Taipei Veterans General Hospital

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Sample Information

Patient Name: 黃錦郎
Gender: Male
ID No.: Q120753408
History No.: 48363651
Age: 62

Ordering Doctor: DOC3064F 陳育民
Ordering REQ.: D6NEH2J
Signing in Date: 2022/04/15

Path No.: S111-99029
MP No.: F22028
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S111-13390A
Percentage of tumor cells: 60%

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

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 amplification***		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*MET amplification* MET proto-oncogene, receptor tyrosine kinase **Prognostic significance:** None **Diagnostic significance:** None	capmatinib crizotinib tepotinib	None	2

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, 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)

Copy Number Variations

Gene	Locus	Copy Number
MET	chr7:116313480	10.27

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

Biomarker Descriptions (continued)

small molecule inhibitor, TPX-0022[32], for MET amplified advanced or metastatic gastric cancer, including gastroesophageal junction 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 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capmatinib	✖	●	✖	✖	✖
crizotinib	✖	●	✖	✖	✖
tepotinib	✖	●	✖	✖	✖
bozitinib	✖	✖	✖	✖	● (I/II)
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 NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2022-02-01. 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 amplification

● capmatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET amplification

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2022]

MET amplification (continued)

crizotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET amplification

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2022]

tepotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** MET amplification

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2022]

Clinical Trials in Taiwan region:

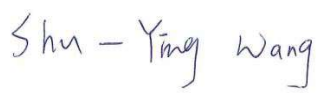
Clinical Trials Summary

MET amplification

NCT ID	Title	Phase
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
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

Signatures

Testing Personnel:



2022.04.18
10:29:55 +08'00'

Laboratory Supervisor:

2022.04.18
10:30:07 +08'00'

Pathologist:

2022.04.18
10:30:30 +08'00'

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Peschard et al. A conserved DpYR motif in the juxtamembrane domain of the Met receptor family forms an atypical c-Cbl/Cbl-b tyrosine kinase binding domain binding site required for suppression of oncogenic activation. J. Biol. Chem. 2004 Jul 9;279(28):29565-71. PMID: 15123609
3. Peschard et al. Mutation of the c-Cbl TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein. Mol. Cell. 2001 Nov;8(5):995-1004. PMID: 11741535
4. Abella et al. Met/Hepatocyte growth factor receptor ubiquitination suppresses transformation and is required for Hrs phosphorylation. Mol. Cell. Biol. 2005 Nov;25(21):9632-45. PMID: 16227611
5. Sierra et al. c-MET as a potential therapeutic target and biomarker in cancer. Ther Adv Med Oncol. 2011 Nov;3(1 Suppl):S21-35. PMID: 22128285
6. Mo et al. Targeting MET in cancer therapy. Chronic Dis Transl Med. 2017 Sep;3(3):148-153. PMID: 29063069
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. Schrock et al. Characterization of 298 Patients with Lung Cancer Harboring MET Exon 14 Skipping Alterations. J Thorac Oncol. 2016 Sep;11(9):1493-502. PMID: 27343443
10. Socinski et al. MET Exon 14 Skipping Mutations in Non–Small-Cell Lung Cancer: An Overview of Biology, Clinical Outcomes, and Testing Considerations. JCO Precis Oncol. 2021;5. PMID: 34036238
11. Frampton et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015 Aug;5(8):850-9. PMID: 25971938
12. Pilotto et al. MET exon 14 juxtamembrane splicing mutations: clinical and therapeutical perspectives for cancer therapy. Ann Transl Med. 2017 Jan;5(1):2. doi: 10.21037/atm.2016.12.33. PMID: 28164087
13. Reungwetwattana et al. The race to target MET exon 14 skipping alterations in non-small cell lung cancer: The Why, the How, the Who, the Unknown, and the Inevitable. Lung Cancer. 2017 Jan;103:27-37. PMID: 28024693
14. Saffroy et al. MET exon 14 mutations as targets in routine molecular analysis of primary sarcomatoid carcinoma of the lung. Oncotarget. 2017 Jun 27;8(26):42428-42437. PMID: 28418914
15. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
16. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
17. Yeh et al. Activating MET kinase rearrangements in melanoma and Spitz tumours. Nat Commun. 2015 May 27;6:7174. doi: 10.1038/ncomms8174. PMID: 26013381
18. Bao et al. RNA-seq of 272 gliomas revealed a novel, recurrent PTPRZ1-MET fusion transcript in secondary glioblastomas. Genome Res. 2014 Nov;24(11):1765-73. PMID: 25135958
19. Sebastian et al. Recurrent MET fusion genes represent a drug target in pediatric glioblastoma. Nat. Med. 2016 Nov;22(11):1314-1320. PMID: 27748748
20. Zeng et al. c-Met gene amplification is associated with advanced stage colorectal cancer and liver metastases. Cancer Lett. 2008 Jul 8;265(2):258-69. PMID: 18395971
21. Tsugawa et al. Amplification of the c-met, c-erbB-2 and epidermal growth factor receptor gene in human gastric cancers: correlation to clinical features. Oncology. 1998 Sep-Oct;55(5):475-81. PMID: 9732228
22. Di et al. Overexpression and amplification of the met/HGF receptor gene during the progression of colorectal cancer. Clin. Cancer Res. 1995 Feb;1(2):147-54. PMID: 9815967
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213591s002lbl.pdf
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf
25. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2022]
26. https://www.pfizer.com/news/press-release/press-release-detail/pfizer_s_xalkori_crizotinib_receives_fda_breakthrough_therapy_designation_in_two_new_indications-0
27. Bean et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc. Natl. Acad. Sci. U.S.A. 2007 Dec 26;104(52):20932-7. PMID: 18093943

References (continued)

28. Chen et al. Clinicopathologic and molecular features of epidermal growth factor receptor T790M mutation and c-MET amplification in tyrosine kinase inhibitor-resistant Chinese non-small cell lung cancer. Pathol Oncol Res. 2009 Dec;15(4):651-8. doi: 10.1007/s12253-009-9167-8. Epub 2009 Apr 21. PMID: 19381876
29. Suda et al. Reciprocal and complementary role of MET amplification and EGFR T790M mutation in acquired resistance to kinase inhibitors in lung cancer. Clin. Cancer Res. 2010 Nov 15;16(22):5489-98. PMID: 21062933
30. Zhang et al. Current mechanism of acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitors and updated therapy strategies in human nonsmall cell lung cancer. J Cancer Res Ther. 2016 Dec;12(Supplement):C131-C137. PMID: 28230005
31. Nguyen et al. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer. 2009 Jul;10(4):281-9. PMID: 19632948
32. https://www.sec.gov/Archives/edgar/data/1595893/000156459021042621/tptx-ex991_20.htm
33. Choueiri et al. Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer. J. Clin. Oncol. 2017 Sep 10;35(26):2993-3001. PMID: 28644771