



## Sample Information

**Patient Name:** 陳榮任  
**Gender:** Male  
**ID No.:** P120026021  
**History No.:** 45753831  
**Age:** 56

**Ordering Doctor:** DOC3160J 羅永鴻  
**Ordering REQ.:** C243PCM  
**Signing in Date:** 2021/08/12

**Path No.:** S110-99265  
**MP No.:** F21066  
**Assay:** Oncomine Focus Assay  
**Sample Type:** FFPE  
**Block No.:** S110-76338B  
**Percentage of tumor cells:** 40%

**Reporting Doctor:** DOC5466K 葉奕成 (Phone: 8#5466)

**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 Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	<b>MET exon 14 skipping</b>		

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	<b>MET exon 14 skipping</b> MET proto-oncogene, receptor tyrosine kinase	<b>capmatinib</b> <sup>1</sup> <b>tepotinib</b> <sup>1</sup> crizotinib	None	4

Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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.(A190T)	c.568G>A	.	chr5:176518070	66.65%	NM_213647.3	missense	1691

### Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
MET-MET	MET-MET.M13M15	chr7:116411708 - chr7:116414935	9954

## 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<sup>1,2,3</sup>. 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<sup>4,5</sup>.

**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%)<sup>6,7</sup>. 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<sup>8,9</sup>. 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<sup>10</sup>. 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<sup>8,11,12</sup>. MET is amplified in 2-5% of ovarian cancer, esophageal adenocarcinoma, stomach adenocarcinoma, glioblastoma, and lung adenocarcinoma<sup>6,7,13</sup>. Recurrent MET fusions, although infrequent, are observed in adult and pediatric glioblastoma, papillary renal cell carcinoma, lung cancer, liver cancer, thyroid cancer, and melanoma<sup>14,15,16</sup>. MET alterations are believed to be enriched in late-stage cancers where they drive tumor progression and metastasis<sup>17,18,19</sup>.

**Potential relevance:** In 2020, the FDA granted accelerated approval to capmatinib<sup>20</sup> for NSCLC harboring MET exon 14 skipping positive as detected by an FDA-approved test<sup>21</sup>. The kinase inhibitor, tepotinib<sup>22</sup>, is also approved (2021) for MET exon 14 skipping mutations in NSCLC<sup>22</sup>. 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<sup>8,11,12,21</sup>. Conversely, amplification of MET has been observed to mediate resistance to EGFR tyrosine kinase inhibitors (TKIs)<sup>23,24,25,26,27</sup>. 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<sup>28</sup>.

## Relevant Therapy Summary

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ No evidence

### MET exon 14 skipping

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capmatinib	●	●	×	●	×
tepotinib	●	●	×	●	×
crizotinib	×	●	×	●	×
datopotamab deruxtecan	×	×	×	×	● (II)
bozitinib	×	×	×	×	● (I/II)
amivantamab	×	×	×	×	● (I)
HLX55	×	×	×	×	● (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

FDA information is current as of 2021-06-09. For the most up-to-date information, search [www.fda.gov](https://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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf)

## MET exon 14 skipping (continued)

### ● tepotinib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-02-03

Variant class: MET exon 14 skipping

#### Indications and usage:

TEPMETKO® is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

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 trials.

#### Reference:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/214096s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf)

## Current NCCN Information

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types

NCCN information is current as of 2021-06-01. For the most up-to-date information, search [www.nccn.org](http://www.nccn.org).  
For NCCN International Adaptations & Translations, search [www.nccn.org/global/international\\_adaptations.aspx](http://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, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2021]

#### 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, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Useful in certain circumstances
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2021]

#### tepotinib

**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, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2021]

## Current ESMO Information

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types

ESMO information is current as of 2021-06-01. For the most up-to-date information, search [www.esmo.org](http://www.esmo.org).

### MET exon 14 skipping

#### ● capmatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: MET exon 14 skipping

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

Population segment (Line of therapy):

- (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

#### ● crizotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: MET exon 14 skipping

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

Population segment (Line of therapy):

- (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

#### ● tepotinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: MET exon 14 skipping

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

Population segment (Line of therapy):

- (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - <https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer>); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

## Clinical Trials in Taiwan region:

### Clinical Trials Summary

#### MET exon 14 skipping

NCT ID	Title	Phase
NCT04484142	Phase II, Single-arm, Open-label Study of DS-1062a in Advanced or Metastatic Non-small Cell Lung Cancer With Actionable Genomic Alterations and Progressed on or After Kinase Inhibitor Therapy and Platinum Based Chemotherapy (TROPION-Lung05)	II
NCT03175224	Phase I/II Multicenter Study of the Safety, Pharmacokinetics, and Preliminary Efficacy of APL-101 in Subjects With Non-Small Cell Lung Cancer With c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advanced Solid Tumors.	I/II
NCT02609776	A Phase I, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer.	I
NCT04169178	A Phase I Dose Finding/Expansion Study of HLX55, A Monoclonal Antibody Targeting Tyrosine-Protein Kinase MET (C-MET) in Patients With Advanced Solide Tumors Refractory to Standard Therapy	I

### Alerts Informed By Public Data Sources

#### Current FDA Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

FDA information is current as of 2021-06-09. For the most up-to-date information, search [www.fda.gov](http://www.fda.gov).

#### MET exon 14 skipping

#### crizotinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** MET exon 14 skipping

#### Supporting Statement:

The FDA has granted Breakthrough Therapy Designation to the tyrosine kinase inhibitor, crizotinib, for metastatic non-small cell lung cancer (NSCLC) with MET exon 14 alterations with disease progression on or after platinum-based chemotherapy.

#### Reference:

[https://www.pfizer.com/news/press-release/press-release-detail/pfizer\\_s\\_xalkori\\_crizotinib\\_receives\\_fda\\_breakthrough\\_therapy\\_designation\\_in\\_two\\_new\\_indications-0](https://www.pfizer.com/news/press-release/press-release-detail/pfizer_s_xalkori_crizotinib_receives_fda_breakthrough_therapy_designation_in_two_new_indications-0)

## Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:



## References

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