Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳憲華
Gender: Female
ID No.: A210049503
History No.: 27885525
Age: 76

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: D572GC5
Signing in Date: 2020/06/23

Path No.: S109-99625
MP No.: F20039
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-76628A
Percentage of tumor cells: 20%
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

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
KIF5B-RET fusion kinesin family member 5B - ret proto-oncogene Tier: IA	cabozantinib vandetanib	None	18

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
KIF5B-RET	KIF5B-RET.K15R12.COSF1232	chr10:32317356 - chr10:43612032

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: Currently, no therapies are approved for RET aberrations. However, the RET inhibitor, pralsetinib[8,9], 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 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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

KIF5B-RET fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	●	✖	✖	● (II)
vandetanib	✖	●	✖	✖	✖
alectinib	✖	✖	✖	✖	● (IV)
alectinib, crizotinib	✖	✖	✖	✖	● (III)
ipilimumab, nivolumab, radiation therapy, surgical intervention	✖	✖	✖	✖	● (III)
erdafitinib	✖	✖	✖	✖	● (II)
ponatinib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)
pralsetinib	✖	✖	✖	✖	● (I/II)
selpercatinib	✖	✖	✖	✖	● (I/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 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 2019-11-01. 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):
- Non-Small Cell Lung Cancer; Emerging targeted agents

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

● **vandetanib**

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging targeted agents

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

Signatures

Testing Personnel:

2020.06.24
15:03:05 +08'00'

Laboratory Supervisor:

2020.06.24
15:03:26 +08'00'

Pathologist:

2020.06.24
15:03:41 +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
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
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
5. Ciampi et al. RET/PTC rearrangements and BRAF mutations in thyroid tumorigenesis. Endocrinology. 2007 Mar;148(3):936-41. PMID: 16946010
6. Kohno et al. KIF5B-RET fusions in lung adenocarcinoma. Nat. Med. 2012 Feb 12;18(3):375-7. PMID: 22327624
7. Wohllk et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. 1996 Oct;81(10):3740-5. PMID: 8855832
8. http://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-reports-first-quarter-2019-financial-results
9. Blueprint Medicines Announces Top-line Data for Pralsetinib and Initiates Rolling NDA Submission to FDA for the Treatment of Patients with RET Fusion-Positive Non-Small Cell Lung Cancer. http://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-announces-top-line-data-pralsetinib-and
10. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]
11. Sherman et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer. 2016 Dec 15;122(24):3856-3864. PMID: 27525386
12. Carlomagno et al. Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. Oncogene. 2004 Aug 12;23(36):6056-63. PMID: 15184865
13. Carlomagno et al. Identification of tyrosine 806 as a molecular determinant of RET kinase sensitivity to ZD6474. Endocr Relat Cancer. 2009 Mar;16(1):233-41. doi: 10.1677/ERC-08-0213. Epub 2008 Nov 24. PMID: 19029224
14. NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2019]