Taipei Veterans General Hospital

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Sample Information

Patient Name: 吳鳳金
Gender: Female
ID No.: Z200065265
History No.: 27473105
Age: 67

Ordering Doctor: DOC3070E 柯宏叡
Ordering REQ.: 0BDJSDA
Signing in Date: 2021/03/17

Path No.: S110-98405
MP No.: F21026
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-07772A+B
Percentage of tumor cells: 30%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Report Highlights

1 Relevant Biomarkers
4 Therapies Available
21 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	***KIF5B-RET fusion***
KRAS	Not detected	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*KIF5B-RET fusion* kinesin family member 5B - ret proto-oncogene	**pralsetinib** [1] **selpercatinib** [1]	**selpercatinib** [1]	21

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.

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.01(005).The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		cabozantinib vandetanib		

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.

Prevalent cancer biomarkers without relevant evidence based on included data sources
CTNNB1 p.(D32N) c.94G>A

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
CTNNB1	p.(D32N)	c.94G>A	COSM5672	chr3:41266097	7.65%	NM_001904.3	missense	2000
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.80%	NM_004304.4	missense	1999
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.89%	NM_000142.4	synonymous	1766
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	54.74%	NM_006206.5	synonymous	1995
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.95%	NM_006206.5	synonymous	2000
PDGFRA	p.(=)	c.2472C>T	.	chr4:55152040	55.28%	NM_006206.5	synonymous	1999
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.15%	NM_213647.2	missense	2000
BRAF	p.(=)	c.2235A>G	.	chr7:140434463	50.90%	NM_004333.4	synonymous	2000
RET	p.(=)	c.2307G>T	.	chr10:43613843	41.28%	NM_020975.4	synonymous	1996
RET	p.(=)	c.2712C>G	.	chr10:43615633	41.60%	NM_020975.4	synonymous	1995

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
KIF5B-RET	KIF5B-RET.K16R12.COSF1230	chr10:32311776 - chr10:43612032	55292

Biomarker Descriptions

CTNNB1 (catenin beta 1)

Background: The CTNNB1 gene encodes catenin beta-1 (β-catenin), an integral component of cadherin-based adherens junctions involved in maintaining adhesion and regulating the growth of epithelial cell layers[1]. CTNNB1 binds to the APC protein in the cytoplasm and also interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling[2]. Steady state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis[3,4,5].

Alterations and prevalence: Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-β and inhibit CTNNB1 degradation[6,7,8,9]. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in hepatocellular carcinoma, 20% of uterine carcinoma, and 15% of adrenocortical carcinoma[10,11,12,13,14,15,16].

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Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations in EGFR positive lung cancer have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors[17].

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)[18]. 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[19].

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[20,21,22]. RET rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[23]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[24]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[24].

Potential relevance: Selpercatinib[25] is approved (2020) for RET fusion-positive NSCLC and thyroid cancer. Selpercatinib[25] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[26], was approved for RET fusion-positive NSCLC (2020) and was granted breakthrough therapy designation (2019) for RET mutation-positive MTC[27]. The FDA approved small-molecule tyrosine kinase inhibitors, vandetanib (2011), and cabozantinib (2012), are recommended for the treatment of NSCLC patients with RET rearrangements[28]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[29]. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[30,31]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[32].

Relevant Therapy Summary

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

KIF5B-RET fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selpercatinib	◑	◑	✖	●	● (II)
pralsetinib	●	●	✖	●	● (III)
cabozantinib	✖	●	✖	✖	● (II)
vandetanib	✖	●	✖	✖	✖
alectinib	✖	✖	✖	✖	● (IV)
ipilimumab, nivolumab, radiation therapy, surgical intervention	✖	✖	✖	✖	● (III)
selpercatinib, chemotherapy, pembrolizumab	✖	✖	✖	✖	● (III)
alectinib, brigatinib	✖	✖	✖	✖	● (II)
ponatinib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)

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

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Relevant Therapy Summary (continued)

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

KIF5B-RET fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TPX-0046	✖	✖	✖	✖	● (I/II)
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 2020-12-16. For the most up-to-date information, search www.fda.gov.

KIF5B-RET fusion

◑ 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: 2020-05-08

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/2020/213246s000lbl.pdf

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KIF5B-RET fusion (continued)

pralsetinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2020-09-04 **Variant class:** RET fusion

Indications and usage:

GAVRETO™ is a kinase inhibitor indicated for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion- positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

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/2020/213721s000lbl.pdf

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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 2020-12-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KIF5B-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, Not otherwise specified (NOS), Squamous Cell; Advanced, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2021]

● 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, Not otherwise specified (NOS), Squamous Cell; Advanced, Metastatic, Progression (Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2021]

● 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, Not otherwise specified (NOS), Squamous Cell; Advanced, Metastatic, Progression (Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2021]

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KIF5B-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, Not otherwise specified (NOS), Squamous Cell; Advanced, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [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 2.2020]

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selpercatinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVC; Metastatic (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

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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 2020-12-01. For the most up-to-date information, search www.esmo.org.

KIF5B-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 Summary

KIF5B-RET fusion

NCT ID	Title	Phase
NCT01639508	A Phase II Study of Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	II
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
No NCT ID	Research For Elucidating The Resistance Mechanism To RET Tyrosine Kinase Inhibitors In Patients With Non-Small-Cell Lung Cancer Harboring With RET Fusion Gene	IV
NCT04222972	A Phase III Study of BLU-667 as First-line Treatment in RET- Altered Advanced Non Small Cell Lung Cancer.	III
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
NCT02314481	Deciphering Antitumour Response and Resistance With INtratumour Heterogeneity - DARWINII	II

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Clinical Trials Summary (continued)

KIF5B-RET fusion (continued)

NCT ID	Title	Phase
NCT03445000	A Single Arm Phase II Trial Evaluating the Activity of Alectinib for the Treatment of Pretreated RET-rearranged Advanced NSCLC	II
NCT04131543	"Phase II Study to Evaluate the Activity and Safety of Cabozantinib in Pretreated, Advanced RET-rearranged Non-small Cell Lung Cancer Patients: CRETA Trial"	II
NCT04268550	A Phase II Study of LOXO-292 in Patients With RET Fusion-Positive Stage IV or Recurrent Non-Small Cell Lung Cancer (LUNG-MAP Sub-Study)	II
No NCT ID	A Single-center, Open-label , Non-randomized Control Clinical Trial On Clinical Features and Medical Treatment of Advanced NSCLC With Rare Gene Mutations	II
NCT03157128	A Phase I/II 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
NCT04161391	A Phase I/II Study of TPX-0046, A Novel Oral RET/SRC Inhibitor in Adult Subjects With Advanced/ Metastatic Solid Tumors Harboring Oncogenic RET Fusions or Mutations	I/II
NCT03780517	A Phase 1 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
NCT03391869	Randomized Phase III Trial of Local Consolidation Therapy (LCT) After Nivolumab and Ipilimumab for Immunotherapy-Naive Patients With Metastatic Non-Small Cell Lung Cancer (LONESTAR) -Strategic Alliance: BMS	III
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
NCT04280081	A Phase II Study of LOXO-292 in Patients with Advanced Solid Tumors, Including Solid Tumors Positive for RET Fusion, Medullary Thyroid Carcinoma with RET Mutations, and Other Tumors with RET Activation	II
NCT02450123	Single-arm Study to Evaluate the Safety and Efficacy of Sunitinib, in Subjects With RET Fusion Positive or FGFR2 Amplification, Refractory Solid Tumors	II
NCT02691793	Study to Evaluate the Safety and Efficacy of Sunitinib, in Subject With Refractory Solid Tumors	II
NCT04320888	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of LOXO-292 in Patients with Tumors Harboring RET Gene Alterations	II
NCT02272998	Phase II Study Of Ponatinib For Advanced Cancers With Genomic Alterations In Fibroblastic Growth Factor Receptor (FGFR) And Other Genomic Targets (KIT, Pdgfra, RET FLT3, ABL1)	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II

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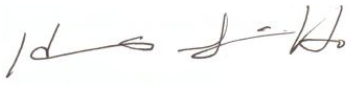
Signatures

Testing Personnel:

2021.03.19
11:31:36 +08'00'

Laboratory Supervisor:



2021.03.19
11:31:48 +08'00'

Pathologist:

2021.03.19
11:32:02 +08'00'

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References

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