Taipei Veterans General Hospital

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Sample Information

Patient Name: 張結坤
Gender: Male
ID No.: N101006900
History No.: 42288824
Age: 69

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: C1NPF1K
Signing in Date: 2020/01/16

Path No.: S109-99051
MP No.: F2001
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-00673A
Percentage of tumor cells: 80%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

2 Clinically Significant Biomarkers
2 Therapies Available
68 Clinical Trials

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		

Clinically Significant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
PIK3CA p.(N345T) c.1034A>C phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Tier: IIC Allele Frequency: 6.15%	None	alpelisib + fulvestrant [1]	9
EGFR exon 20 insertion epidermal growth factor receptor Tier: IA Allele Frequency: 26.84%	osimertinib gefitinib [2]	None	60

Sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Prevalent cancer biomarkers without clinical significance based on included data sources
CTNNB1 p.(S37F) c.110C>T

Tier Criteria Met

Genomic Alteration	Tier Classification for Non-Small Cell Lung Cancer
PIK3CA p.(N345T) c.1034A>C Tier: IIC	IIC: Biomarker predicts response or resistance to FDA or EMA approved therapies in other cancer types IIC: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in other cancer types IIC: Biomarker is an inclusion criteria for clinical trials
EGFR exon 20 insertion Tier: IA	IA: Biomarker predicts response or resistance to FDA or EMA approved therapies in this cancer type IA: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in this cancer type IIC: Biomarker is an inclusion criteria for clinical trials

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
CTNNB1	p.(S37F)	c.110C>T	COSM5662	chr3:41266113	29.85%	NM_001904.3	missense	2000
PIK3CA	p.(N345T)	c.1034A>C	COSM446001	chr3:178921552	6.15%	NM_006218.3	missense	2000
EGFR	p.(D770delinsGY)	c.2308_2309insGTT	COSM12427	chr7:55249010	26.84%	NM_005228.4	nonframeshift Insertion	1956
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	82.48%	NM_002227.3	synonymous	1986

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
ALK	p.(L1533M)	c.4597C>A	.	chr2:29416356	10.51%	NM_004304.4	missense	1999
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	100.00%	NM_004304.4	missense	1997
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.75%	NM_004304.4	missense	1999
ALK	p.(=)	c.3375C>A	.	chr2:29445458	48.52%	NM_004304.4	synonymous	1997
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.95%	NM_000142.4	synonymous	1995
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.95%	NM_006206.5	synonymous	1997
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.70%	NM_213647.2	missense	2000
EGFR	p.(G724S)	c.2170G>A	.	chr7:55241722	33.72%	NM_005228.4	missense	1999

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 clinical 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

Biomarker Descriptions (continued)

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 clinical 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].

PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[43]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples the p110α subunit (PI3K) to activated tyrosine protein kinases. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[44,45]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[44,45,46,47]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in activation of the PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[48,49,50].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[15,16]. Activating mutations in PIK3CA commonly cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase (codon H1047) domains, each having distinct mechanisms of activation[51,52,53]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[15,16].

Potential clinical relevance: The PI3K inhibitor, alpelisib[54], is FDA approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer, the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[55]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[55]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[56]. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[57,58].

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

PIK3CA p.(N345T) c.1034A>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	✖	✖	✖

* 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

PIK3CA p.(N345T) c.1034A>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capivasertib	✖	✖	✖	✖	● (II)
everolimus	✖	✖	✖	✖	● (II)
samotolisib	✖	✖	✖	✖	● (II)
sirolimus	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
atezolizumab + ipatasertib	✖	✖	✖	✖	● (I/II)
GDC-0077	✖	✖	✖	✖	● (I)
gedatolisib + palbociclib	✖	✖	✖	✖	● (I)

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)
atezolizumab, bevacizumab, chemotherapy	✖	✖	✖	✖	● (III)
bevacizumab (Innovent Biologics), chemotherapy, sintilimab	✖	✖	✖	✖	● (III)
bevacizumab + chemotherapy, bevacizumab (Shanghai Hengrui Pharmaceutical) + chemotherapy	✖	✖	✖	✖	● (III)
chemotherapy, durvalumab	✖	✖	✖	✖	● (III)
chemotherapy, icotinib hydrochloride	✖	✖	✖	✖	● (III)
chemotherapy, nivolumab	✖	✖	✖	✖	● (III)

* 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*
chemotherapy, toripalimab	✖	✖	✖	✖	● (III)
afatinib, bevacizumab	✖	✖	✖	✖	● (II)
afatinib, chemotherapy, radiation therapy	✖	✖	✖	✖	● (II)
anlotinib hydrochloride + sintilimab	✖	✖	✖	✖	● (II)
apatinib + chemotherapy	✖	✖	✖	✖	● (II)
bevacizumab, osimertinib	✖	✖	✖	✖	● (II)
chemotherapy, ramucirumab	✖	✖	✖	✖	● (II)
chemotherapy, targeted therapy	✖	✖	✖	✖	● (II)
erlotinib	✖	✖	✖	✖	● (II)
erlotinib + chemotherapy	✖	✖	✖	✖	● (II)
erlotinib, radiation therapy	✖	✖	✖	✖	● (II)
gefitinib + chemotherapy	✖	✖	✖	✖	● (II)
icotinib hydrochloride	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
KN046	✖	✖	✖	✖	● (II)
poziotinib	✖	✖	✖	✖	● (II)
radiation therapy, tyrosine kinase inhibitors	✖	✖	✖	✖	● (II)
sintilimab	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
tarloxotinib	✖	✖	✖	✖	● (II)
afatinib + necitumumab	✖	✖	✖	✖	● (I/II)
bevacizumab + erlotinib + chemotherapy	✖	✖	✖	✖	● (I/II)
DZD-9008	✖	✖	✖	✖	● (I/II)
EMB01	✖	✖	✖	✖	● (I/II)
gefitinib + ningetinib	✖	✖	✖	✖	● (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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

EGFR exon 20 insertion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
icotinib hydrochloride + chemotherapy + radiation therapy	✖	✖	✖	✖	● (I/II)
oleclumab + osimertinib	✖	✖	✖	✖	● (I/II)
TAK788	✖	✖	✖	✖	● (I/II)
APG-1252, osimertinib	✖	✖	✖	✖	● (I)
cetuximab, FATE-NK100	✖	✖	✖	✖	● (I)
durvalumab + oleclumab, oleclumab	✖	✖	✖	✖	● (I)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✖	✖	✖	✖	● (I)
JNJ-61186372	✖	✖	✖	✖	● (I)
necitumumab, osimertinib	✖	✖	✖	✖	● (I)
osimertinib, osimertinib + radiation therapy	✖	✖	✖	✖	● (I)
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 FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

FDA information is current as of 2019-11-25. For the most up-to-date information, search www.fda.gov.

PIK3CA p.(N345T) c.1034A>C

○ alpelisib + fulvestrant

Cancer type: Breast Cancer **Label as of:** 2019-05-24 **Variant class:** PIK3CA mutation

Other criteria: ERBB2 negative, Hormone receptor positive

Indications and usage:
PIQRAY® is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212526s000lbl.pdf

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 2019-08-15. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

PIK3CA p.(N345T) c.1034A>C

alpelisib + fulvestrant

Cancer type: Breast Cancer **Variant class:** PIK3CA mutation

Other criteria: ERBB2 negative

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Recurrent or Stage IV Invasive Breast Cancer (Not specified) (Preferred)

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 3.2019]

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 1.2019]

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 7.2019]

EGFR exon 20 insertion (continued)

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 7.2019]

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 2019-11-25. 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

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