. Frampton et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015 Aug;5(8):850-9. PMID: 25971938
31. Schrock et al. Characterization of 298 Patients with Lung Cancer Harboring MET Exon 14 Skipping Alterations. J Thorac Oncol. 2016 Sep;11(9):1493-502. PMID: 27343443
32. Pilotto et al. MET exon 14 juxtamembrane splicing mutations: clinical and therapeutical perspectives for cancer therapy. Ann Transl Med. 2017 Jan;5(1):2. doi: 10.21037/atm.2016.12.33. PMID: 28164087
33. Reungwetwattana et al. The race to target MET exon 14 skipping alterations in non-small cell lung cancer: The Why, the How, the Who, the Unknown, and the Inevitable. Lung Cancer. 2017 Jan;103:27-37. PMID: 28024693
34. Saffroy et al. MET exon 14 mutations as targets in routine molecular analysis of primary sarcomatoid carcinoma of the lung. Oncotarget. 2017 Jun 27;8(26):42428-42437. PMID: 28418914
35. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
36. Yeh et al. Activating MET kinase rearrangements in melanoma and Spitz tumours. Nat Commun. 2015 May 27;6:7174. doi: 10.1038/ncomms8174. PMID: 26013381
37. Bao et al. RNA-seq of 272 gliomas revealed a novel, recurrent PTPRZ1-MET fusion transcript in secondary glioblastomas. Genome Res. 2014 Nov;24(11):1765-73. PMID: 25135958
38. International Cancer Genome Consortium PedBrain Tumor Project. Recurrent MET fusion genes represent a drug target in pediatric glioblastoma. Nat. Med. 2016 Nov;22(11):1314-1320. PMID: 27748748
39. Zeng et al. c-Met gene amplification is associated with advanced stage colorectal cancer and liver metastases. Cancer Lett. 2008 Jul 8;265(2):258-69. PMID: 18395971
40. Tsugawa et al. Amplification of the c-met, c-erbB-2 and epidermal growth factor receptor gene in human gastric cancers: correlation to clinical features. Oncology. 1998 Sep-Oct;55(5):475-81. PMID: 9732228
41. Di et al. Overexpression and amplification of the met/HGF receptor gene during the progression of colorectal cancer. Clin. Cancer Res. 1995 Feb;1(2):147-54. PMID: 9815967
42. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf
43. https://www.emdgroup.com/en/news/tepotinib-breakthrough-therapy-designation-11-09-2019.html
44. Bean et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc. Natl. Acad. Sci. U.S.A. 2007 Dec 26;104(52):20932-7. PMID: 18093943
45. Chen et al. Clinicopathologic and molecular features of epidermal growth factor receptor T790M mutation and c-MET amplification in tyrosine kinase inhibitor-resistant Chinese non-small cell lung cancer. Pathol Oncol Res. 2009 Dec;15(4):651-8. doi: 10.1007/s12253-009-9167-8. Epub 2009 Apr 21. PMID: 19381876
46. Suda et al. Reciprocal and complementary role of MET amplification and EGFR T790M mutation in acquired resistance to kinase inhibitors in lung cancer. Clin. Cancer Res. 2010 Nov 15;16(22):5489-98. PMID: 21062933
47. Zhang et al. Current mechanism of acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitors and updated therapy strategies in human nonsmall cell lung cancer. J Cancer Res Ther. 2016 Dec;12(Supplement):C131-C137. PMID: 28230005
48. Nguyen et al. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer. 2009 Jul;10(4):281-9. PMID: 19632948
49. Choueiri et al. Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer. J. Clin. Oncol. 2017 Sep 10;35(26):2993-3001. PMID: 28644771