Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 趙黃素
Gender: Female
ID No.: H200499516
History No.: 3642657
Age: 83

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: D567J4J
Signing in Date: 2020/06/11

Path No.: S109-99579
MP No.: F20033
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S108-30676E
Percentage of tumor cells: 50%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	***EGFR exon 20 insertion***	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
EGFR exon 20 insertion epidermal growth factor receptor Tier: IA Allele Frequency: 18.51%	osimertinib **gefitinib** [2]	None	60

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.

Prevalent cancer biomarkers without relevant evidence based on included data sources
CTNNB1 p.(D32V) c.95A>T

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
CTNNB1	p.(D32V)	c.95A>T	COSM5691	chr3:41266098	3.41%	NM_001904.3	missense	1996
EGFR	p.(A767_S768insSVDN)	c.2313_2314insAGCGTGGACAAC	.	chr7:55249002	18.51%	NM_005228.4	nonframeshift Insertion	1956
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	49.32%	NM_002227.3	synonymous	1991
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.85%	NM_004304.4	missense	1996
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.90%	NM_004304.4	missense	1997
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.80%	NM_004304.4	synonymous	1983
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.68%	NM_000142.4	synonymous	629
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	47.74%	NM_006206.5	synonymous	1988
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.90%	NM_006206.5	synonymous	1999
KIT	p.(=)	c.1638A>G	.	chr4:55593481	47.15%	NM_000222.2	synonymous	1998
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.88%	NM_213647.2	missense	1709
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	23.63%	NM_213647.2	synonymous	1096
RET	p.(=)	c.2307G>T	.	chr10:43613843	49.31%	NM_020975.4	synonymous	1815
RET	p.(=)	c.2712C>G	.	chr10:43615633	50.83%	NM_020975.4	synonymous	1800

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 human epidermal growth factor receptor (HER) family. Along with EGFR/ERBB1/HER1, ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[18]. 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 of EGFR are observed in approximately 10-20% of lung adenocarcinoma and at higher frequencies in never-smoker, female, and in Asian populations with lung cancer[15,16,21,22]. The most common mutations occur near the ATP-binding pocket of the kinase domain 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 the EGFR kinase resulting in downstream signaling and represent 80% of the EGFR mutations observed in lung cancer. A second group of recurrent activating mutations that are less common include E709K, G719X, S768I, L861Q, and short in-frame insertions in exon 20[24,25,26,27]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[28]. Although these variants are common in lung cancer, they are rare in other cancer types. In glioblastoma, recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V[23,29]. The recurrent focal amplification of the EGFR gene leads to an increase in expression in several cancer types. EGFR is amplified in up to 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 which is frequently observed in glioblastoma and has been shown to lead to lung cancer development as well as sensitivity to TKIs[31,32,33].

Potential relevance: Erlotinib[34] (2004), afatinib[35] (2013), gefitinib[36] (2015), osimertinib[37] (2015), and dacomitinib[38] (2018) are small molecule TKIs that are FDA approved for non-small cell lung cancer (NSCLC) patients with sensitizing exon 19 deletions and exon 21 L858R mutations. Acquired secondary mutations often confer resistance to first line TKI therapy with the T790M amino acid substitution accounting for 50-60% of cases[23]. Osimertinib is also indicated for NSCLC patients harboring EGFR T790M mutations whose disease has progressed on or after treatment with a first line TKI. EGFR targeting antibodies including cetuximab[39] (2004), panitumumab[40] (2006), and necitumumab[41] (2016) are also under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The use of cetuximab in combination with afatinib is currently recommended by the NCCN for patients who have progressed after receiving erlotinib, afatinib, dacomitinib, or gefitinib and chemotherapy[42].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	✖	●	✖	✖	● (II)
gefitinib	✖	✖	⊘	✖	● (III)
apatinib + erlotinib, apatinib + gefitinib, apatinib + icotinib hydrochloride	✖	✖	✖	✖	● (IV)
apatinib + gefitinib	✖	✖	✖	✖	● (IV)
gefitinib, radiation therapy	✖	✖	✖	✖	● (IV)
icotinib hydrochloride, radiation therapy	✖	✖	✖	✖	● (IV)
bevacizumab (Shanghai Hengrui Pharmaceutical) + chemotherapy, bevacizumab + chemotherapy	✖	✖	✖	✖	● (III)
bevacizumab, atezolizumab, chemotherapy	✖	✖	✖	✖	● (III)
durvalumab, chemotherapy	✖	✖	✖	✖	● (III)
icotinib hydrochloride, chemotherapy	✖	✖	✖	✖	● (III)
nivolumab, chemotherapy	✖	✖	✖	✖	● (III)
sintilimab, bevacizumab (Innovent Biologics), chemotherapy	✖	✖	✖	✖	● (III)
toripalimab, chemotherapy	✖	✖	✖	✖	● (III)
afatinib, bevacizumab	✖	✖	✖	✖	● (II)
afatinib, cetuximab	✖	✖	✖	✖	● (II)
afatinib, chemotherapy, radiation therapy	✖	✖	✖	✖	● (II)
anlotinib hydrochloride + sintilimab	✖	✖	✖	✖	● (II)
apatinib + chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, osimertinib	✖	✖	✖	✖	● (II)
chemotherapy, ramucirumab	✖	✖	✖	✖	● (II)
erlotinib	✖	✖	✖	✖	● (II)
erlotinib + chemotherapy	✖	✖	✖	✖	● (II)
erlotinib, radiation therapy	✖	✖	✖	✖	● (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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 20 insertion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
famitinib, HS-10296	✖	✖	✖	✖	● (II)
icotinib hydrochloride	✖	✖	✖	✖	● (II)
KN046	✖	✖	✖	✖	● (II)
nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
poziotinib	✖	✖	✖	✖	● (II)
sintilimab	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)
tarloxotinib	✖	✖	✖	✖	● (II)
tyrosine kinase inhibitors, radiation therapy	✖	✖	✖	✖	● (II)
afatinib + necitumumab	✖	✖	✖	✖	● (I/II)
bevacizumab + erlotinib + chemotherapy	✖	✖	✖	✖	● (I/II)
DZD-9008	✖	✖	✖	✖	● (I/II)
EMB01	✖	✖	✖	✖	● (I/II)
icotinib hydrochloride + chemotherapy + radiation therapy	✖	✖	✖	✖	● (I/II)
ningetinib, gefitinib	✖	✖	✖	✖	● (I/II)
oleclumab + osimertinib	✖	✖	✖	✖	● (I/II)
TPC-064	✖	✖	✖	✖	● (I/II)
APG-1252, osimertinib	✖	✖	✖	✖	● (I)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✖	✖	✖	✖	● (I)
JNJ-61186372	✖	✖	✖	✖	● (I)
lazertinib, JNJ-61186372	✖	✖	✖	✖	● (I)
nivolumab, ipilimumab, radiation therapy	✖	✖	✖	✖	● (I)
osimertinib + radiation therapy, osimertinib	✖	✖	✖	✖	● (I)
osimertinib, necitumumab	✖	✖	✖	✖	● (I)

* 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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 20 insertion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pirotinib	✖	✖	✖	✖	● (I)
TP-0903	✖	✖	✖	✖	● (I)
tyrosine kinase inhibitors, tyrosine kinase inhibitors + 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 ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

NCCN information is current as of 2019-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

EGFR exon 20 insertion

● **osimertinib**

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Brain metastases; Newly diagnosed (Not specified)
- Non-Small Cell Lung Cancer; Leptomeningeal and Spine metastases (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2019]

EGFR exon 20 insertion (continued)

pembrolizumab

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

Other criteria: CD274 overexpression

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "A small study suggests that single-agent pembrolizumab is not effective as first-line therapy in patients with metastatic NSCLC and EGFR mutations, even those with PD-L1 levels more than 50%."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

EGFR tyrosine kinase inhibitor

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 TKIs, although there are rare exceptions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

Current EMA Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

EMA information is current as of 2020-02-28. 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:** 2019-05-28 **Variant class:** EGFR exon 20 insertion

Reference:

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

Signatures

Testing Personnel:

2020.06.11
18:23:15 +08'00'

Laboratory Supervisor:

2020.06.11
18:23:33 +08'00'

Pathologist:

2020.06.11
18:23:54 +08'00'

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