



Sample Information

Patient Name: 李黃寶雲  
Gender: Female  
ID No.: F202629958  
History No.: 49783451  
Age: 82  
  
Ordering Doctor: DOC1878G 沈佳儀  
Ordering REQ.: OCRHRVL  
Signing in Date: 2023/09/27

Path No.: M112-00256  
MP No.: F23071  
Assay: Oncomine Focus Assay  
Sample Type: FFPE  
Block No.: S112-46185A  
Percentage of tumor cells: 60%

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

**Note:** In this sample, a CD74::ROS1 fusion with a relatively low read count was detected by Oncomine Focus Assay. To validate the presence of this fusion, we conducted additional analyses, including Archer Lung FusionPlex next-generation sequencing and ROS1 fluorescence in situ hybridization (FISH). However, both of these analyses yielded negative results for the ROS1 fusion. Consequently, the clinical significance of this low read count CD74::ROS1 fusion remains uncertain and should be interpreted with caution.

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	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	CD74::ROS1 fusion
MET	None detected		

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	<b>CD74::ROS1 fusion</b> CD74 molecule - ROS proto-oncogene 1, receptor tyrosine kinase	<b>crizotinib</b> <sup>1, 2</sup> <b>entrectinib</b> <sup>1, 2</sup> ceritinib lorlatinib repotrectinib	crizotinib entrectinib	4

Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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
EGFR	p.(S484=)	c.1452C>T	.	chr7:55227985	48.67%	NM_005228.5	synonymous	1997

### Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
CD74-ROS1	CD74-ROS1.C6R34.COSF1200	chr5:149784243 - chr6:117645578	3893
CD74-ROS1	CD74-ROS1.C6R35.COSF1478	chr5:149784243 - chr6:117642557	178

## Biomarker Descriptions

### ROS1 (ROS proto-oncogene 1, receptor tyrosine kinase)

**Background:** The ROS1 gene encodes the ROS proto-oncogene receptor tyrosine kinase 1 which exhibits structural similarity to anaplastic lymphoma kinase (ALK)<sup>1,2</sup>. Like ALK, ROS1 is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact ROS1 tyrosine kinase domain combined with numerous fusion partner genes<sup>3</sup>. ROS1 fusion kinases are constitutively activated and drive oncogenic transformation<sup>4</sup>.

**Alterations and prevalence:** ROS1 fusions occur in approximately 1-2% of patients with non-small cell lung cancer (NSCLC) and are also observed in cholangiocarcinoma, gastric cancer, ovarian cancer, and glioblastoma<sup>1,5,6,7,8,9</sup>.

**Potential relevance:** The tyrosine kinase inhibitor, entrectinib<sup>10</sup>, is approved (2019) for the treatment of ROS1 fusion positive metastatic NSCLC. Crizotinib<sup>11</sup>, originally approved for the treatment of ALK positive NSCLC (2011), is also approved (2016) for the treatment of ROS1 positive NSCLC<sup>12</sup>. Acquired resistance to crizotinib in ROS1 positive NSCLC is associated with kinase domain mutations S1986F/Y, G2032R, D2033N, and L2155S<sup>13,14,15</sup>. The ROS1 tyrosine kinase inhibitor, repotrectinib<sup>16</sup>, was granted fast track and breakthrough designations (2020) for ROS1 positive NSCLC. The ROS-1 inhibitor, taletrectinib<sup>17</sup>, was also granted breakthrough therapy designation (2022) for the treatment of adult patients with advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) who are ROS1 tyrosine kinase inhibitor (TKI) treatment naïve or previously treated with crizotinib. Ceritinib is a second generation ALK inhibitor approved (2017) for ALK positive NSCLC that has also shown efficacy in ROS1 positive NSCLC. In a phase II study, ceritinib demonstrated systemic and intra-cranial activity with an objective response rate (ORR) of 62% in patients with advanced ROS1 positive NSCLC<sup>18</sup>. In addition to crizotinib and entrectinib, ceritinib is recommended for first-line treatment of ROS1-positive NSCLC<sup>19</sup>. Lorlatinib is a CNS-penetrant third-generation ALK and ROS1 inhibitor with preclinical activity against almost all known ALK and ROS1 resistance mutations<sup>20,21</sup>. Lorlatinib is currently FDA approved (2018) for ALK positive metastatic NSCLC. In a phase I study testing lorlatinib in advanced ROS1-positive NSCLC, objective response was observed in 6/12 (50%) of patients<sup>22</sup>. Lorlatinib is recommended for subsequent therapy in ROS1 fusion-positive NSCLC in patients who have progressed after treatment with crizotinib, entrectinib, or ceritinib<sup>19</sup>.

## Relevant Therapy Summary

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

### CD74::ROS1 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	●	●	●	●	×
entrectinib	●	●	●	●	×
lorlatinib	×	●	×	×	● (IV)
ceritinib	×	●	×	×	×
repotrectinib	×	×	×	●	● (I/II)
entrectinib, durvalumab	×	×	×	×	● (III)

\* 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 2023-08-16. For the most up-to-date information, search [www.fda.gov](https://www.fda.gov).

### CD74::ROS1 fusion

#### ● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-07-14

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.
- 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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/202570s033lbl.pdf)

**CD74::ROS1 fusion (continued)****● entrectinib****Cancer type:** Non-Small Cell Lung Cancer**Label as of:** 2023-06-16**Variant class:** ROS1 fusion**Indications and usage:**

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

- Adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.
- Adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion as detected by an FDA-approved test 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/2023/212725s007lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212725s007lbl.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 2023-08-01. For the most up-to-date information, search [www.nccn.org](http://www.nccn.org).  
For NCCN International Adaptations & Translations, search [www.nccn.org/global/what-we-do/international-adaptations](http://www.nccn.org/global/what-we-do/international-adaptations).

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

### 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, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention
- 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 3.2023]

#### ● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

NCCN Recommendation category: 2A

##### 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
- 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 3.2023]

## CD74::ROS1 fusion (continued)

### ● entrectinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** ROS1 fusion

**NCCN Recommendation category:** 2A

**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
- 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 3.2023]

### ● lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** ROS1 fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of 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 3.2023]

### ● crizotinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** ROS1 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 1.2023]

### ○ crizotinib

**Cancer type:** Cutaneous Melanoma

**Variant class:** ROS1 fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**

- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]

## CD74::ROS1 fusion (continued)

### ○ entrectinib

Cancer type: Cutaneous Melanoma

Variant class: ROS1 fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]

## 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 2023-08-16. For the most up-to-date information, search [www.ema.europa.eu/ema](https://www.ema.europa.eu/ema).

### CD74::ROS1 fusion

#### ☒ crizotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2022-12-02

Variant class: ROS1 fusion

Reference:

[https://www.ema.europa.eu/en/documents/product-information/xalkori-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/xalkori-epar-product-information_en.pdf)

#### ☒ entrectinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2023-07-18

Variant class: ROS1 positive

Reference:

[https://www.ema.europa.eu/en/documents/product-information/rozlytrek-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/rozlytrek-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 2023-08-01. For the most up-to-date information, search [www.esmo.org](http://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; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 3
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 3

**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> (Published)]

#### ● entrectinib

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; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 3
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 3

**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> (Published)]

#### ● repotrectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

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

**Population segment (Line of therapy):**

- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy)
- Stage IV; Advanced, Metastatic (First-line 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> (Published)]

## Clinical Trials in Taiwan region:

### Clinical Trials Summary

#### CD74::ROS1 fusion

NCT ID	Title	Phase
<a href="#">NCT05170204</a>	A Phase I-III, Multicenter Study Evaluating the Efficacy and Safety of Multiple Therapies in Cohorts of Patients Selected According to Biomarker Status, With Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer	III
<a href="#">NCT03093116</a>	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
<a href="#">NCT05144997</a>	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
<a href="#">NCT04094610</a>	A Phase I/II, Open-Label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects With Advanced or Metastatic Malignancies Harboring ALK, ROS1, NTRK1-3 Alterations	I/II

### Alerts Informed By Public Data Sources

#### Current FDA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2023-08-16. For the most up-to-date information, search [www.fda.gov](https://www.fda.gov).

#### CD74::ROS1 fusion

##### repotrectinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** ROS1 positive

**Supporting Statement:**

The FDA has granted Breakthrough Designation to the ALK/ROS1/TRK inhibitor, repotrectinib, for the treatment of ROS1-positive metastatic non-small cell lung cancer (NSCLC) that has not been treated with a ROS1 tyrosine kinase inhibitor (TKI).

**Reference:**

<https://ir.tptherapeutics.com/news-releases/news-release-details/turning-point-therapeutics-granted-fda-breakthrough-therapy>

##### taletrectinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** ROS1 positive

**Supporting Statement:**

The FDA has granted Breakthrough Therapy Designation (BTD) to the ROS-1 inhibitor, taletrectinib, for the treatment of adult patients with advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) who have not been previously treated with ROS1 tyrosine kinase inhibitors or crizotinib.

**Reference:**

<https://www.anhearttherapeutics.com/news/press-releases/080322/>

**CD74::ROS1 fusion (continued)****A repotrectinib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** ROS1 positive**Supporting Statement:**

The FDA has granted Fast Track Designation to the ALK/ROS1/TRK inhibitor, repotrectinib, for:

- ROS1-positive advanced non-small cell lung cancer (NSCLC) previously treated with one prior platinum chemotherapy and one prior ROS1 TKI.
- ROS1-positive advanced non-small cell lung cancer (NSCLC) without prior ROS1 TKI treatment.
- NTRK fusion positive advanced solid tumors that have progressed following treatment with at least one prior line of chemotherapy and one or two prior TRK TKIs.

**Reference:**

<https://ir.tptherapeutics.com/news-releases/news-release-details/turning-point-therapeutics-granted-fast-track-designation>

## References

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