Taipei Veterans General Hospital

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Sample Information

Patient Name: 林身立
Gender: Male
ID No.: A100456781
History No.: 36579201
Age: 67

Ordering Doctor: DOC3072G吳佳儒
Ordering REQ.: 0AVPVLP
Signing in Date: 2020/09/03

Path No.: S109-99968
MP No.: F20068
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-28076A+B
Percentage of tumor cells: 50%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

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Relevant Non-Small Cell Lung Cancer Findings

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	**selpercatinib** [1] cabozantinib vandetanib	**selpercatinib** [1]	22

Public data sources included in relevant therapies: FDA1, 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.(S33C) c.98C>G

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
CTNNB1	p.(S33C)	c.98C>G	COSM5677	chr3:41266101	27.20%	NM_001904.3	missense	1125
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	48.42%	NM_002227.3	synonymous	1991
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.95%	NM_004304.4	missense	1996
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	100.00%	NM_004304.4	missense	1999
ALK	p.(=)	c.3375C>A	.	chr2:29445458	100.00%	NM_004304.4	synonymous	1996
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.75%	NM_000142.4	synonymous	1997
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	52.41%	NM_006206.5	synonymous	1994
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	100.00%	NM_006206.5	synonymous	1679
PDGFRA	p.(=)	c.2472C>T	.	chr4:55152040	43.89%	NM_006206.5	synonymous	1996
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.35%	NM_213647.2	missense	2000
FGFR1	p.(=)	c.2178T>G	.	chr8:38271771	4.92%	NM_001174067.1	synonymous	772
RET	p.(=)	c.2307G>T	.	chr10:43613843	47.35%	NM_020975.4	synonymous	1998
JAK3	p.(E547*)	c.1639G>T	.	chr19:17948803	4.50%	NM_000215.3	nonsense	1999

Gene Fusions (RNA)

Genes	Variant ID	Locus
KIF5B-RET	KIF5B-RET.K15R12.COSF1232	chr10:32317356 - chr10:43612032

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].

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

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

KIF5B-RET fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selpercatinib	◑	●	✖	✖	● (II)
cabozantinib	✖	●	✖	✖	● (II)
vandetanib	✖	●	✖	✖	✖
alectinib	✖	✖	✖	✖	● (IV)
alectinib, crizotinib	✖	✖	✖	✖	● (III)
ipilimumab, nivolumab, radiation therapy, surgical intervention	✖	✖	✖	✖	● (III)
pralsetinib	✖	✖	✖	✖	● (III)
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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

KIF5B-RET fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
erdafitinib	✖	✖	✖	✖	● (II)
ponatinib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)
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 ⊘ Contraindicated ⛔ Not recommended 🛡 Resistance

FDA information is current as of 2020-05-26. 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

Current NCCN Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

NCCN information is current as of 2020-05-01. 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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; RET rearrangement discovered prior to or during first-line systemic therapy (First-line therapy) (Useful in Certain Circumstances)
- Non-Small Cell Lung Cancer; Advanced or metastatic disease; Progression after first-line systemic therapy (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

selpercatinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; RET rearrangement discovered prior to or during first-line systemic therapy (First-line therapy) (Preferred)
- Non-Small Cell Lung Cancer; Advanced or metastatic disease; Subsequent therapy if not previously used in first-line (Subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

vandetanib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; RET rearrangement discovered prior to or during first-line systemic therapy (First-line therapy) (Useful in Certain Circumstances)
- Non-Small Cell Lung Cancer; Advanced or metastatic disease; If not previously used in first-line (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

KIF5B-RET fusion (continued)

atezolizumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with RET rearrangements have minimal response (6%) to immunotherapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

durvalumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with RET rearrangements have minimal response (6%) to immunotherapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

nivolumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with RET rearrangements have minimal response (6%) to immunotherapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

pembrolizumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with RET rearrangements have minimal response (6%) to immunotherapy."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

Signatures

Testing Personnel:

Shu-Ying Wang 2020.09.03 15:08:32 +08'00'

Laboratory Supervisor:

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Pathologist:

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15:09:27 +08'00'

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