Taipei Veterans General Hospital

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Sample Information

Patient Name: 倪晉南
Gender: Male
ID No.: J100672158
History No.: 31568942
Age: 67

Ordering Doctor: DOC6427H 李欣恬
Ordering REQ.: 0CKRNQA
Signing in Date: 2023/05/18

Path No.: M112-00101
MP No.: F23034
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-04804A
Percentage of tumor cells: 20%

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	***CCDC6-RET fusion***
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*CCDC6-RET fusion* coiled-coil domain containing 6 - ret proto-oncogene	**pralsetinib** [1, 2] **selpercatinib** [1, 2] cabozantinib	**pralsetinib** [1] **selpercatinib** [1, 2]	2

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
CCDC6-RET	CCDC6-RET.C1R12.COSF1271	chr10:61665880 - chr10:43612032	16562

Biomarker Descriptions

RET (ret proto-oncogene)

Background: The RET gene encodes the RET receptor tyrosine kinase which is activated by a ligand family of glial cell line-derived neurotrophic factors (GDNF)[1]. RET is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact RET tyrosine kinase domain combined with several fusion partner genes. RET fusion kinases are constitutively activated and drive oncogenic transformation which can lead to activation of PI3K/AKT, RAS/RAF/MEK/ERK, and PLCγ/PKC pathways resulting in cell survival and proliferation[2].

Alterations and prevalence: RET fusions occur in approximately 55% of papillary thyroid carcinomas (PTC) with even higher frequencies observed in PTC patients with radiation exposure[3,4,5]. RET rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[6]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[7]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[7].

Potential relevance: The FDA approved small-molecule tyrosine kinase inhibitor, cabozantinib (2012), is recommended for the treatment of NSCLC patients with RET rearrangements[8]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[9]. Selpercatinib[10] is approved (2020) for RET fusion-positive NSCLC, thyroid cancer, and metastatic solid tumors that have progressed following systemic treatment. Selpercatinib[10] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[11], was approved (2020) for RET fusion-positive NSCLC and thyroid cancer as well as RET mutation-positive MTC. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[12,13]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[14].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

CCDC6-RET fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selpercatinib	◑	◑	◑	◑	● (III)
pralsetinib	◑	◑	●	◑	● (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 ✖ No evidence

CCDC6-RET fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	●	✖	✖	✖

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

Relevant Therapy Details

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2023-03-15. For the most up-to-date information, search www.fda.gov.

CCDC6-RET fusion

◑ pralsetinib

Cancer type: Non-Small Cell Lung Cancer, Thyroid Cancer **Label as of:** 2020-12-01 **Variant class:** RET fusion

Indications and usage:

GAVRETO™ is a kinase inhibitor indicated for treatment of:

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer as detected by an FDA approved test (NSCLC)[1].
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy [1].
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)[1].

[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214701s000lbl.pdf

CCDC6-RET fusion (continued)

selpercatinib

Cancer type: Non-Small Cell Lung Cancer, Poorly Differentiated Thyroid Gland Carcinoma, Solid Tumor, Thyroid Gland Anaplastic Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma

Label as of: 2022-09-21

Variant class: RET fusion

Indications and usage:

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

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test
- Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy[1]
- Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)[1]
- Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options[1]

[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213246s008lbl.pdf

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2023-03-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

CCDC6-RET fusion

● cabozantinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** RET 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); Useful in certain circumstances
- 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 (Subsequent therapy); Useful in certain circumstances

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

● pralsetinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** RET 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 (Subsequent therapy); Preferred intervention

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

● selpercatinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2022]

CCDC6-RET fusion (continued)

selpercatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** RET 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 (Subsequent therapy); Preferred intervention

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

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pralsetinib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Locally Recurrent, Advanced, Metastatic, Radioactive Iodine Ablation refractory (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2022]

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pralsetinib

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVA, Stage IVB; Local, Unresectable, Regional (Neoadjuvant therapy); Consider
- Stage IVC; Metastatic (Second-line therapy); Preferred intervention, Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2022]

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selpercatinib

Cancer type: Triple Negative Breast Cancer **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional, Locally Advanced, Metastatic, Progression (Third-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 2.2023]

CCDC6-RET fusion (continued)

selpercatinib

Cancer type: Breast Cancer **Variant class:** RET fusion

Other criteria: ERBB2 negative, Hormone receptor positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional, Locally Advanced, Metastatic, Progression (Third-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 2.2023]

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selpercatinib

Cancer type: Cervical Cancer **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Squamous Cell, Adenocarcinoma, Adenosquamous; Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2023]

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selpercatinib

Cancer type: Colon Cancer **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2022]

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selpercatinib

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 1.2023]

CCDC6-RET fusion (continued)

selpercatinib

Cancer type: Head and Neck Cancer **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 1.2023]

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selpercatinib

Cancer type: Extrahepatic Cholangiocarcinoma, Intrahepatic Cholangiocarcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2022]

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selpercatinib

Cancer type: Large Cell Neuroendocrine Carcinoma, Mixed Neuroendocrine Non-Neuroendocrine Neoplasm **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Extrapulmonary, Poorly Differentiated; Progression, Unresectable, Metastatic (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 2.2022]

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selpercatinib

Cancer type: Extrapulmonary Small Cell Neuroendocrine Carcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Poorly Differentiated; Progression, Unresectable, Metastatic (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 2.2022]

CCDC6-RET fusion (continued)

selpercatinib

Cancer type: Ovarian Cancer **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

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selpercatinib

Cancer type: Pancreatic Cancer **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic, Locally Advanced, Recurrent (Subsequent therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2022]

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selpercatinib

Cancer type: Rectal Cancer **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2022]

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selpercatinib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Locally Recurrent, Advanced, Metastatic, Radioactive Iodine Ablation refractory (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2022]

CCDC6-RET fusion (continued)

selpercatinib

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVA, Stage IVB; Local, Unresectable, Regional (Neoadjuvant therapy); Consider
- Stage IVC; Metastatic (Second-line therapy); Preferred intervention, Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2022]

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pralsetinib

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Unresectable, Metastatic (Primary therapy); Useful in certain circumstances
- Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2022]

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selpercatinib

Cancer type: Extrahepatic Cholangiocarcinoma, Hepatocellular Carcinoma, Intrahepatic Cholangiocarcinoma **Variant class:** RET fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Unresectable, Metastatic (Primary therapy); Useful in certain circumstances
- Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2022]

Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

EMA information is current as of 2023-03-15. For the most up-to-date information, search www.ema.europa.eu/ema.

CCDC6-RET fusion

◑ selpercatinib

Cancer type: Non-Small Cell Lung Cancer, Thyroid Cancer **Label as of:** 2022-12-20 **Variant class:** RET fusion

Reference:

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

● pralsetinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-06-10 **Variant class:** RET-CCDC6 fusion

Reference:

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

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2023-03-01. For the most up-to-date information, search www.esmo.org.

CCDC6-RET fusion

● pralsetinib

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

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

Population segment (Line of therapy):
- 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 (pre-proof)]

● selpercatinib

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

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

Population segment (Line of therapy):
- 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 (pre-proof)]

○ pralsetinib

Cancer type: Differentiated Thyroid Gland Carcinoma, Poorly Differentiated Thyroid Gland Carcinoma **Variant class:** RET fusion

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

Population segment (Line of therapy):
- Advanced, Metastatic (Line of therapy not specified); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Ann Oncol. 2022; https://doi.org/10.1016/j.annonc.2022.04.009]

CCDC6-RET fusion (continued)

selpercatinib

Cancer type: Differentiated Thyroid Gland Carcinoma, Poorly Differentiated Thyroid Gland Carcinoma

Variant class: RET fusion

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

Population segment (Line of therapy):

- Advanced, Metastatic (Subsequent therapy); ESMO-MCBS v1.1 score: 3
- Advanced, Metastatic (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Ann Oncol. 2022; https://doi.org/10.1016/j.annonc.2022.04.009]

Clinical Trials in Taiwan region:

Clinical Trials Summary

CCDC6-RET fusion

NCT ID	Title	Phase
NCT04819100	LIBRETTO-432: A Placebo-controlled Double-Blinded Randomized Phase III Study of Adjuvant Selpercatinib Following Definitive Locoregional Treatment in Participants With Stage IB-IIIA RET Fusion-Positive NSCLC	III
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II

References

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2. Ibáñez. Structure and physiology of the RET receptor tyrosine kinase. Cold Spring Harb Perspect Biol. 2013 Feb 1;5(2). PMID: 23378586
3. Santoro et al. Central role of RET in thyroid cancer. Cold Spring Harb Perspect Biol. 2013 Dec 1;5(12):a009233. PMID: 24296167
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