Taipei Veterans General Hospital

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Sample Information

Patient Name: 連杏華
Gender: Male
ID No.: A120164097
History No.: 23799566
Age: 58

Ordering Doctor: DOC6278K 陳逸安
Ordering REQ.: 0AVZMEE
Signing in Date: 2020/09/16

Path No.: S109-89601
MP No.: F20072
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-24692B
Percentage of tumor cells: 95%
Note:

Sample Cancer Type: Thyroid Cancer

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Relevant Thyroid Cancer Findings

Gene	Finding
BRAF	Not detected
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*RET p.(M918T) c.2753T>C* ret proto-oncogene Allele Frequency: 45.67%	**selpercatinib** [1] cabozantinib	None	16

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.

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
RET	p.(M918T)	c.2753T>C	COSM965	chr10:43617416	45.67%	NM_020975.4	missense	1997

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 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[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

RET p.(M918T) c.2753T>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selpercatinib	●	✖	✖	✖	● (II)
cabozantinib	✖	✖	✖	●	● (IV)
vandetanib	✖	✖	✖	✖	● (IV)
selpercatinib, vandetanib, cabozantinib	✖	✖	✖	✖	● (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

RET p.(M918T) c.2753T>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
erdafitinib	✖	✖	✖	✖	● (II)
ponatinib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
sunitinib, regorafenib	✖	✖	✖	✖	● (II)
pralsetinib	✖	✖	✖	✖	● (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 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.

RET p.(M918T) c.2753T>C

● selpercatinib

Cancer type: Thyroid Gland Medullary Carcinoma

Label as of: 2020-05-08

Variant class: RET M918T mutation

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 ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⊖ Not recommended ⛊ Resistance

ESMO information is current as of 2020-05-01. For the most up-to-date information, search www.esmo.org.

RET p.(M918T) c.2753T>C

● cabozantinib

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** RET M918T mutation

ESMO Level of Evidence/Grade of Recommendation: II / C

Population segment (Line of therapy):
- Metastatic Thyroid Gland Medullary Carcinoma (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology 30: 1856–1883, 2019 doi:10.1093/annonc/mdz400]

Signatures

Testing Personnel:

2020.09.21
08:58:43 +08'00'

Laboratory Supervisor:

2020.09.21
08:59:43 +08'00'

Pathologist:

2020.09.21
08:59:57 +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
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8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213246s000lbl.pdf
9. http://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-reports-first-quarter-2019-financial-results
10. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]
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]