



Sample Information

Patient Name: 錢華山
Gender: Male
ID No.: U120002937
History No.: 26736298
Age: 58

Ordering Doctor: DOC6369D 呂宛頤
Ordering REQ.: 0CPPFQE
Signing in Date: 2023/08/17

Path No.: M112-00218
MP No.: F23063
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-39070A
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	EGFR p.(L747P) c.2239_2240delTTinsCC	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	capmatinib crizotinib tepotinib	None	1
IIC	EGFR p.(L747P) c.2239_2240delTTinsCC epidermal growth factor receptor Allele Frequency: 32.85%	None	None	4

Public data sources included in relevant therapies: FDA¹, NCCN, EMA², 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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

CCND1 amplification

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
EGFR	p.(L747P)	c.2239_2240delTTins CC	COSM24267	chr7:55242469	32.85%	NM_005228.5	missense	1942

Copy Number Variations

Gene	Locus	Copy Number
MET	chr7:116313480	12.45
CCND1	chr11:69456942	9.17

Biomarker Descriptions

CCND1 (cyclin D1)

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3^{1,2,3}. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein^{1,2}. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis^{1,2,4}. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1^{3,5}.

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)^{6,7,8,9}. These mutations block phosphorylation-dependent nuclear export and proteolysis^{10,11,12,13}. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers^{6,8,14}. MCL is genetically characterized by the t(11;14) (q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis^{15,16}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma¹⁷.

EGFR (epidermal growth factor receptor)

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the ERBB/human epidermal growth factor receptor (HER) family. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4¹⁸. EGFR ligand induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways. Activation of these pathways promote cell proliferation, differentiation, and survival^{19,20}.

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations^{6,8,21,22}. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21²³. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer. A second group of less prevalent activating mutations include E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{24,25,26,27}. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations²⁸. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V and are primarily observed in glioblastoma^{23,29}. Amplification of EGFR is observed in several cancer types including 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma^{6,8,14,22,29}. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma^{30,31,32}.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib³³ (2004) and gefitinib³⁴ (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations. Second-generation TKIs afatinib³⁵ (2013) and dacomitinib³⁶ (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies^{37,38,39,40}. However, in 2021, the irreversible tyrosine kinase inhibitor, mobocertinib⁴¹ was FDA approved for the treatment of NSCLC with EGFR exon 20 insertion mutations. Additionally, in 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)⁴² and sunvozertinib⁴³, for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance⁴⁴. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases²³. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib⁴⁵ (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance. In this case, resistance is associated with the C797S mutation and occurs in 22-44% of cases⁴⁴. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa⁴⁶. T790M and C797S can occur in either cis or trans allelic orientation⁴⁶. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs⁴⁶. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone^{46,47}. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs⁴⁶. Fourth-generation TKIs are in development to overcome acquired C797S and T790M resistance mutations after osimertinib treatment. EGFR targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, amivantamab⁴⁸, targeting EGFR and MET was approved (2021) NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy quaratusugene ozeplasmid⁴⁹ in combination with osimertinib received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. BDTX-189⁵⁰ was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

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 domain⁵¹. Ubiquitin-dependent proteolysis is responsible for regulating the steady state level of the MET protein

Biomarker Descriptions (continued)

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^{52,53,54}. 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^{55,56}.

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^{6,8}. 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)^{6,8}. Mutation of the Y1003 phosphorylation site is reported in approximately 2% of MET altered lung cancer⁵⁷. In contrast, splice-site mutations flanking exon 14 are observed in 3-4% of all non-small cell lung cancer (NSCLC)⁵⁸. These mutations include canonical splice site mutations affecting exon 14 and deletions that extend into the splicing motifs within intron 13^{57,59}. 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 protein⁶⁰. 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^{59,61,62}. MET is amplified in 2-5% of ovarian cancer, esophageal adenocarcinoma, stomach adenocarcinoma, glioblastoma, and lung adenocarcinoma^{6,29,63}. Recurrent MET fusions, although infrequent, are observed in adult and pediatric glioblastoma, papillary renal cell carcinoma, lung cancer, liver cancer, thyroid cancer, and melanoma^{64,65,66}. MET alterations are believed to be enriched in late-stage cancers where they drive tumor progression and metastasis^{67,68,69}.

Potential relevance: In 2020, the FDA granted accelerated approval to capmatinib⁷⁰ for NSCLC harboring MET exon 14 skipping positive as detected by an FDA-approved test. The kinase inhibitor, tepotinib⁷¹, 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^{37,59,61,62}. 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 chemotherapy⁷². Conversely, amplification of MET has been observed to mediate resistance to EGFR tyrosine kinase inhibitors (TKIs)^{73,74,75,76,77}. However, the FDA has granted Fast Track designation (2021) to the MET/CSF1R/SRC small molecule inhibitor, TPX-0022⁷⁸, for MET amplified advanced or metastatic gastric cancer, including gastroesophageal junction adenocarcinoma (GEJ) after prior chemotherapy. Tepotinib has also been recommended for treatment of NSCLC with high-level MET amplification³⁷. 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, respectively⁷⁹.

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	×	●	×	×	×
HLX55	×	×	×	×	● (I)

EGFR p.(L747P) c.2239_2240delTTinsCC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BLU-451, chemotherapy	×	×	×	×	● (I/II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

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

EGFR p.(L747P) c.2239_2240delTTinsCC (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sunvozertinib	×	×	×	×	● (I/II)
ABBV 400	×	×	×	×	● (I)
lazertinib, amivantamab, chemotherapy	×	×	×	×	● (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 2023-06-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

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 3.2023]

● 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 3.2023]

MET amplification (continued)

● 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 3.2023]

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

EGFR p.(L747P) c.2239_2240delTTinsCC

NCT ID	Title	Phase
NCT05241873	Phase I/II Study of BLU-451 in Advanced Cancers With EGFR Exon 20 Insertion Mutations	I/II
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation	I/II
NCT05029882	A Phase I First in Human Study Evaluating Safety, Pharmacokinetics and Efficacy of ABBV-400 in Adult Subjects With Advanced Solid Tumors	I
NCT04077463	An Open-label Phase I/Ib Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer	I

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2023-06-14. For the most up-to-date information, search www.fda.gov.

EGFR p.(L747P) c.2239_2240delTTinsCC

CPO-301

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR mutation

Supporting Statement:

The FDA has granted Fast Track Designation to a first-in-class antibody drug conjugate, CPO301, for EGFR mutations in patients with metastatic non-small cell lung cancer (NSCLC) who are relapsed/refractory to or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors including Osimertinib.

Reference:

<http://iis.aastocks.com/20230612/10770455-0.PDF>

EGFR p.(L747P) c.2239_2240delTTinsCC (continued)

A osimertinib + quaratusugene ozeplasmid**Cancer type:** Non-Small Cell Lung Cancer**Variant class:** EGFR mutation**Supporting Statement:**

The FDA has granted Fast Track Designation to the immunogene therapy, quaratusugene ozeplasmid, in combination with EGFR inhibitor osimertinib for the treatment of non-small cell lung cancer (NSCLC) with EFGR mutations that progressed after treatment with osimertinib alone.

Reference:

<https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>

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