Taipei Veterans General Hospital

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Sample Information

Patient Name: 丁助
Gender: Male
ID No.: P102133667
History No.: 15635639
Age: 88

Ordering Doctor: DOC6273E 葉雲凱
Ordering REQ.: 0BUUXCE
Signing in Date: 2022/05/04

Path No.: S111-99209
MP No.: F22038
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S111-00178D
Percentage of tumor cells: 40%

Reporting Doctor: DOC5452C 周德盈 (Phone: 8#5452)

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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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	***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] **tepotinib** [1] crizotinib	None	4

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.

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
MET-MET	MET-MET.M13M15	chr7:116411708 - chr7:116414935	34627

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. MET is expressed as multiple isoforms with transcript variant 1 (NM_001127500.3) encoding a 1408 amino acid protein and transcript variant 2 (NM_000245.4) encoding a 1390 amino acid protein, both of which possess an intact protein kinase domain[1]. Ubiquitin-dependent proteolysis is responsible for regulating the steady state level of the MET protein via recognition of the tyrosine phosphorylation site Y1003(NM_000245.4), sometimes referred to as Y1021 (NM_001127500.3), in the MET Cbl-binding domain within the juxtamembrane region[2,3,4]. 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[5,6].

Alterations and prevalence: Somatic mutations in MET are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 8% of papillary renal cell carcinoma (PRCC), and 4% of lung adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[7,8]. 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 PRCC and include M1250T, H1094Y, and V1070E (NM_000245.4)[7,8]. Mutation of the Y1003 phosphorylation site is reported in approximately 2% of MET altered lung cancer[9]. In contrast, splice-site mutations flanking exon 14 are observed in 3-4% of all non-small cell lung cancer (NSCLC)[10]. These mutations include canonical splice site mutations affecting exon 14 and deletions that extend into the splicing motifs within intron 13[9,11]. 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 the steady-state level of the MET protein[12]. 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[11,13,14]. MET is amplified in 2-5% of ovarian cancer, esophageal adenocarcinoma, stomach adenocarcinoma, glioblastoma, and lung adenocarcinoma[7,15,16]. Recurrent MET fusions, although infrequent, are observed in adult and pediatric glioblastoma, papillary renal cell carcinoma, lung cancer, liver cancer, thyroid cancer, and melanoma[17,18,19]. MET alterations are believed to be enriched in late-stage cancers where they drive tumor progression and metastasis[20,21,22].

Potential relevance: In 2020, the FDA granted accelerated approval to capmatinib[23] for NSCLC harboring MET exon 14 skipping positive as detected by an FDA-approved test. The kinase inhibitor, tepotinib[24], is also approved (2021) for MET exon 14 skipping mutations in 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[11,13,14,25]. The FDA also granted breakthrough therapy designation (2018) to crizotinib for metastatic non-small cell lung cancer (NSCLC) with MET exon 14 alterations with disease progression on or after platinum-based chemotherapy[26]. Conversely, amplification of MET has been observed to mediate resistance to EGFR tyrosine kinase inhibitors (TKIs)[27,28,29,30,31]. However, the FDA has granted Fast Track designation (2021) to the MET/CSF1R/SRC small molecule inhibitor, TPX-0022[32], for MET amplified advanced or metastatic gastric cancer, including gastroesophageal junction

Biomarker Descriptions (continued)

adenocarcinoma (GEJ) after prior chemotherapy. 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[33].

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 2022-03-16. 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:** 2022-01-21 **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/2022/213591s002lbl.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

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 2022-02-28. 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):
- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

● 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 1.2022]

● 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 1.2022]

MET exon 14 skipping (continued)

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 1.2022]

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 2022-02-28. For the most up-to-date information, search 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 Applicable Targeted 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 Refactory 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 2022-03-16. For the most up-to-date information, search 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

Signatures

Testing Personnel:

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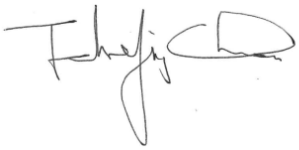
Laboratory Supervisor:

2022.05.09
09:44:29 +08'00'

Pathologist:



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