Taipei Veterans General Hospital

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Sample Information

Patient Name: 吳明壽
Gender: Male
ID No.: Q101656528
History No.: 37716226
Age: 69

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: D53DPJ6
Signing in Date: 2020/05/13

Path No.: S109-99477
MP No.: F2021
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S108-29773B
Percentage of tumor cells: 50%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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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	Not detected
KRAS	Not detected	ROS1	Not detected
MET	***MET exon 14 skipping***		

Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
MET exon 14 skipping MET proto-oncogene, receptor tyrosine kinase Tier: IA	crizotinib	None	19

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
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	10.11%	NM_213647.2	synonymous	1999
MET	p.(D1028Y)	c.3082G>T	.	chr7:116412043	21.00%	NM_001127500.2	missense	2000

Gene Fusions (RNA)

Genes	Variant ID	Locus
MET-MET	MET-MET.M13M15	chr7:116411708 - chr7:116414935

Biomarker Descriptions

MET (MET proto-oncogene, receptor tyrosine kinase)

Background: The MET proto-oncogene encodes a receptor tyrosine kinase for the hepatocyte growth factor (HGF) protein, which is expressed by mesenchymal cells. Ubiquitin-dependent proteolysis regulates the steady state level of the MET protein via recognition of the tyrosine phosphorylation site Y1003 in the MET Cbl-binding domain within the juxtamembrane region[1,2,3]. Growth factor signaling leads to MET dimerization and subsequent initiation of downstream effectors including those involved in the RAS/RAF/MEK/ERK and PI3K/AKT signaling pathways, which regulate cell migration, proliferation, and survival[4,5].

Alterations and prevalence: Recurrent somatic MET alterations include activating mutations, gene amplification, and translocations generating MET gene fusions. Recurrent somatic mutations fall into two classes, mutations in the MET kinase domain, which are uncommon, and splice-site mutations affecting exon 14. Recurrent kinase domain mutations are observed in papillary renal cell carcinoma (PRCC) (1-2%) and include M1250T, H1094Y, and V1070E. Mutation of the Y1003 phosphorylation site is reported in lung cancer but is uncommon (<1%)[6,7]. In contrast, splice-site mutations flanking exon 14 are observed in 4% of non-small cell lung cancer (NSCLC). These mutations include canonical splice site mutations affecting exon 14 and deletions that extend into the splicing motifs within intron 13[8,9]. Such mutations disrupt splicing leading to the formation of an alternative transcript that joins exon 13 directly to exon 15 and skips exon 14 entirely. The MET exon 14 skipping transcript lacks the juxtamembrane domain that contains the recognition motif for ubiquitin-dependent proteolysis and thus leads to a marked increase in steady-state level of the MET protein[10]. MET exon 14 skipping mutations act as oncogenic drivers in lung cancer mutually exclusive to activating mutations in EGFR and KRAS and other oncogenic fusions such as ALK and ROS1[8,11,12]. MET is amplified in 2-5% of ovarian cancer, esophageal adenocarcinoma, stomach adenocarcinoma, glioblastoma, and lung adenocarcinoma[6,7,13]. Recurrent MET fusions, although infrequent, are observed in adult and pediatric glioblastoma, papillary renal cell carcinoma, lung cancer, liver cancer, thyroid cancer, and melanoma[14,15,16]. MET alterations are believed to be enriched in late-stage cancers where they drive tumor progression and metastasis[17,18,19].

Biomarker Descriptions (continued)

Potential relevance: The FDA has granted designations for two investigational MET inhibitors— capmatinib[20] has been granted FDA orphan drug and breakthrough therapy designations for MET exon 14 skipping positive metastatic NSCLC following platinum-based chemotherapy, and tepotinib[21] has been granted FDA breakthrough designation (2019) for advanced MET exon 14 skipping NSCLC. MET exon 14 skipping mutations confer sensitivity to approved kinase inhibitors including crizotinib (2011), which is recommended for MET amplifications and exon 14 skipping mutations[8,11,12,22]. Conversely, amplification of MET has been observed to mediate resistance to EGFR tyrosine kinase inhibitors (TKIs)[23,24,25,26,27]. In a phase II trial testing the MET inhibitor savolitinib, patients with advanced PRCC exhibited median progression free survival (PFS) of 6.2 and 1.4 months for MET-driven and MET-independent PRCC, respectively[28].

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

MET exon 14 skipping

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	✖	●	✖	●	● (II)
cabozantinib	✖	✖	✖	✖	● (II)
capmatinib	✖	✖	✖	✖	● (II)
capmatinib + nivolumab	✖	✖	✖	✖	● (II)
savolitinib	✖	✖	✖	✖	● (II)
tepotinib	✖	✖	✖	✖	● (II)
bozitinib	✖	✖	✖	✖	● (I/II)
REGN-5093	✖	✖	✖	✖	● (I/II)
glumetinib	✖	✖	✖	✖	● (I)
JNJ-61186372	✖	✖	✖	✖	● (I)
metatinib	✖	✖	✖	✖	● (I)
TPX-0022	✖	✖	✖	✖	● (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.

MET exon 14 skipping

● crizotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET exon 14 skipping

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]

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 2019-11-01. For the most up-to-date information, search www.esmo.org.

MET exon 14 skipping

● crizotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET exon 14 skipping

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

Population segment (Line of therapy):
- Demonstrated potential clinical efficacy that needs to be confirmed (Not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

Signatures

Testing Personnel:

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Laboratory Supervisor:

2020.05.14 17:38:08 +08'00'

Pathologist:

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