Taipei Veterans General Hospital

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Sample Information

Patient Name: 蘇徐清
Gender: Male
ID No.: A129014605
History No.: 26591480
Age: 36

Ordering Doctor: DOC5310D 曾彥寒
Ordering REQ.: D7816CA
Signing in Date: 2023/09/14

Path No.: M112-00248
MP No.: F23069
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-41383F
Percentage of tumor cells: 50%

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

Note:

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	*CD74::ROS1 fusion* CD74 molecule - ROS proto-oncogene 1, receptor tyrosine kinase	**crizotinib** [1, 2] **entrectinib** [1, 2] ceritinib lorlatinib repotrectinib	crizotinib entrectinib	4

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

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

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
CD74-ROS1	CD74-ROS1.C6R34.COSF1200	chr5:149784243 - chr6:117645578	34288
CD74-ROS1	CD74-ROS1.C6R35.COSF1478	chr5:149784243 - chr6:117642557	4398
CD74-ROS1	CD74-ROS1.C6R33.Non-Targeted	chr5:149784243 - chr6:117647577	3398

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)[1,2]. 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[3]. ROS1 fusion kinases are constitutively activated and drive oncogenic transformation[4].

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[1,5,6,7,8,9].

Potential relevance: The tyrosine kinase inhibitor, entrectinib[10], is approved (2019) for the treatment of ROS1 fusion positive metastatic NSCLC. Crizotinib[11], originally approved for the treatment of ALK positive NSCLC (2011), is also approved (2016) for the treatment of ROS1 positive NSCLC[12]. Acquired resistance to crizotinib in ROS1 positive NSCLC is associated with kinase domain mutations S1986F/Y, G2032R, D2033N, and L2155S[13,14,15]. The ROS1 tyrosine kinase inhibitor, repotrectinib[16], was granted fast track and breakthrough designations (2020) for ROS1 positive NSCLC. The ROS-1 inhibitor, taletrectinib[17], 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[18]. In addition to crizotinib and entrectinib, ceritinib is recommended for first-line treatment of ROS1-positive NSCLC[19]. Lorlatinib is a CNS-penetrant third-generation ALK and ROS1 inhibitor with preclinical activity against almost all known ALK and ROS1 resistance mutations[20,21]. 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[22]. Lorlatinib is recommended for subsequent therapy in ROS1 fusion-positive NSCLC in patients who have progressed after treatment with crizotinib, entrectinib, or ceritinib[19].

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 2023-07-19. 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:** 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

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

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 2023-07-03. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search 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]

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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]

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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]

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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 2023-07-19. 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:** 2022-12-02 **Variant class:** ROS1 fusion

Reference:

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

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 2023-07-03. 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; 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
NCT05170204	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
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
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
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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-07-19. For the most up-to-date information, search 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)

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

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