Taipei Veterans General Hospital

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Sample Information

Patient Name: 林麗蘭
Gender: Female
ID No.: G220508748
History No.: 28565255
Age: 47

Ordering Doctor: DOC3072G 吳佳儒
Ordering REQ.: 0AUUNHF
Signing in Date: 2020/08/12

Path No.: S109-99817
MP No.: F20054
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-11279E
Percentage of tumor cells: 60%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Report Highlights

1 Relevant Biomarkers
2 Therapies Available
21 Clinical Trials

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

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*MET exon 14 skipping* MET proto-oncogene, receptor tyrosine kinase	**capmatinib** [1] crizotinib	None	21

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.

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	99.70%	NM_002227.3	synonymous	1992
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	54.60%	NM_004304.4	missense	1998
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.90%	NM_004304.4	missense	1999
ALK	p.(=)	c.3375C>A	.	chr2:29445458	54.71%	NM_004304.4	synonymous	1996
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.85%	NM_000142.4	synonymous	1320
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	46.87%	NM_006206.5	synonymous	1999
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.55%	NM_006206.5	synonymous	1999
PDGFRA	p.(=)	c.2472C>T	.	chr4:55152040	49.17%	NM_006206.5	synonymous	1999
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.25%	NM_213647.2	missense	2000
EGFR	p.(=)	c.2361G>A	.	chr7:55249063	43.34%	NM_005228.4	synonymous	1998
RET	p.(=)	c.2307G>T	.	chr10:43613843	99.85%	NM_020975.4	synonymous	1995

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

Biomarker Descriptions (continued)

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].

Potential relevance: In 2020, the FDA granted accelerated approval to capmatinib[20] for NSCLC harboring MET exon 14 skipping positive as detected by an FDA-approved test[21]. Tepotinib[22] 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[8,11,12,21]. 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*
capmatinib	●	●	✖	✖	● (II)
crizotinib	✖	●	✖	●	● (II)
cabozantinib	✖	✖	✖	✖	● (II)
capmatinib + nivolumab	✖	✖	✖	✖	● (II)
savolitinib	✖	✖	✖	✖	● (II)
bozitinib	✖	✖	✖	✖	● (I/II)
glumetinib	✖	✖	✖	✖	● (I/II)
REGN-5093	✖	✖	✖	✖	● (I/II)
HLX55	✖	✖	✖	✖	● (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 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.

MET exon 14 skipping

● capmatinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2020-05-06 **Variant class:** MET exon 14 skipping

Indications and usage:

TABRECTA™ is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test.

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/2020/213591s000lbl.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.

MET exon 14 skipping

capmatinib

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

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; MET exon 14 skipping mutation discovered prior to or during first-line systemic therapy (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Progression after first-line systemic therapy (Subsequent therapy) (Preferred)

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

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crizotinib

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

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; MET exon 14 skipping mutation discovered prior to or during first-line systemic therapy (First-line therapy) (Useful in Certain Circumstances)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; 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]

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atezolizumab

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

Other criteria: CD274 overexpression

Summary:

NCCN Guidelines® include the following supporting statement(s):
- "In addition, those with METex14 mutations and high PD-L1 expression do not respond to immunotherapy."

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

MET exon 14 skipping (continued)

durvalumab

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

Other criteria: CD274 overexpression

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "In addition, those with METex14 mutations and high PD-L1 expression do not respond to immunotherapy."

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

nivolumab

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

Other criteria: CD274 overexpression

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "In addition, those with METex14 mutations and high PD-L1 expression do not respond to immunotherapy."

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

pembrolizumab

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

Other criteria: CD274 overexpression

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "In addition, those with METex14 mutations and high PD-L1 expression do not respond to immunotherapy."

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

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 2020-05-01. 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:

2020.08.13 14:48:38 +08'00'

Pathologist:

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References

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