



Sample Information

Patient Name: 高珮綺**Gender:** Female**ID No.:** A224437182**History No.:** 45884740**Age:** 43**Ordering Doctor:** DOC3175F 蔡宗燁**Ordering REQ.:** 0AMYCFA**Signing in Date:** 2019/12/20**Path No.:** S108-99134**MP No.:** F1908**Assay:** Oncomine Focus Assay**Sample Type:** FFPE**Block No.:** S108-47975A**Percentage of tumor cells:** 70%**Note:**

Sample Cancer Type: Non-Small Cell Lung Cancer

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Clinically Significant Biomarkers

■ Indicated ■ Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
CD74-ROS1 fusion CD74 molecule - ROS proto-oncogene 1, receptor tyrosine kinase Tier: IA	■ crizotinib ^{1,2} ■ entrectinib ¹ ■ ceritinib ■ lorlatinib	None	23

Sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Tier Criteria Met

Genomic Alteration	Tier Classification for Non-Small Cell Lung Cancer
CD74-ROS1 fusion Tier: IA	IA: Biomarker predicts response or resistance to FDA or EMA approved therapies in this cancer type IA: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in this cancer type IIC: Biomarker is an inclusion criteria for clinical trials

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.(G1600fs)	c.4796_4797insC	.	chr2:29416156	14.50%	NM_004304.4	frameshift Insertion	1924
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	42.49%	NM_004304.4	missense	1998
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	100.00%	NM_004304.4	missense	2000
ALK	p.(L1145fs)	c.3433_3434insC	.	chr2:29445399	26.20%	NM_004304.4	frameshift Insertion	1985
ALK	p.(=)	c.3375C>A	.	chr2:29445458	43.34%	NM_004304.4	synonymous	1975
PIK3CA	p.(L58fs)	c.172_173insC	.	chr3:178916780	15.97%	NM_006218.3	frameshift Insertion	1973
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.85%	NM_000142.4	synonymous	1995
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	36.99%	NM_006206.5	synonymous	1995
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.55%	NM_006206.5	synonymous	1985
KIT	p.(=)	c.1638A>G	.	chr4:55593481	53.48%	NM_000222.2	synonymous	1999
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	98.80%	NM_213647.2	missense	2000
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	31.45%	NM_213647.2	synonymous	1997
ROS1	p.(F2004C)	c.6011T>G	.	chr6:117638430	19.06%	NM_002944.2	missense	1999
EGFR	p.(=)	c.2361G>A	.	chr7:55249063	59.33%	NM_005228.4	synonymous	1999
MET	p.(N375S)	c.1124A>G	.	chr7:116340262	51.73%	NM_001127500.2	missense	1999
RET	p.(=)	c.2307G>T	.	chr10:43613843	99.95%	NM_020975.4	synonymous	1991
RET	p.(R886fs)	c.2655_2656insG	.	chr10:43615572	11.51%	NM_020975.4	frameshift Insertion	1973
RET	p.(=)	c.2712C>G	.	chr10:43615633	36.37%	NM_020975.4	synonymous	1999
ERBB3	p.(N62fs)	c.183_184insG	.	chr12:56477631	13.45%	NM_001982.3	frameshift Insertion	1985
CDK4	p.(?)	c.-477G>CG	.	chr12:58145977	12.63%	NM_000075.3	unknown	1932

Gene Fusions (RNA)

Genes	Variant ID	Locus
CD74-ROS1	CD74-ROS1.C6R34.COSF1200	chr5:149784243 - chr6:117645578
CD74-ROS1	CD74-ROS1.C6R35	chr5:149784243 - chr6:117642557
CD74-ROS1	CD74-ROS1.C4R33.NGS	chr5:149785849 - chr6:117647525
CD74-ROS1	CD74-ROS1.C6R33.Non-Targeted	chr5:149784243 - chr6:117647525



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

CD74-ROS1 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	●	●	●	●	● (IV)
entrectinib	●	✕	✕	✕	● (II/III)
ceritinib	✕	●	✕	●	● (II)
lorlatinib	✕	●	✕	✕	● (II)
ipilimumab, nivolumab, radiation therapy, surgical intervention	✕	✕	✕	✕	● (III)
bevacizumab + crizotinib	✕	✕	✕	✕	● (II)
cabozantinib	✕	✕	✕	✕	● (II)
ensartinib	✕	✕	✕	✕	● (II)
targeted therapy, targeted therapy + chemotherapy	✕	✕	✕	✕	● (II)
ceritinib + trametinib	✕	✕	✕	✕	● (I/II)
repotrectinib	✕	✕	✕	✕	● (I/II)
U3-1402	✕	✕	✕	✕	● (I/II)
WX-0593	✕	✕	✕	✕	● (I/II)
ceritinib, ceritinib + everolimus	✕	✕	✕	✕	● (I)
RF-A089	✕	✕	✕	✕	● (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 2019-08-23. For the most up-to-date information, search www.fda.gov.

CD74-ROS1 fusion

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2019-06-25

Variant class: ROS1 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

● entrectinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2019-08-15

Variant class: ROS1 fusion

Indications and usage:

ROZLYTREK® is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.
- Adult and pediatric patients 12 years of age and older with solid tumors that:
 - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,
 - are metastatic or where surgical resection is likely to result in severe morbidity, and
 - have progressed following treatment or have no satisfactory alternative therapy

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212726s000lbl.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 2019-05-15. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

CD74-ROS1 fusion

● ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ROS1 rearrangement discovered prior to first-line systemic therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ROS1 rearrangement discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2019]

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ROS1 rearrangement discovered prior to first-line systemic therapy (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; ROS1 rearrangement discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2019]

● lorlatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 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 crizotinib or ceritinib (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2019]



CD74-ROS1 fusion (continued)

● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2019]

🗨 alectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

Summary:

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

- "Alectinib or brigatinib are not recommended in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib or ceritinib."
- "Alectinib, brigatinib, and ceritinib are not recommended in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2019]

🗨 brigatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

Summary:

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

- "Alectinib or brigatinib is not recommended in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib or ceritinib."
- "Alectinib, brigatinib, and ceritinib are not recommended in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2019]

🗨 ceritinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

Summary:

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

- "Alectinib, brigatinib, and ceritinib are not recommended in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2019]



CD74-ROS1 fusion (continued)

EGFR tyrosine kinase inhibitor

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

Summary:

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

- "EGFR TKI therapy is not effective in patients with KRAS mutations, BRAF V600E mutations, ALK gene rearrangements, or ROS1 rearrangements."
- "Thus, EGFR TKI therapy is not recommended as subsequent therapy in patients with ALK or ROS1 rearrangements who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2019]



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 2019-08-23. For the most up-to-date information, search www.ema.europa.eu/ema.

CD74-ROS1 fusion

☒ crizotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2019-04-03

Variant class: ROS1 fusion

Reference:

https://www.ema.europa.eu/documents/product-information/xalkori-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 2019-05-15. For the most up-to-date information, search www.esmo.org.

CD74-ROS1 fusion

● crizotinib

Cancer type: Non-Small Cell Lung Cancer Variant class: ROS1 fusion

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

Population segment (Line of therapy):

- Stage IV Non-Squamous Non-Small Cell Carcinoma; ESMO-Magnitude of Clinical Benefit Scale Version v1.1 Score: 3 (First-line therapy)
- Stage IV Non-Squamous Non-Small Cell Carcinoma; Not received crizotinib in the first-line setting (Second line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237. (Corrigendum: 30 January 2019)]

● ceritinib

Cancer type: Non-Small Cell Lung Cancer Variant class: ROS1 fusion

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

Population segment (Line of therapy):

- Non-Small Cell Lung Cancer; Crizotinib-naïve (Not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237. (Corrigendum: 30 January 2019)]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist: