Taipei Veterans General Hospital

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Sample Information

Patient Name: 林陳淑媛
Gender: Female
ID No.: P201176311
History No.: 45445963
Age: 68

Ordering Doctor: DOC3153J 黃煦晴
Ordering REQ.: D54397K
Signing in Date: 2020/05/21

Path No.: S109-99489
MP No.: F2023
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-76164A
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

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
MYC amplification MYC proto-oncogene, bHLH transcription factor Tier: IIC	None	None	3

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	49.47%	NM_002227.3	synonymous	1993
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	48.45%	NM_004304.4	missense	2000
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.95%	NM_004304.4	missense	1999
ALK	p.(=)	c.3600G>C	.	chr2:29443617	50.28%	NM_004304.4	synonymous	1997
ALK	p.(=)	c.3375C>A	.	chr2:29445458	50.48%	NM_004304.4	synonymous	1995
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.78%	NM_000142.4	synonymous	904
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	47.94%	NM_006206.5	synonymous	1994
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.90%	NM_006206.5	synonymous	1996
KIT	p.(=)	c.1638A>G	.	chr4:55593481	99.75%	NM_000222.2	synonymous	1994
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.30%	NM_213647.2	missense	2000
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	5.92%	NM_213647.2	synonymous	1741
RET	p.(=)	c.2307G>T	.	chr10:43613843	50.45%	NM_020975.4	synonymous	1996

Gene Fusions (RNA)

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

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748885	8.1

Biomarker Descriptions

MYC (MYC proto-oncogene, bHLH transcription factor)

Background: The MYC gene encodes the MYC proto-oncogene (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation[1,2,3,4]. MYC is part of the MYC oncogene family that includes related transcription factors MYCN and MYCL that regulate transcription in 10-15% of promoter regions[5]. MYC functions as a heterodimer in complex with the transcription factor MAX[2,6].

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including codon T58, are infrequent and hypothesized to increase the stability of the MYC protein[7,8]. MYC gene amplification is particularly common in diverse solid tumors. MYC amplification is observed in 30% of serous ovarian cancer, 20% of uterine serous carcinoma, 15% of esophageal and breast cancers, and is common (1-10%) in numerous other cancer types[9,10,11]. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt's lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, which results in increased MYC expression[12,13].

Potential relevance: Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression[1,14,15,16].

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)[17]. 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[18].

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[19,20,21]. RET rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[22]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[23]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[23].

Potential relevance: Currently, no therapies are approved for RET aberrations. However, the RET inhibitor, pralsetinib[24,25], 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[26]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[27]. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[28,29]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[30].

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)

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
VX-970	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BMS-986158	✖	✖	✖	✖	● (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:

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Pathologist:

Yi-Chu Yeh 2020.05.21 13:40:30 +08'00'

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