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: 倪晉南
Gender: Male
ID No.: J100672158
History No.: 31568942
Age: 65

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: 0BPNVXE
Signing in Date: 2021/12/09

Path No.: S110-94778
MP No.: F21103
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S108-38277H
Percentage of tumor cells: 60%

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 **Prognostic significance:** None **Diagnostic significance:** None	**pralsetinib** [1] **selpercatinib** [1, 2] cabozantinib vandetanib	**pralsetinib** [1] **selpercatinib** [1, 2]	5

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, 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
ALK	p.(G1137E)	c.3410G>A	.	chr2:29445423	4.64%	NM_004304.5	missense	388
PIK3CA	p.(P57L)	c.170C>T	.	chr3:178916783	5.77%	NM_006218.4	missense	52
PIK3CA	p.(W552*)	c.1656G>A	.	chr3:178936114	13.64%	NM_006218.4	nonsense	88
PIK3CA	p.(L719F)	c.2155C>T	.	chr3:178938913	7.09%	NM_006218.4	missense	254
FGFR3	p.(N262D)	c.784A>G	.	chr4:1803606	11.28%	NM_000142.4	missense	647
FGFR3	p.(G382C)	c.1144G>T	.	chr4:1806125	7.93%	NM_000142.4	missense	164
FGFR3	p.(L385=)	c.1155G>A	.	chr4:1806136	7.53%	NM_000142.4	synonymous	146
PDGFRA	p.(V832=)	c.2496G>A	.	chr4:55152064	5.75%	NM_006206.6	synonymous	626
MET	p.(Y84*)	c.252delC	.	chr7:116339389	7.47%	NM_001127500.3	nonsense	241
MET	p.(D1117=)	c.3351C>T	.	chr7:116417480	7.04%	NM_001127500.3	synonymous	71
SMO	p.(V411L)	c.1231G>C	.	chr7:128846395	6.14%	NM_005631.5	missense	814
BRAF	p.(G474E)	c.1421G>A	.	chr7:140481387	11.87%	NM_004333.6	missense	1996
BRAF	p.(S335F)	c.1004C>T	.	chr7:140494244	4.71%	NM_004333.6	missense	488
FGFR1	p.(T726=)	c.2178T>G	.	chr8:38271771	4.94%	NM_001174067.1	synonymous	162
MYC	p.(G123R)	c.367G>A	.	chr8:128750830	4.60%	NM_002467.6	missense	2000
FGFR2	p.(I383L)	c.1147A>T	.	chr10:123274771	4.65%	NM_000141.5	missense	301
FGFR2	p.(P256L)	c.767C>T	.	chr10:123279665	5.22%	NM_000141.5	missense	901
KRAS	p.(N26=)	c.78T>C	.	chr12:25398241	4.68%	NM_033360.4	synonymous	1005
ERBB3	p.(S346=)	c.1038C>T	.	chr12:56482581	8.96%	NM_001982.4	synonymous	1082
CDK4	p.(A205=)	c.615A>G	.	chr12:58144456	5.92%	NM_000075.4	synonymous	1148
MAP2K1	p.(K64R)	c.191A>G	.	chr15:66727475	15.18%	NM_002755.4	missense	1568
MAP2K1	p.(Y134F)	c.401A>T	.	chr15:66729193	6.75%	NM_002755.4	missense	1171
MAP2K1	p.(G210=)	c.630G>T	.	chr15:66774154	12.10%	NM_002755.4	synonymous	785

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

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
BRCA1	p.(N1774Y)	c.5320A>T	.	chr17:41203092	12.90%	NM_007294.4	missense	124

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
CCDC6-RET	CCDC6-RET.C1R12.COSF1271	chr10:61665880 - chr10:43612032	16077

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: Selpercatinib[8] is approved (2020) for RET fusion-positive NSCLC and thyroid cancer. Selpercatinib[8] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[9], was approved (2020) for RET fusion-positive NSCLC and thyroid cancer as well as RET mutation-positive MTC. The FDA approved small-molecule tyrosine kinase inhibitors, vandetanib (2011), and cabozantinib (2012), are recommended for the treatment of NSCLC patients with RET rearrangements[10]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[11]. 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	◑	◑	◑	●	● (I/II)
pralsetinib	◑	◑	✖	●	● (II)
cabozantinib	✖	●	✖	✖	✖
vandetanib	✖	●	✖	✖	✖
selpercatinib, chemotherapy, pembrolizumab	✖	✖	✖	✖	● (III)

* 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*
BOS172738	✖	✖	✖	✖	● (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

FDA information is current as of 2021-08-18. 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, Thyroid Gland Anaplastic Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma

Label as of: 2021-01-28

Variant class: RET fusion

Indications and usage:

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

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (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/2021/213246s002lbl.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 2021-08-02. 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 (First-line therapy); Useful in certain circumstances
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent 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 5.2021]

● 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 (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent 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 5.2021]

● 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 (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent 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 5.2021]

CCDC6-RET fusion (continued)

vandetanib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Useful in certain circumstances
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent 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 5.2021]

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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 (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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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 (Neoadjuvant therapy)
- Stage IVC; Metastatic (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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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 (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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 (Neoadjuvant therapy)
- Stage IVC; Metastatic (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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 2021-08-18. 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: 2021-07-08

Variant class: RET fusion

Reference:

https://www.ema.europa.eu/en/documents/product-information/retsevmo-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 2021-08-02. 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 / B

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

● selpercatinib

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

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

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

Clinical Trials in Taiwan region:

Clinical Trials Summary

CCDC6-RET fusion

NCT ID	Title	Phase
NCT04194944	LIBRETTO-431: A Multicenter, Randomized, Open-Label, Phase III Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy With or Without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer	III
NCT03037385	A Phase I/II Study of the Highly-selective RET Inhibitor, BLU-667, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors.	I/II
NCT03157128	A Study of Oral LOXO-292 in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (LIBRETTO-001)	I/II
NCT03780517	A Phase I Study of BOS172738 in Patients With Advanced Solid Tumors With RET Gene Alterations Including Non-Small Cell Lung Cancer (NSCLC) and Medullary Thyroid Cancer (MTC)	I
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II

Signatures

Testing Personnel:

2021.12.09
15:26:58 +08'00'

Laboratory Supervisor:

2021.12.09
15:27:11 +08'00'

Pathologist:

2021.12.09
15:27:20 +08'00'

References

1. Knowles et al. Structure and chemical inhibition of the RET tyrosine kinase domain. J. Biol. Chem. 2006 Nov 3;281(44):33577-87. PMID: 16928683
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4. Elisei et al. RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. J. Clin. Endocrinol. Metab. 2001 Jul;86(7):3211-6. PMID: 11443191
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