Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳呂串妹
Gender: Female
ID No.: H200904183
History No.: 21464813
Age: 79

Ordering Doctor: DOC3064F 陳育民
Ordering REQ.: D73F8A9
Signing in Date: 2022/12/15

Path No.: M111-00029
MP No.: F22132
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: C111-44352
Percentage of tumor cells: 20%

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 exon 20 insertion***	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*EGFR exon 20 insertion* epidermal growth factor receptor Allele Frequency: 29.26%	**amivantamab** [1, 2] **mobocertinib** [1]	None	7

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.
*** Includes biosimilars/generics**

Alerts informed by public data sources: ⊘ Contraindicated, Resistance

EGFR exon 20 insertion	⊘ **gefitinib*** [2] afatinib, dacomitinib, erlotinib, gefitinib

Public data sources included in alerts: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources
CTNNB1 p.(S33C) c.98C>G

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
CTNNB1	p.(S33C)	c.98C>G	COSM5677	chr3:41266101	31.23%	NM_001904.4	missense	1998
EGFR	p.(A767_V769dup)	c.2308_2309insCCAGCGTGG	COSM12376	chr7:55248998	29.26%	NM_005228.5	nonframeshift Insertion	1948
BRAF	p.(S273=)	c.819T>C	.	chr7:140501253	4.95%	NM_004333.6	synonymous	2000

Biomarker Descriptions

CTNNB1 (catenin beta 1)

Background: The CTNNB1 gene encodes catenin beta-1 (β-catenin), an integral component of cadherin-based adherens junctions involved in maintaining adhesion and regulating the growth of epithelial cell layers[1]. CTNNB1 binds to the APC protein in the cytoplasm and also interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling[2]. Steady state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis[3,4,5].

Alterations and prevalence: Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-β and inhibit CTNNB1 degradation[6,7,8,9]. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in hepatocellular carcinoma, 20% of uterine carcinoma, and 15% of adrenocortical carcinoma[10,11,12,13,14,15,16].

Potential relevance: Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations in EGFR positive lung cancer have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors[17].

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/HER4[18]. EGFR ligand induced dimerization results in kinase activation and leads to stimulation

Biomarker Descriptions (continued)

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[15,16,21,22]. 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 21[23]. 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 mutations[28]. 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[15,16,22,29,30]. 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[31,32,33].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[34] (2004) and gefitinib[35] (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 afatinib[36] (2013) and dacomitinib[37] (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[38,39,40,41]. However, in 2021, the irreversible tyrosine kinase inhibitor, mobocertinib[42]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)[43] and sunvozertinib[44], 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 resistance[45]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[23]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib[46] (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 cases[45]. 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 versa[47]. T790M and C797S can occur in either cis or trans allelic orientation[47]. 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 TKIs[47]. 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[47,48]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[47]. 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, amivantamab[49], targeting EGFR and MET was approved (2021) NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy quaratusugene ozeplasmid[50] 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-189[51] was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
amivantamab	●	●	●	✖	● (I)
mobocertinib	●	●	✖	✖	● (III)
amivantamab, chemotherapy	✖	✖	✖	✖	● (III)
sunvozertinib	✖	✖	✖	✖	● (I/II)
TPC-064	✖	✖	✖	✖	● (I/II)
BAY-2927088	✖	✖	✖	✖	● (I)
lazertinib, amivantamab	✖	✖	✖	✖	● (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 2022-10-19. For the most up-to-date information, search www.fda.gov.

EGFR exon 20 insertion

● amivantamab

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2021-12-21 **Variant class:** EGFR exon 20 insertion

Indications and usage:

RYBREVANT® is a bispecific EGF receptor-directed and MET receptor directed antibody indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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 the confirmatory trials.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s001lbl.pdf

EGFR exon 20 insertion (continued)

mobocertinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2021-09-15 **Variant class:** EGFR exon 20 insertion

Indications and usage:

EXKIVITY™ is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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/2021/215310s000lbl.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 2022-10-03. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

EGFR exon 20 insertion

● amivantamab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

● mobocertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

Current EMA Information

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

EMA information is current as of 2022-10-19. For the most up-to-date information, search www.ema.europa.eu/ema.

EGFR exon 20 insertion

● amivantamab

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-09-26 **Variant class:** EGFR exon 20 insertion

Reference:

https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf

Clinical Trials in Taiwan region:

Clinical Trials Summary

EGFR exon 20 insertion

NCT ID	Title	Phase
NCT04538664	A Randomized, Open-label Phase III Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared With Carboplatin-Pemetrexed, in Patients With EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer	III
NCT04129502	A Randomized Phase III Multicenter Open-label Study to Compare the Efficacy of TAK-788 as First-line Treatment Versus Platinum-Based Chemotherapy in Patients With Non-Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations	III
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
NCT04036682	A Phase I/IIa, Open-Label, Multi-Center Trial To Assess Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, And Efficacy Of CLN-081 In Patients With Non-Small Cell Lung Cancer Harboring EGFR Exon 20 Insertion Mutations	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
NCT05099172	An Open Label, First-in-human Study of BAY 2927088 in Participants With Advanced Non-small Cell Lung Cancer (NSCLC) Harboring an EGFR and/or HER2 Mutation	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 2022-10-19. For the most up-to-date information, search www.fda.gov.

EGFR exon 20 insertion

sunvozertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 20 insertion

Supporting Statement:
The FDA has granted Breakthrough Therapy Designation to a selective, irreversible, novel epidermal growth factor receptor (EGFR) inhibitor, DZD9008 (Sunvozertinib) for EGFR exon 20 insertion mutation positive locally advanced or metastatic non-small cell lung cancer.

Reference:

https://www.biospace.com/article/releases/fda-grants-breakthrough-therapy-designation-for-dizal-pharmaceutical-s-dzd9008-in-patients-with-locally-advanced-or-metastatic-non-small-cell-lung-cancer-harboring-egfr-exon20-insertion/

EGFR exon 20 insertion (continued)

sunvozertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

Supporting Statement:
The FDA has granted Breakthrough Designation to a small molecule inhibitor, DZD9008 (sunvozertinib), for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

Reference:

https://www.prnewswire.com/news-releases/fda-grants-breakthrough-therapy-designation-for-dizal-pharmaceuticals-dzd9008-in-patients-with-locally-advanced-or-metastatic-non-small-cell-lung-cancer-harboring-egfr-exon20-insertion-301469692.html

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TPC-064

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

Supporting Statement:
The FDA has granted Breakthrough Therapy Designation to an irreversible EGFR inhibitor, CLN-081, for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations who have previously received platinum-based systemic chemotherapy.

Reference:

https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncologys

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BDTX-189

Cancer type: Solid Tumor **Variant class:** EGFR exon 20 insertion

Supporting Statement:
The FDA has granted Fast Track Designation to BDTX-189 for solid tumors harboring a HER2 mutation or an EGFR or HER2 exon 20 insertion after progression on prior therapy.

Reference:

https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda

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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/

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2022-10-03. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

EGFR exon 20 insertion

atezolizumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

Summary:

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

Summary:

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

pembrolizumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

Summary:

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

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

- "Patients with EGFR exon 20 insertion mutations are usually resistant to erlotinib, gefitinib, afatinib, or dacomitinib, although there are rare exceptions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

EGFR exon 20 insertion (continued)

dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with EGFR exon 20 insertion mutations are usually resistant to erlotinib, gefitinib, afatinib, or dacomitinib, although there are rare exceptions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with EGFR exon 20 insertion mutations are usually resistant to erlotinib, gefitinib, afatinib, or dacomitinib, although there are rare exceptions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with EGFR exon 20 insertion mutations are usually resistant to erlotinib, gefitinib, afatinib, or dacomitinib, although there are rare exceptions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2022-10-19. For the most up-to-date information, search www.ema.europa.eu/ema.

EGFR exon 20 insertion

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-07-05 **Variant class:** EGFR exon 20 insertion

Reference:

https://www.ema.europa.eu/en/documents/product-information/iressa-epar-product-information_en.pdf

EGFR exon 20 insertion (continued)

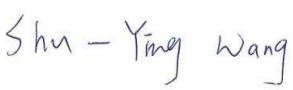
⊘ gefitinib (Mylan)

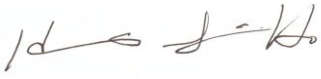
Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-06-16 **Variant class:** EGFR exon 20 insertion

Reference:

https://www.ema.europa.eu/en/documents/product-information/gefitinib-mylan-epar-product-information_en.pdf

Signatures

Testing Personnel:  2022.12.15 16:07:05 +08'00'

Laboratory Supervisor:  2022.12.15 16:07:19 +08'00'

Pathologist:  2022.12.15 16:07:39 +08'00'

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